Mylan

Mylan Laboratories Limited

To,

The Controller of Patents
Delhi Patent Office.

From:

Sandeep K. Rathod,
Mylan Laboratories Limited
Plot no. 31-34 ANRICH Industrial Estate,
Bollaram (V), Jinnaram (Mandal)
Medak District, AP
INDIA - 502 325

Email: sandeep.rathod@mylan.in

Date: June 10, 2013

Dear Sir,

Sub: Filing of pre-grant Opposition to Application # 6733/DELNP/2007

on behalf of Mylan Laboratories Limited

I, Sandeep Rathod, on behalf of my employer- Mylan Laboratories Limited, am filing a pre-grant opposition u/s 25(1) against the afore mentioned application.

The statement of opposition and accompanying exhibits are attached (in duplicate). We request you to take our opposition on record and send us an acknowledgment of the same. We also request a personal hearing, before any adverse decision is taken in this matter.

Thank you.

With best regards,

Sandeep K. Rathod

Attachments:

a) Statement of Opposition and
b) Exhibits 1 to 19
[both- in duplicate]

GOVT. OF INDIA PATENT OFFICE
D No. 10309
11 JUN 2013
BAUDHIK SAMPADA BHAWAN
NEW DELHI

11/06/13

BEFORE THE CONTROLLER OF PATENTS,

DELHI

IN THE MATTER OF:

A representation under section 25(1) of The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005 ("the Act") and Rule 55 of The Patents Rules, 2003 as amended by the Patents Rules, 2006 ("the Rules")

by
M/s Mylan Laboratories Limited
(the "Opponent")

And

IN THE MATTER OF:

Indian Patent Application No. 6733/DELNP/2007, filed on 30/Aug/2007 by Abbott Laboratories (the "Applicant")

STATEMENT OF OPPOSITION

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1. ***The Opposition in brief:***

1.1 The Opponent hereby files a pre-grant opposition under Section 25(1) of the Patent Act 1970, as amended by the Patents (Amendment) Act, 2005 against the application entitled:
"A Solid Pharmaceutical Dosage Formulation", filed by Abbott Laboratories, Filed on 30/Aug/2007, bearing No. 6733/DELNP/2007 (the "Application").

The bibliographic details of the Application were published in the Official Journal of the Patent Office dated 21/Sep/2007, and a first examination report was issued on 20/Mar/2013. A copy of the examination report from IPO site is attached as **Exhibit 1**.

2 ***Maintainability of the present Opposition:***

2.1 The Act states:

"25. Opposition to the patent:
(1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground --..."

Thus, the Act clearly allows any person to oppose a published Application for Patent that has not matured into a Patent.

2.2 Mylan Laboratories Limited ("Mylan"), the Opponent herein, is a key player and has significant commercial interests on a global level in the business of anti-retro viral drugs, including HIV protease inhibitor compositions, [the field to which the present Application pertains to]. It is a leading supplier of generic anti-retro viral drug compositions in the global market such as the US President's Emergency Plan for AIDS Relief [PEPFAR] as well as other National tenders issued by governments.

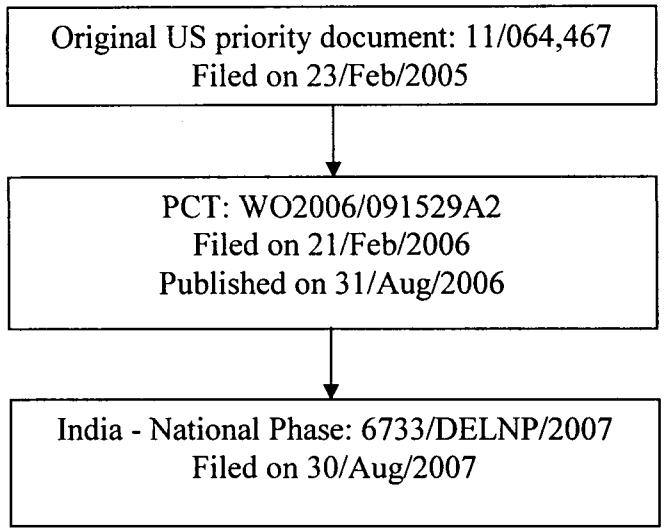
As noted earlier, the Application is currently under examination and has not matured into a granted patent. Hence the present pre-grant opposition is covered within the framework envisaged in the Act and the Rules made there-under.

3 ***Jurisdiction of the Patent Office:***

3.1 The Application was filed at the Patent Office in Delhi. Therefore the Delhi Patent Office has the jurisdiction to hear and deliberate upon this pre-grant opposition.

4 ***The Application – Filing details:***

4.1 The Application principally claims a solid dispersion of at least one HIV protease inhibitor in a polymer and a surfactant. The Application was filed as a national phase filing for a PCT Application. Its genesis is represented below:



4.2 In view of the above, it is clear that publications or public use prior to 23/Feb/2005 will generally be considered as prior art against the Application and the invention claimed therein.

5 ***The Application – in brief:***

5.1 The invention in the Application principally relates to a pharmaceutical dosage form comprising HIV protease inhibitor (PI) in undissolved form. The claims, while focused on lopinavir as the main drug, also have ritonavir as a standalone drug in some claims. According to the patent specification, undissolved PI refers to PI in solid form. Preferably dosage form comprises a solid solution or solid dispersion of least one HIV protease inhibitor in at least one water soluble polymer and at least one surfactant. The specification defines the term "undissolved PI", "solid solution" and "solid dispersion" as follows:

> "... undissolved PI's as used herein means that the PI is in a solid form .."
> Page 5, lines 27
>
> "A preferred dosage form, will generally comprise at least one HIV protease inhibitor in a therapeutically effective amount, at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant.
>
> "More preferably, a solid solution or solid' dispersion can be formed into one, of the above pharmaceutical dosage forms,"
> Page 6, lines 19-23
>
> '"Solid solution" is defined as a system in a solid state wherein the drug is (molecularly dispersed throughout a matrix such that the system is chemically and physically uniform or homogenous throughout.'
> Page 4, lines 11-13
>
> '"Solid dispersion" is defined as a system having small particles, typically of

less than 400 μm in size, more typically less than 100 μm in size, and most typically less than 10 μm in size, of one phase dispersed in another phase (the carrier phase).'

Page 4, lines 14-16

"The preferred solid dispersion or solid solution based dosage form of the present invention can be produced by preparing a solid solution or solid dispersion of the HIV protease inhibitor, or the combination of HIV protease inhibitors, in a matrix of a water-soluble polymer and a surfactant, and then shaping into the 'required tablet form."

Page 9, lines 19-22

"Various techniques exist for preparing solid solutions or solid dispersion including melt-extrusion, spray drying and solution-evaporation..."

Page 9, lines 25-26

5.2 The Application, on IPAIRS, contains the following <u>independent</u> claims (as of 04/June/2013):

1. A pharmaceutical dosage form comprising an undissolved form of (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-l,6-diphenyl hexane (ABT-378; lopinavir) in a therapeutically effective amount.

6. A pharmaceutical dosage form comprising at an undissolved HIV protease inhibitor in a therapeutically effective amount wherein upon administration of a single dose of the protease inhibitor to each member of a study population, the mean of a AUC_{∞}(fed) over AUC_{∞}(fasted) ratio for the members of the study population is in the range of about 0.7 to about 1.43.

7. A pharmaceutical dosage formulation comprising an undissolved HIV protease inhibitor in a therapeutically effective amount wherein upon administration of a single dose of the protease inhibitor to each member of a study population, the mean of a C_{max}(fed) over C_{max}(fasted) ratio for the members of the study population is in the range of about 0.7 to about 1.43.

8. A pharmaceutical dosage form comprising an undissolved HIV protease inhibitor in a therapeutically effective amount wherein upon administration of a single dose of the protease inhibitor to each member of a study population, the difference in AUC_{∞} between a 95^{th} percentile of the study population the and a 5^{th} percentile of the study population is less than about 180.

9. A pharmaceutical dosage form comprising an undissolved HIV protease inhibitor in a therapeutically effective amount wherein upon administration of a single dose of the protease inhibitor to each member of a study population under fasting conditions, the difference in C_{max} between the 95^{th} percentile of the study population and the 5^{th} percentile of the study population is less than about 15.

12. A pharmaceutical dosage form comprising lopinavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (polyoxyethylene 10 Lauryl Ether) medium at 37°C wherein:

about 20 % to about 30 % of lopinavir is released from about 0 to about 15 minutes;
about 43 % to about 63 % of lopinavir is released from about 15 to about 30 minutes;
about 61.3 % to about 81.7 % of lopinavir is released from about 30 to about 45 minutes; and
about 75.4 % to about 93.2 % of lopinavir is released from about 45 to about 60 minutes.

13. A pharmaceutical dosage form comprising ritonavir in a therapeutically effective amount, said dosage form providing an in vitro dissolution profile using a USP apparatus 2 (paddle) at 75 rpm with a 0.06M POE10LE (polyoxyethylene 10 Lauryl Ether) medium at 37°C wherein:

about 19.8 % to about 34.4 % of ritonavir is released from about 0 to about 15 minutes;
about 41.6 % to about 76.5 % of ritonavir is released from about 15 to about 30 minutes;
about 59.4 % to about 91.1 % of ritonavir is released from about 30 to about 45 minutes; and
about 73.4 % to about 95 % of ritonavir is released from about 45 to about 60 minutes.

5.3 It is clear from the above paragraphs of the specification that an undissolved PI, according to the specification, refers to PI in solid form and one that is not dissolved in a liquid carrier in its final dosage form. Applicant's preferred dosage form comprises a solid solution or solid dispersion of least one HIV protease inhibitor in at least one water soluble polymer and at least one surfactant.

Hence it is Opponents submission that lopinavir and/ or ritonavir or HIV protease inhibitor(s) in undissolved form as claimed in claim 1 and 6 to 9, should be actually read as "A solid pharmaceutical dosage form comprising lopinavir and/ or ritonavir or HIV protease inhibitor, at least one water soluble polymer and at least one surfactant" as that is the basis for 'dissolved form'.

5.4 The specification goes on to disclose examples for lopinavir and/ or ritonavir formulation and bioavailability aspects of the same. However, the Application does not provide any data/ working example/ guidance for making a composition comprising HIV protease inhibitor(s) other than the two drugs (lopinavir and

ritonavir). Moreover the bioavailability data is only for the lopinavir and ritonavir in combination and not for the individual drugs, unlike the claims 12 and 13 which claim standalone drugs.

6 *Discussion of grounds for opposition:*

6.1 The Opponent opposes the present Application on the following grounds allowed under section 25(1):

> 25. Opposition to the patent: –
> (1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground –
>
> (b) that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim –
>
> ... (ii) in India or elsewhere, in any document:...
>
> c) that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;
>
> (e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step,
>
> having regard to the matter published as mentioned in clause (b)
>
> or
>
> having regard to what was used in India before the priority date of the applicant's claim;
>
> (f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;
>
> (g) that the complete application does not sufficiently and clearly describe the invention or the method by which it is to be performed;
>
> (h) that the applicant failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;
>
> ...

6.2 The Opponent opposes the Application, in its entirety. The grounds stated herein are distinct and independent of each other. Each ground provides sufficient reason to bar the issuance of a Patent from this Application.

7 *S. 25(1)(b) Prior publication [Anticipation]*

For independent claims 1, 6 to 9, 12 and 13 – and their dependent claims

7.1 S. 25(1)(b) states:

> (b) that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim –

(i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January 1912; or
(ii) in India or elsewhere, in any document:
Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29; (emphasis ours)

7.2 Claim 1 requires only two core components – the product should be a pharmaceutical composition and such composition should have lopinavir drug in an undissolved state. The words 'in a therapeutically effective amount' do not bring in any new, patentable element since it is unclear from a dose limit perspective.

7.3 The Opponent states that the claimed invention is not novel in view of Applicant's own PCT publication WO01/34119 ('119) [**Exhibit 2**; published on 17/May/2001]. The Application discloses:

"A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC)." [Claim 1]

"The composition of Claim 3 wherein said HIV protease inhibitor is a combination of 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) L-valinyl)amino-2-(N-((5-thiazolyl) methoxy-carbonyl) -amino)-amino-1,6-diphenyl-3-hydroxyhexane (**ritonavir**) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (**ABT-378**)." [Claim 7]

7.4 It is clear from the above paragraph that the '119 Application provides a solid pharmaceutical composition comprising an HIV protease inhibitor(s) such as ritonavir and/ or lopinavir (ABT-378) in undissolved form and water soluble carrier and polyvinylpyrrolidone. PVP has a T_g of about 90 °C to 185 °C (see Volker Buhler (1996), Kollidon "Polyvinylpyrrolidone for the pharmaceutical industry" - Page 107; Para 2.4.4.2 published by BASF in March, 1996, attached as **Exhibit 3).**

The '119 Application further discloses that the composition can further comprise additives such as pharmaceutically acceptable surfactants. The teaching is identical as that of the present invention and discloses all the essential components of the present invention. Hence claim 1 is not novel over the disclosure and teachings of WO 01/34119.

7.5 In the alternative, Opponent states that the claimed invention is not novel in view of US Patent No. 6,599,528 ('528) **[Exhibit 4;** published on 29/July/2003]. The Patent teaches and discloses the following:

> "The present invention relates to mechanically stable pharmaceutical presentations for oral administration, comprising in addition to one or more active ingredients and at least one melt-processable matrix-forming excipient more than 10 and up to 40% by weight of a **surface-active substance with an HLB of from 2 to 18**, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C."
>
> Col 1, line 9-15

> "It is an object of the present invention to find mechanically **stable solid formulations for oral use** which can be used in particular for rapid and nevertheless long-lasting solubilization of active ingredients of low solubility after they have been liberated from the drug form."
>
> Col 2, line 30-34

> "Particularly suitable active ingredients are immunosuppressants, **protease inhibitors,** reverse transcriptase inhibitors, cytostatics or antimycotics, in addition to CNS-active substances or dihydropyrimidine derivatives."
>
> Col 2, line 47-50

> "Suitable and preferred surface-active substances are low molecular weight substances which have an HLB (HLB hydrophilic lipophilic balance) and are liquid at 20° C. or have a drop point in the range from 20° C. to 50° C., preferably up to 40° C. Preferred substances have an **HLB of from 7 to 18**, particularly preferably 10 to 15.
>
> Col 2, line 60-65

> "Pharmaceutically acceptable polymers are, in particular, homo- and copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone with Fikentscher K values of from 12 to 100, in particular K 17 to K30, or copolymers with vinyl carboxylates such as vinyl acetate or vinyl propionate, for example **copovidone** (VP/VAc-60/40)"
>
> Col 3, line 29-34

> "The resulting drug forms comprise the active ingredient embedded amorphously. The preferred result is **solid dispersions in which the active ingredient is in the form of a molecular dispersion**. The drug forms according to the invention make it possible for even active ingredients of low solubility to be sufficiently solubilized and stably dispersed in aqueous medium."
>
> Col 3, line 52-58

7.6 The '528 Patent claims solid dispersion compositions, wherein the drug is in undissolved form and comprises active ingredient (like HIV protease inhibitor(s)), homo- and copolymers of N-vinylpyrrolidone and a surfactant of HLB value 7 to 18.

Hence claim 1 is not novel over the disclosure and teachings of US Patent No. 6,599,528.

7.7 In yet another alternative, Opponent states that the claimed invention is not novel in view of Rosenberg et. al., AU patent application 2003/283261 ('261) [**Exhibit 5**; published on 04/May/2004].

Rosenberg *et. al.*, teaches composition and process of preparing solid dosage form comprising active agent and at least one crosslinked nonthermoplastic carrier, at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilising agents.

According to the specification

> "The nonthermoplastic carrier is preferably selected from crosslinked polyvinylpyrrolidone and crosslinked sodium carboxymethylcellulose."
>
> Page 4, lines 13-16

> "Examples of suitable thermoplastic polymers are polyvinylpyrrolidone (PVP), **copolymers of N-vinyl-pyrrolidone and vinyl acetate** or vinyl propionate, copolymers of vinyl acetate and crotonic acid ....."
>
> Page 4, lines 26-29

> "The thermoplastic polymers preferably have a **softening temperature** of from **60 to 180°C**, in particular 70 to 130°C."
>
> Page 5, lines 12-15

> "Solubilizers mean pharmaceutically acceptable nonionic surface-active compounds. Suitable solubilizers include **sorbitan fatty acid esters,** polyalkoxylated fatty acid esters such as, for example, **polyalkoxylated glycerides** ....."
>
> Page 5, lines 28-32

> "Suitable sorbitan fatty acid esters are **sorbitan monolaurate, sorbitan monopalmitate** ....."
>
> Page 6, lines 1-2

> "Suitable polyalkoxylated glycerides are obtained for example by alkoxylation of natural or hydrogenated glycerides or by transesterification of natural or hydrogenated glycerides with polyalkylene glycols. Commercially available examples are polyoxyethylene glycerol ricinoleate 35, polyoxyethylene **glycerol trihydroxystearate 40 (Cremophor® RH40, BASF AG)** and ....."
>
> Page 6, lines 17-23

> "Active ingredients mean for the purposes of the invention all substances with a desired physiological effect on the human or animal body or plants. They are in particular active pharmaceutical ingredients. ..... Combinations of active ingredients can also be employed."
>
> Page 7, lines 23-30

7.8 Rosenberg *et. al.*, discloses seven working examples, all featuring lopinavir as an active ingredient and wherein it is present in undissolved form.

Specifically comparative example 3, provides a solid composition comprising

- Lopinavir [HIV protease inhibitor]
- Copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate (Kollidon VA-64) [a water soluble polymer] and
- Polyoxyethylene glycerol trihydroxystearate 40 (Cremophor® RH-40) [a surfactant].

Page 13, lines 10-15

Working examples disclosed by Rosenberg *et. al.*, specifically provides granules as well as tablet compositions comprising lopinavir in undissolved form.

Importantly claim 2 of Rosenberg *et. al.*, covers a pharmaceutical dosage form comprising an active ingredient, at least cross-linked non-thermoplastic carrier, at least one thermoplastic polymer (which includes copolymers of N-vinyl-pyrrolidone and vinyl acetate) and at least one solubilizer (which includes sorbitan monolaurate).

According to the present invention water soluble polymers are defined as having a T_g of at least about 50 °C, the numerous water soluble polymers exemplified includes copolymers of N-vinyl pyrrolidone and vinyl acetate (at Page 04; line 26-28) and surfactant is defined as having an HLB value of from about 4 to about 10 including sorbitan monolaurate (at Page 06; line 05). Hence claim 1 is not novel over the disclosure and teachings of AU 2003/283261.

7.9 The Opponent submits that each and every element generically claimed in claim 1, of the alleged invention is specifically disclosed by WO 01/34119 (**Exhibit 2**), US 6,599,528 (**Exhibit 4**) and AU 2003/283261A (**Exhibit 5**). Hence WO 01/34119 (**Exhibit 2**), US 6,599,528 (**Exhibit 4**) and AU 2003/283261 (**Exhibit 5**) individually anticipate claim 1 of the present application.

7.10 The Opponent further submits that claims 6 to 9 and 12 to 13 are also anticipated by WO 01/34119 (**Exhibit 2**), US 6,599,528 (**Exhibit 4**) and AU 2003/283261A (**Exhibit 5**) individually, as claimed properties/ characteristics such as AUC, C_{max}

and dissolution profile would be inherent properties/ characteristics of compositions comprising HIV protease inhibitor(s), a water soluble polymer and a surfactant as disclosed and taught in prior art. Hence, it is the Opponent's position that the alleged invention of the Application is anticipated by the disclosure and teachings of WO 01/34119 (**Exhibit 2**), US 6,599,528 (**Exhibit 4**) and AU 2003/283261A (**Exhibit 5**) individually. Further, the independent claims 1, 6 to 9 and 12 to 13 and all dependent claims from 2 to 5, 10 to 11 and 14 of the present Application are liable for rejection, in *toto as being anticipated by the disclosure and teachings of* WO 01/34119 (**Exhibit 2**), US 6,599,528 (**Exhibit 4**) and AU 2003/283261A (**Exhibit 5**).

8 ***S. 25(1)(c)*** ***Prior claiming in India***

For claims 1, 6 to 9 and 12 to 13 **and claims dependent thereon**

8.1 S. 25(1)(c) states:

> c) that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;

8.2 The present Application was filed as a national phase filing for a PCT application, claiming priority from US priority document: 11/064,467, filed on 23/Feb/2005.

8.3 The Opponent states that the claimed invention is already claimed in a claim of an Indian complete specification published on or after the priority date of the Application, but having a priority date earlier than that of the Applicant's claim.

8.4 Indian Application # **339/MUMNP/2006** was filed as a national phase filing for PCT application, claiming priority from US priority document: 10/650,178, filed on 28/Aug/2003. A copy of '339 specification is attached as **Exhibit 6**.

8.5 The '339 Application claims pharmaceutical compositions comprising a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer (having T_g of at least about 50 °C) and at least one pharmaceutically acceptable surfactant (HLB value of from about 4 to about 10),

wherein HIV protease inhibitor can be selected from lopinavir or ritonavir or combination of lopinavir and ritonavir.

According to '339 specification:

> "In one embodiment, ritonavir (Abbott Laboratories, Abbott Park, IL, USA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention."
>
> page 4, line 16-17

> "In another embodiment, lopinavir (Abbott Laboratories, Abbott Park, IL, USA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention."
>
> page 4, line 25-26

> "The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant. In one embodiment, the dosage form is comprising at least one surfactant having an hydrophilic lipophilic balance (MB) value of from about 4 to about 10, preferably from about 7 to about 9."
>
> page 7, line 9-12

> "sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalmitate (Span® (40), or sorbitan stearate, or mixtures of one or more thereof.
> The sorbitan mono fatty acid esters are preferred, with sorbitan mono laurate and sorbitan monopalmitate being particularly preferred.
>
> page 8, line 4-10

> "Water-soluble polymers suitable for use in the present invention include for example, but are not limited thereto:
> homopolymers and copolymers of N-vinyl lactams, especially homopolymers and copolymers of N-vinyl pyrrolidone, e.g. pelyvinylpyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate,"
>
> page 8, line 19-24

> "Of these, homopolymers or copolymers of N-vinyl pyrrolidone, in particular a copolymer of N-vinyl pyrrolidone and vinyl acetate, are preferred. A particularly preferred polymer is a copolymer of about 60 % by weight of the copolymer, N-vinyl pyrrolidone and about 40 % by weight of the copolymer, vinyl acetate."
>
> page 9, line 19-22

> "Exemplary compositions of the present invention for combined administration of ritonavir/ lopinavir are shown below in Table 1, and the values are % by weight.
> Table 1"
>
> page 13, line 22 – 25 to page 14

> "Example 2
> **Copovidone** (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 853.8 parts by weight) was blended with Span 20 (**Sorbitan monolaurate**; 83.9 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with **ritonavir** (50 parts by weight), **lopinavir** (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of

1120 mg were thus obtained."

page 16, line 32 to page 17, line 9

8.6 Relevant claims of the '339 application (as originally filed) are:

> "1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.
>
> ...
>
> 4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about 10 and at least one further pharmaceutically acceptable surfactant.
>
> ...
>
> 11. The dosage form of claim 10 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of lopinavir plasma concentration of at least about 20 (ig.h/ml/100 mg.
>
> ...
>
> 13. The dosage form of claim 12 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least 9 about ng.h/ml/100 mg and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 ug.h/ml/100 mg.
>
> ...
>
> 14. The solid dosage form of Claim 1 wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate."

8.7 The presently opposed Application as well as claims of '339 Application, both cover same subject matter i.e. a solid pharmaceutical composition comprising an HIV protease inhibitor(s) in un-dissolved form i.e. in solid dispersion form, together with at least one water soluble polymer (having Tg of at least about 50 °C which includes copovidone) and at least one surfactant (HLB value of from about 4 to about 10 which includes sorbitan monolaurate). Hence the Opponent submits that claim 1 of the present Application should be rejected in view of claims of '339, since these claim the same subject matter and the '339 has a priority date which is earlier than that of the present Application's priority date.

8.8

Claimed composition of present '6733	**Composition in 339**
Claim 1 of both application	
A pharmaceutical dosage form comprising an undissolved form of (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-l,6-diphenyl hexane (ABT-378; lopinavir) in a therapeutically	A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.

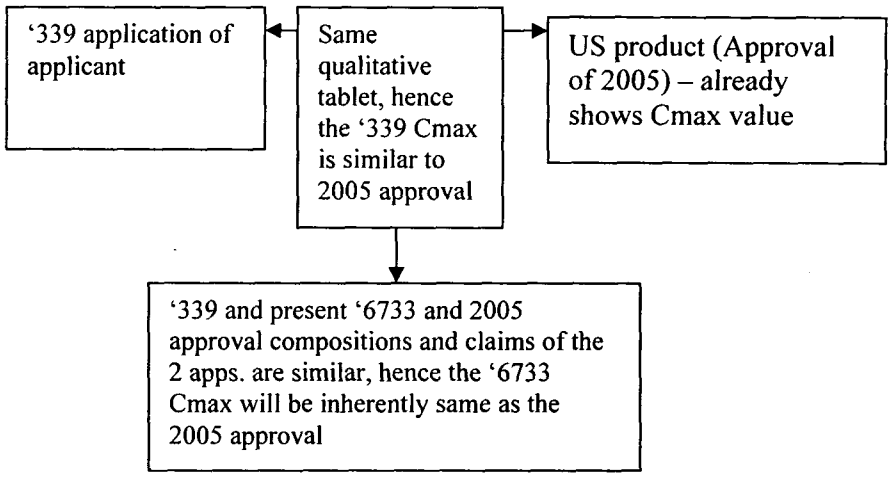
effective amount.	
The undissolved drug of 6733 has been explained as covering a solid dispersion of the drug with a water soluble polymer and a surfactant. The components of both the inventions are as below:	
Lopinavir and Ritonavir	Lopinavir and Ritonavir
Copovidone (Water soluble polymer)	a copolymer of N-vinyl pyrrolidone and vinyl acetate from about 50 % to about 85 % by weight of the dosage form
Sorbitan monolaurate (Surfactant)	a sorbitan fatty acid ester

8.9 The Opponent further submits that claims 6 to 9 and claims 12 to 13, which claims the values for AUC, C_{max} and dissolution profile are inherent characteristics of composition as claimed in claim 1 as well as taught by '339 application.

Kaletra™ tablets were approved in 2005 (attached as **Exhibit 7**) and they comprise lopinavir, ritonavir, copovidone (a water soluble polymer), sorbitan monolaurate (surfactant), exhibits C_{max} of 9.8 ± 3.7 µg/mL (i.e. in between 6.1 to 13.5) and AUC about 92.6 ± 36.7 µg•h/mL (i.e. in between 55.9 to 129.1 µg•h/mL).

The composition according to the present invention comprising HIV protease inhibitor(s) in undissolved form, at least one water soluble polymer (having Tg of at least about 50 °C) and at least one surfactant (HLB value of from about 4 to about 10) exhibits ΔAUC_{∞} of 141.15 µg•h/mL from the 5th to the 95th percentile, and ΔC_{max} of 11.98 µg/mL from the 5th to the 95th percentile.

There is very insignificant difference in between the AUC values and the C_{max} values for the composition (same qualitative composition) according to the present invention and the Kaletra™ tablets approved in 2005 and which were as disclosed in the '339 application. Table 1 and Example 2 of the '339 Application also contains lopinavir, ritonavir, copovidone (a water soluble polymer) and sorbitan monolaurate (surfactant), without any pharmacokinetics and dissolution data. But as the qualitative composition of the approved Kaletra™ tablets as well as the prior art composition disclose in '339 Application are similar, additionally the Kaletra™ tablet composition is same as what has been claimed in the opposed Application's claim 1, hence the Opponent submits that the values for AUC, C_{max} as well as the dissolution profile claimed in the above opposed claims 6 to 9 and 12 to 13 would be inherent characteristics of composition disclosed in example 2 of the '339 application and approved in 2005.



8.10 Hence the claimed invention in the opposed Application is already claimed in a claim of a complete specification published as 339/MUMNP/2006, after the priority date of the opposed Application, but having a priority date earlier than that of the opposed Application and hence merit rejection of claim 1, 6 to 9 and 12 to 13 and all dependent claims in *toto*.

9 S. 25(1)(e) Lack of inventive step/ Obviousness:

For claims 1, 6 to 9 and 12, 13 and claims dependent thereon

9.1 S. 25(1)(e) states:

> (e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b)
> or
> having regard to what was used in India before the priority date of the applicant's claim;

The following definitions from the Act, are important for the present argument:

> 'S. 2(j) "invention" means a new product or process involving an inventive step and capable of industrial application;
> S. 2(ja) "inventive step" means a feature of an invention that involves technical advance as compared to existing knowledge or having economic significance or both and makes the invention not obvious to a person skilled in the art; '
> S. 2(l) "new invention" means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject matter has not fallen in public domain or that it does not form part of the state of the art;'

9.2 According to the specification the most critical aspect to the present invention is to providing an HIV protease inhibitor in undissolved form;

The specification discloses

> "... undissolved PI's as used herein means that the PI is in a solid form .."
> Page 5, lines 27

> "A preferred dosage form, will generally comprise at least one HIV protease inhibitor in a therapeutically effective amount, at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant.
> Page 6, lines 19-21

> "The preferred solid dispersion or solid solution based dosage form of the present invention can be produced by preparing a solid solution or solid dispersion of the HIV protease inhibitor, or the combination of HIV protease inhibitors, in a matrix of a water-soluble polymer and a surfactant, and then shaping into the 'required tablet form."
> Page 9, lines 19-22

Hence it is Opponents submission that in undissolved form as claimed in the present claims should be construed as "A solid pharmaceutical dosage form comprising HIV protease inhibitor, at least one water soluble polymer and at least one surfactant".

9.3 The present invention is obvious and does not involve any inventive step in view of WO 01/34119 ('119) **[Exhibit 2]** and in combination with US 6,599,528 ('528) **[Exhibit 4]**.

'119 Application teaches and discloses the following:

> "For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a **suitable solid dosage form is to obtain a bioavailability of the drug** that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug."
> Page 2, lines 8-17

> "An alternative **dosage form is a solid dispersion**. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, Journal of Pharmaceutical Sciences, 60, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions."
> Page 2, lines 18-21 and Page 3, lines 1-2

> "Specifically, PVP PF 17 is used within the PEG matrix to inhibit the crystallization of the drug of interest. A range of 1%-95% (w/w) of PVP can be employed, with a range of 1%-15% (w/w) being preferred."
> Page 11, lines 3-6

> PVP has the added advantage of **having a high Tg**, which imparts stabilization of amorphous regions by reducing mobility.
>
> Page 11, lines 16-18

> "A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC)." [Claim 1]

> "The composition of Claim 1 wherein said pharmaceutical compound is an HIV protease inhibitor dissolved in an organic solvent." [Claim 3]

> "The composition of Claim 3 wherein said HIV protease inhibitor is a combination of 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) L-valinyl)amino-2-(N-((5-thiazolyl) methoxy-carbonyl) -amino)-amino-1,6-diphenyl-3-hydroxyhexane (**ritonavir**) and and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (**ABT-378**)." [Claim 7]

> "The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from the group **consisting of pharmaceutically acceptable surfactants** and antioxidants." [Claim 10]

It is clear from the above teachings that the object of the '119 is to provide a solid pharmaceutical composition comprising an HIV inhibitor(s) such as ritonavir and/ or lopinavir (ABT-378) and water soluble polymer of higher T_g, as well as it further discloses that the composition can further comprise additives such as pharmaceutically acceptable surfactants.

The teachings of '119 are same as that of the present invention and discloses all its essential components i.e. HIV protease inhibitor in undissolved form and a water soluble polymer. The main difference of the instant invention from the prior art lies in the selecting a surfactant(s) having HLB value from 4 to 10.

9.4 '528 Patent teaches and discloses the following:

> "The present invention relates to mechanically stable pharmaceutical presentations for oral administration, comprising in addition to one or more active ingredients and at least one melt-processable matrix-forming excipient more than 10 and up to 40% by weight of a **surface-active substance with an HLB of from 2 to 18**, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C."
>
> Col 1, line 9-15

> "It is an object of the present invention to find mechanically **stable solid formulations for oral use** which can be used in particular for rapid and nevertheless long-lasting solubilization of active ingredients of low solubility after they have been liberated from the drug form."
>
> Col 2, line 30-34

> "Particularly suitable active ingredients are immunosuppressants, **protease**

inhibitors, reverse transcriptase inhibitors, cytostatics or antimycotics, in addition to CNS-active substances or dihydropyrimidine derivatives."

Col 2, line 47-50

"Suitable and preferred surface-active substances are low molecular weight substances which have an HLB (HLB hydrophilic lipophilic balance) and are liquid at 20° C. or have a drop point in the range from 20° C. to 50° C., preferably up to 40° C. Preferred substances have an **HLB of from 7 to 18**, particularly preferably 10 to 15.

Col 2, line 60-65

"Pharmaceutically acceptable polymers are, in particular, homo- and copolymers of N-vinylpyrrolidone such as polyvinylpyrrolidone with Fikentscher K values of from 12 to 100, in particular K 17 to K30, or copolymers with vinyl carboxylates such as vinyl acetate or vinyl propionate, for example **copovidone** (VP/VAc-60/40)"

Col 3, line 29-34

"The resulting drug forms comprise the active ingredient embedded amorphously. The preferred result is **solid dispersions in which the active ingredient is in the form of a molecular dispersion**. The drug forms according to the invention make it possible for even active ingredients of low solubility to be sufficiently solubilized and stably dispersed in aqueous medium."

Col 3, line 52-58

9.5 The teachings in '528 highlight the importance of selecting a surfactant(s) based on its HLB value for preparing solid oral formulations of protease inhibitors. It also discloses that the solid formulation can be prepared with suitable active ingredients such as protease inhibitors and water soluble polymer such as copovidone along with surfactant having HLB value from 2 to 18.

Thus it is clear that a person skilled in the art after taking into consideration the teachings of the above prior art would be motivated to select a surfactant with suitable HLB value while preparing solid formulations of protease inhibitor. Therefore, selecting a surfactant(s) of particular HLB value form 4 to 10, while developing solid dispersion formulations of protease inhibitors like lopinavir and/or ritonavir along with a water soluble polymer such as copovidone can be achieved through routine experimentation by combining the disclosures of cited document '528 with the teachings of '119.

9.6 Hence, the Opponent submits that claim 1, of alleged invention of the Application is obvious to a person skilled in the art and does not involve any inventive step.

The Opponent further submits that claims 6 to 9 and 12 to 13 are also obvious and involve no inventive step as the values for AUC, C_{max} and dissolution profile as

claimed in the instant claims are inherent characteristics/ properties of composition claimed in claim 1.

9.7 In the alternative, Opponent states that the claimed invention is obvious and does not involve any inventive step in view of L. Dias *et al.* (1996) *Pharmaceutical Research Supplement* 13(9): page S-351 PDD 7475 published in September, 1996 **[Exhibit 8]** in combination with WO 01/34119 ('119) **[Exhibit 2]** and US Patent No. 6,599,528 ('528) **[Exhibit 4;** published on 29/July/2003].

9.8 The Applicant has, over the years, published a number of papers/ articles on the development of HIV protease inhibitors and their formulations, L. Dias *et al.,* PDD 7475 is one such publication.

L. Dias discloses the following:

> 'Poly vinyl pyrrolidone (PVP) has been used to form coprecipitates of an insoluble antiviral compound, ABT-538, in an effort to increase bioavailability of this drug. PVP: drug coprecipitates were prepared using solvent evaporation method.
> ...
> The drug:PVP co-precipitates also showed further improvement in bioavailabilties when combined with surfactants and acidifying agents.'

This PDD 7475 document clearly discloses following aspects of the present claims:

- solid dispersion of
- **ABT-538** [i.e. Ritonavir an HIV protease inhibitor]
- in PVP [a water soluble polymer] and
- a surfactant [to further enhance bioavailability].

Hence, it is the Opponent's submission that there is a clear teaching in PDD 7475 that by formulating a solid dispersion composition of HIV protease inhibitor (in undissolved form) along with a water soluble polymer and a surfactant will provide improved dissolution of HIV protease inhibitor which ultimately results into enhancement of oral bioavailability.

The object of the '119 Application is to provide a pharmaceutical composition comprising an HIV inhibitors such as ritonavir, lopinavir (ABT-378) and water soluble polymer having a higher T_g, as well as it further discloses that the composition may further comprise additives such as pharmaceutically acceptable

surfactants.

While the teachings of '528 Patent highlight the importance of selecting surfactants based on their HLB values for preparing solid oral formulations of protease inhibitors. The '528 Patent also disclosed that the solid formulation can be prepared with suitable active ingredients such as protease inhibitors and water soluble polymer such as copovidone along with surfactant having HLB value from 2 to 18.

9.9 Thus it is obvious that a person skilled in the art would have applied the combined teachings and suggestions given in PDD 7475, '119 Application and '528 Patent to develop solid dispersion composition comprising HIV protease inhibitor such as lopinavir and/ or ritonavir (in undissolved form) along with a water soluble polymer of higher T_g and a surfactant of HLB value 4 to 10, that can provide improved dissolution of HIV protease inhibitor in order to enhance oral bioavailability, with reasonable expectation of success and without undue experimentation.

Hence, the Opponent submits that claim 1, of alleged invention of the Application is obvious to a person skilled in the art and does not involve any inventive step.

The Opponent further submits that claims 6 to 9 and 12 to 13 are also obvious and involve no inventive step as the values for AUC, C_{max} and dissolution profile as claimed in the instant claims are inherent characteristics of composition claimed in claim 1.

9.10 In another alternative, Opponent states that the claimed invention is obvious and does not involve any inventive step in view of Fort *et al.;* PCT Application No. WO 01/34118 ('118) [**Exhibit 9**; Published on 17/05/2001] in combination with Rosenberg *et al.,* US Patent No. 6,599,528 ('528) [**Exhibit 4;** published on 29/July/2003] and Petersen *et al.*; U.S. Pat. Appl. No. 2004/0186066 ('066) [**Exhibit 10**; Published on 23/09/2004].

9.11 '118 Application specifically discloses solid dispersion tablet composition comprising a protease inhibitor(s) such as ABT-378 (lopinavir.), ritonavir or Nelfinavir and a water soluble carrier.

> "ABT-538 (ritonavir) was preferably used as the HIV protease inhibitor in the instant invention. Additionally, two other protease

> inhibitors, ABT-378 and nelfinavir mesylate, were tested in solid dispersions to demonstrate the improved dissolution which can be achieved with this system."
>
> at page 10, ln. 18 – page 11, ln. 2

> "The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus improving the bioavailability of a drug exhibiting dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.
>
> at page 8, ln. 20 – page 9, ln. 10

> "Solid dispersions of HIV protease inhibitors (for example, ABT-538 (ritonavir), ABT-378, and nelfinavir mesylate) markedly improve the dissolution rate ..."
>
> at page 18, ln. 20-22

> "The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from the group **consisting of pharmaceutically acceptable surfactants** and antioxidants."
>
> [Claim 11, page 25]

The '528 Patent teaches the required water-soluble polymers and surfactants of the opposed Application as well as highlight the importance of selecting surfactants based on their HLB values for preparing solid formulations of protease inhibitors for oral use. Suitable water soluble polymers according to the '528 Patent include surfactants having HLB value from 2 to about 18.

With respect to water soluble polymers in particular, the '528 Patent teaches copovidone (VP/Vac-60/40) as a pharmaceutically acceptable polymer. Reference is made to the Handbook of Pharmaceutical Excipients as an evidentiary reference depicting that copovidone is a copolymer of N-vinyl pyrrolidone and vinyl acetate having a glass transition temperature of 106°C, which is greater than 50°C as required by the impugned invention of the Application **[attached as Exhibit 11].**

Petersen *et al.*, specifically disclose that lopinavir (and other protease inhibitors) can be administered with or without food. Specifically, Petersen *et al.* disclose the following:

> Some HIV medications have shown strong food effects on bioavailability. Some anti-HIV reverse transcriptase inhibitors are recommended to be administered on an empty stomach, including efavirenz, AZT, ddC, and ddI. Other reverse transcriptase inhibitors can be taken without or with food. Inhibitors of HIV protease vary in

> their food effects. Indinavir is recommended for administration without food, but with copious amounts of water. In contrast, saquinavir, another HIV protease inhibitor, is recommended for administration with a high fat meal. Amprenavir and **lopinavir may be taken without or with food**. The differing effect of food on protease inhibitors suggests a lack of a common mechanism underlying the processing and uptake of the protease inhibitors from the gastrointestinal tract.
>
> at Col. 2, para 0011

9.12 Fort *et al.,* do not explicitly disclose that the polymer (water soluble carrier) is a water-soluble polymer having a glass transition temperature of at least 50°C or that the disclosed pharmaceutically acceptable surfactants have HLB value of from 4 to 10.

It would have be obvious for a person skilled in the art to develop solid dispersion composition comprising HIV protease inhibitor such as lopinavir and/ or ritonavir (in undissolved form) having no food effect and with improved dissolution and enhanced oral bioavailability, by combining the teachings of Fort *et al., with* '528 Patent and Petersen *et al.*, with reasonable expectation of success and without undue experimentation.

9.13 Hence, the Opponent submits that claim 1, of alleged invention of the Application is obvious to a person skilled in the art and involves any inventive step.

The Opponent further submits that claims 6 to 9 and 12 to 13 are also obvious and involve no inventive step as the values for AUC, C_{max} and dissolution profile claimed in the instant claims are inherent characteristics/ properties of composition as claimed in claim 1.

10 S. 25(1)(f) Not an invention

10.1 S. 25(1)(f) states:

> (f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

Chapter II of the Act is titled 'Inventions not patentable' and specifically enumerates categories of developments that are, by statute, not considered to be patentable inventions. The relevant section is set forth:

'The following inventions are not inventions within the meaning of this Act, -
....
(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance
or the mere discovery of any new property
or new use of a known substance
or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same'

(e) a substance obtained by mere admixture resulting only in aggregation of the properties of the components thereof or a process for producing such substance;
....
(i) any process for the medicinal, surgical, curative, prophylactic, diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment to animals to render them free of disease or to increase their economic value or that of their products;

10.2 At the outset, claim 14 of the Application is for a method of treating human beings. That said, claim 14 is not patentable under the Act in view of S. 25(1)(i) in conjunction with S. 3(i).

10.3 As noted previously, the present claims are for a combination of known substances - a HIV protease inhibitor drug(s) dispersed in polymer(s) and further comprising surfactant(s). All of these individual constituents are known in the field of pharmaceuticals.

Very interestingly, '339 Application **[Exhibit 6]** discloses similar composition comprising solid dispersion of HIV protease inhibitor(s) (undissolved form) in a water soluble polymer having T_g of at least about 50 °C and a surfactant having an HLB value of about 4 to about 10.

According to the specification the composition according to the invention provides 'enhanced stability/ shelf life' in comparison to Kaletra™ capsules, but failed to provide any data that can support enhanced properties or differentiating characteristics of compositions according to the impugned invention, in comparison to the compositions disclosed in '339 Application as well as tablets comprising combination of lopinavir and ritonavir disclosed in Poster #H-844 **[Exhibit 12;** Published on Sep/ 2003].

10.4 It is the Opponent's contention that a combination of known substances is not patentable per section 3(d) if enhanced efficacy is not shown. It is worthwhile to note that enhanced stability is NOT the same as enhanced efficacy and this position has been upheld by the Patent Office on multiple occasions, for instance the Controller held:

> '...a mere enhancement in stability by way of lesser degradabilty by 1 to 2% only, does not entitle an applicant to a grant of patent. Moreover this amounts to improvement in the quality of the product rather than the therapeutic efficacy.'
>
> [Refer decision 1577/DEL/1996]

Importantly, in a case very similar to the present Application – a new composition claimed in view of a prior art composition, the Controller squarely rejected the argument that greater stability resulting in extended shelf life should be equated as enhanced efficacy [refer decision IN/PCT/2000/00119]. This is the exact situation as the present case, wherein the earlier capsule has the same efficacy as the 'new' dispersion tablet.

> This composition may be considered as "same substances" as defined in section 3(d) of the Patents (Amended) Act, 2005. The claimed invention in complete specification does not describe anything relevant that can show "new composition differ significantly in properties with the known composition". Therefore the claim 1 to 11 are mere use of known substance and attracts the provision of not patentable invention under section 3(d) of the Patents (Amended) Act, 2005.
>
> [Refer decision IN/PCT/2000/00119].

10.5 The earlier Kaletra™ capsule (containing 133.3 mg lopinavir/ 33.3 mg ritonavir i.e. 4:1 proportion in each capsule) dosage was 3 capsules twice daily, providing an aggregate of 800 mg lopinavir and 200 mg ritonavir (over the course of entire day). The present solid solution or solid dispersion composition also known as Kaletra™ heat stable tablet (contains 200 mg lopinavir/ 50 mg ritonavir in each tablet] has exactly the same gross dosage – 2 tablets twice daily for a total daily dose of 800 mg/200 mg. This is what the specification of the impugned application also discloses

> "..... Specifically, the so called dosage form contained 400 mg of lopinavir and 100 mg of ritonovir evenly divided between two dosage forms".
>
> at Page 16, lines 21-23

The present solid dispersion tablet does not result in the patient taking lesser amount of drug, but merely results in lesser number of tablets *viz-a-viz* capsules to be

administered daily. The final amount of drug(s) i.e. total daily dose that a patient ingests in the present dispersion tablet is the same as the earlier capsule [i.e. 800 mg lopinavir and 200 mg ritonavir]. The Applicant has failed to prove enhanced *'in vivo'* efficacy for the formulation. The efficacy of the drug, as per the Madras High Court's interpretation of section 3(d), in the case of pharmaceuticals will mean therapeutic efficacy. Hence the Opponent submits that the composition according to the invention should have been supported with data to demonstrate enhancement of efficacy *in-vivo* as required by the Act.

10.6 The Opponent has noted that the specification of the opposed Application does not contain any data regarding the comparative tests on enhanced efficacy of 'solid solution or solid dispersion formulation of HIV protease inhibitors' versus its earlier known form [capsule] as well as the composition disclosed in '339 Application. Nor does this new solid dosage form in the form of tablet provides better *in-vivo* pharmacokinetic profile w.r.t. to peak plasma concentration (C_{max}) and AUC for lopinavir.

It is very important to note that the approved label for Kaletra™ capsules [**Exhibit 13**; published on 15/Sep/2000], on page 4, states

> "..... multiple dosing with 400/100 mg KALETRA BID for 3 to 4 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/mL, occurring approximately 4 hours after administration ..... Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL.".

While the approved label for Kaletra™ tablets [**Exhibit 7**; published on 28/Oct/2005], on page 7-8, states

> "..... multiple dosing with 400/100 mg KALETRA twice daily with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 µg/mL, occurring approximately 4 hours after administration ..... Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg•h/mL".

Hence it can be seen that Kaletra™ capsules provides C_{max} in between 5.2 to 14 µg/mL, while Kaletra™ tablets provides C_{max} in between 6.1 to 13.5 µg/mL and AUC for Kaletra™ capsules averaged in between 38.3 to 127.3 while AUC for Kaletra™ tablets averaged in between 55.59 to 129.3. The difference in C_{max} and AUC values for Kaletra™ capsules and Kaletra™ tablets is minimal/ insignificant.

The Applicant over the year has published various research articles in the field of antiviral drug development and specifically in relation to lopinavir and ritonavir. One such publication is "New Tablet Formulation of Lopinavir/Ritonavir is Bioequivalent to the Capsule at a Dose of 800/200 mg." Zhu et al., Abbott Laboratories, Poster H-1894 presented in 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC),Washington DC, December 16-19, 2005 **[Exhibit 14]**. This poster clearly states that the new Kaletra™ tablets are bioequivalent to Kaletra™ capsules.

Very interestingly the Applicant has also admitted that the new solid dispersion tablet (Kaletra™ tablets) formulation will provide similar efficacy profile as that of Kaletra™ capsules. See review document published by US FDA for Kaletra™ tablets **[Exhibit 15**; published on 28/Oct/2005], on page 3, states

> **"1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**
> Single dose BE studies indicate that the **to-be-marketed tablet formulation is about 20% more bioavailable than the currently marketed capsules** under non-fasting conditions. However, the results from a cross-study comparison indicate that the steady-state pharmacokinetics of lopinavir and ritonavir after administration of lopinavir/ritonavir 400/100 mg BID as the to-be-marketed tablet formulation were similar to that seen in previous multiple-dose studies in healthy subjects using SGC formulations."
>
> Page 3; para 4

> "The new tablet formulation with slightly higher exposures compared to the capsule formulation **is expected to have an efficacy profile similar to the capsule formulation.**"
>
> Page 3; para 6

The Opponent further submits that the Applicant has claimed a new form (solid form) of a known substance (HIV protease inhibitor(s)). Known substance are the commercially available dosage form Kaletra™ capsules is a soft gel capsule filed with a liquid comprising HIV protease inhibitor(s), and the '339 Application discloses solid composition comprising HIV protease inhibitor(s), whereas the opposed Application claims composition comprising HIV protease inhibitor(s) in undissolved form i.e. solid form.

Section 3(d) takes into account the various obvious physical forms in which a substance can exist and the solid formulation covered by the present Application would come under the ambit of section 3(d). Therefore the Opponent contends that

the present Application does not provide enhanced efficacy for new dispersion formulation over the prior art capsule and the composition disclosed in '339 Application. As well as Applicants own admission that the new tablets efficacy profile will be similar to the capsule formulation [**Exhibit 15: Page 3; para 6**].

Hence all claims of the opposed Application are not patentable in view of S.25(f) read in conjunction with S. 3(d) and merit rejection.

10.7 Additionally, all claims of the present Application are not patentable in view of S.25(f) read in conjunction with S. 3(e). The Opponent submits that Section 3(e) of the Act precludes from patenting a substance which is a mere admixture resulting in only aggregation of the properties of the components thereof, as well as processes for preparing such admixtures.

The present claims cover pharmaceutical dosage formulation comprising a known HIV protease inhibitor(s), as an active ingredient(s) in admixture with known water soluble polymer(s) and surfactant(s), which is nothing but a mere admixture of know substances, resulting in only aggregation of properties. No synergistic effect was shown for the combination of drug dispersed in a polymer with a surfactant. In order to overcome rejection under Section 3(e) the composition claimed must be a synergistic composition having improved and unexpected properties. The Applicant has not given any comparative example, to prove synergy between the use of HIV protease inhibitor(s), water soluble polymer(s) and surfactant(s). It is worth while to note that the Patent Office has decided multiple cases on synergy, for instance refer decisions in IN/PCT/2000/00119 & 63/BOM/1975. The Controller has held:

> '... The composition of the alleged invention does not bear any further synergism over the composition described in WO 95/17207 therefore the arguments of synergistic composition never gets space to justify it as patentable invention.'
>
> [Refer decision IN/PCT/2000/00119]

> "..... As such it is obviously clear, that the antiperspirant composition has got the sum total of the properties of its two components namely the property of the polymer particles to absorb moisture which has not been in any way influenced by the presence of the carrier and the usual property of a 'carrier to act as a 'carrier' or diluent. Therefore the antiperspirant composition as claimed in the applicants' complete specification falls within the scope of clause (e) of Section 3 of the Patents Act, 1970 and thus is not an invention within the meaning of the Act.
>
> [Refer decision 63/BOM/1975]

The Applicant should not only prove synergism but should also show that such synergism is not known or obvious to a person skilled in the art. Section 3(e) of the Patents Act states that a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance cannot be regarded as an invention within the meaning of the Patents Act. Thus, an admixture is *prima facie* treated as known and obvious. It is for the Applicant to prove synergism. The burden of proving synergism [as against additive effect] has not been discharged by the Applicant to merit the grant of a patent.

The Patent Office Manual of Procedure (2008) states at para 4.6.6 that "the existence of a combination invention requires that the relationship between the features or group of features be one of functional reciprocity or that they show a combinative effect **beyond** the sum of their individual effect". The Manual clearly states that the "combinative effect" should be beyond the sum of their "individual effects". The Applicant has failed to prove synergy as the Applicant has not compared the combinative effect with the individual effects.

10.8 To prove synergy, the applicant should have compared the "combinative effect" with the "individual effects" of the following components:

a) HIV protease inhibitor in a solid dispersion;

b) a water soluble polymer having a T_g of at least about 50 °C; and

c) a surfactant.

No synergistic effect was shown for the combination of drug dispersed in a polymer with a surfactant. The Applicant has failed to demonstrate the presence of synergy which is critical for the grant of a patent in the light of the bar under Section 3(e). To prove synergistic effects in a combination, the comparison must be with the individual parts. The Patentee has failed to show synergy between the known components. At best, the components in the combination act "additively" and not "synergistically" (where the presence of one would improve the action of another).

10.9 The Opponent asserts that there is no synergy in the claimed invention and the individual ingredients are acting in an additive, obvious and anticipated manner in the alleged invention. It is therefore the Opponent's submission that the present

composition does not demonstrate synergistic effect over the individual components and hence the product claims of the Application are not patentable in S.25(f) read in conjunction with S. 3(e).

11 S. 25(1)(g) Invention not sufficiently and clearly described:

11.1 The Opponent believes that the present claims are overly broad compared to the technical disclosure in the Specification.

The Applicant is trying to cover any solid pharmaceutical composition comprising HIV protease inhibitor in undissolved from (i.e. solid form). But according to the specification a composition must contain at least one HIV protease inhibitor, at least one water soluble polymer and at least one surfactant. Further the specification provides bioavailability studies comparing commercially available Kaletra™ capsules and a claimed dosage form, but the entire specification fails to point out which composition according to the invention was indeed compared with Kaletra™ Capsules.

The specification fails to provide mean ± standard deviation (SD) lopinavir peak plasma concentration (C_{max}) for composition according to the invention that was compared with Kaletra™ capsules.

The specification at Page 13; ln. 22-27 states:

> "The dosage forms provided herein will have substantially the same C_{max} and AUC∞ values in patients in a fasted state as well as in a fed state, regardless of the dose given. In particular, the mean of the individual patient ratios in a patient population for either the C_{max} or AUC∞ in the fed state to fasted state will be in the range of about 0.7 to about 1.43; more preferably between about 0.75 and about 1.35; and most preferably between about 0.8 and about 1.25."

But in the specification the Applicant very cleverly tried to show superiority of claimed dosage form, w.r.t. Kaletra™ capsules in only fasted conditions, by comparing the ΔAUC_{∞} and ΔC_{max} values calculated based on the results given in Table 3, but it is unclear from the specification what is the significance of this ΔAUC_{∞} and ΔC_{max} values.

Interestingly Table 3, provides the AUC_{∞} and C_{max} values for Kaletra™ capsules and claimed dosage form only under fasted conditions, there are two other tables,

namely Table 4 which provides AUC_{∞} and C_{max} values for Kaletra™ capsules and claimed dosage form under Moderate-Fat Meal conditions, and Table 5 providing AUC_{∞} and C_{max} values for Kaletra™ capsules and claimed dosage form under High-Fat Meal conditions. The entire specification does not provide any ΔAUC_{∞} and ΔC_{max} values, for results given Table 4 and Table 5.

The specification further states at Page 34, Line 16;

"The dosage form of the present invention demonstrate no food effect"

It provides ratio "X" which is the ratio of AUC_{∞} (fed)/ AUC_{∞} (fasted) "Y" which is the ratio of C_{max} (fed)/ C_{max} (fasted) for lopinavir and concludes that when the values are in the range of 0.7 to about 1.43 as depicted in Table 6, the dosage form has no food effect and will have substantially the same bioavailability whether it is administered on full or empty stomach.

The entire specification fails to provide similar "X" and "Y" ratio for ritonavir or any other HIV protease inhibitor, but claims the said ratio generally for any HIV protease inhibitor in claim 6. It is also important to note that when the values for AUC_{∞} (fed) and C_{max} (fed) are not given either for moderate meal or high fatty diet in the entire specification. The derivative value "X" or "Y" calculated form said AUC_{∞} (fed) and C_{max} (fed) then is totally out of specification and the same is not enablement.

The entire specification fails to provide similar "X" and "Y" ratio for Kaletra™ capsule, as well as a comparison between "X" and "Y" ratio of Kaletra™ capsule and composition disclosed in example 2 of '339 Application vs. "X" and "Y" ratio of claimed dosage form.

11.2 Additionally claim 12 and claim 13 covers pharmaceutically composition comprising lopinavir or ritonavir individually, without any limitation on the dosage form and excipients/ materials that ensures the claimed release profile. The only limitation recites into the claim is dissolution profile which in itself so broad that any solid pharmaceutical composition will possess the release profile recited in claim 12 and claim 13.

12 S. 25(1)(h) Non intimation of information under S. 8 to the Controller:

12.1 The Opponent also opposes all claims of the present Application under S.25(1)(h) pertaining to non-disclosure of information required under S. 8 of the Act. The section states:

> (h) that the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;

12.2 The Applicant is under a statutory duty to inform the Controller on the counterpart national phase filing details, critical objections and/ or rejections and claims allowed for these counterpart national phase filings till the Indian Application matures into an Indian Patent. The Application has a number of national phase filings, which the Applicant has intimated to the controller on 01/July/2010. For instance:

- AU2006216856;
- BRPI0609173;
- CA2598827;
- CN101163479;
- EP1855683;
- EP2206500;
- JP2008531565;
- KR20070114294;
- NO20074807;
- US20070249643;
- US20080299203;
- US2013004578 and
- WO2006091529

12.3 USPTO has rejected the entire set of claims of US 2007/0249643; which is a continuation application of US 2005/0084529. See the USPTO rejection dated 01/May/2008, the Examiner held that the set of claims as filed on 03/July/2007 as being unpatentable in view of Rosenberg et at (US 6,599,528) and Everitt et al (U.S. 2002/0198160) and further in view of Shaner and U.S. Patent 6,579,521. The

Applicant, without traversing the objection, did not replied to office rejection dated 01/May/2008, and the application was deemed abandoned by US PTO on 12/11/2008.

USPTO has also rejected the US 2008/0299203 application; which is a continuation application of US 2005/0143404. The entire set of claims was rejected on multiple occasions. See the USPTO rejections dated 12/Oct/2011, 17/Mar/2010 and 13/May/2009.

In its latest Office Action [12/Oct/2011], the Examiner held that the pending claims as being unpatentable in view of Everitt et al (U.S. 2002/0198160) and Rosenberg et at (US 6,599,528). The Applicant has never responded to the last Office rejection dated 12/Oct/2011 and therefore the US 2008/0299203 application was deemed abandoned on 24/Apr/2012.

12.4 Apart from US, in the above European filing [EP '683], the European Patent Office [EPO] rejection dated 04/Nov/2008, was based on lack of Novelty in view of WO 2005/039551. The Applicant tried to assert patentability to the EPO, including amending claims, and finally in oral proceedings in order to overcome Novelty rejection, restricted its claims to only cover "composition for use in the treatment at a HIV patient [only in fasted state] comprising HIV protease inhibitor, least one water soluble polymer and at least one surfactant." and even these restricted claims were once again rejected on 02/Dec/2009 **[Exhibit 16]**, as being not novel in view of WO 2005/039551.

The Applicant, did not replied to the above rejection and the application was finally deemed withdrawn by EPO on 26/05/2010 **[Exhibit 17]** and the file was closed on 06/09/2010 **[Exhibit 18]**.

The Applicant has filed a divisional of EP '683 application i.e. EP2206500 [EP '500], this further divisional application was rejected by EPO on 02/Dec/2011 **[Exhibit 19]**., based on lack of Novelty in view of WO 2005/039551 and lack of inventiveness in view of WO 2004/032903.

12.5 The Opponent further believes that the Applicant has not informed in writing, from time to time the details of earlier unfavourable International Search Report

[08/Feb/2007] and the International Preliminary Report on patentability [28/Aug/2007] as well as the various search reports and/ or examination report and rejections issued by USPTO and EPO to the Controller as required under section 8(1) of the Patents Act.

12.6 The Opponent believes that

a) Multiple rejections by EPO to the EP counterpart;

b) Multiple rejections by USPTO and Abandonment of several US application;

c) Negative Search and Patentability reports from the WO phase were

not submitted by the Applicant to the Patent Office. This failure to submit critical required information is, by itself, an independent ground for rejecting the present Application in its entirety, and such action is respectfully requested by the Opponent. It is worthwhile to note that the Patent Office decisions in **1119/MUMNP/2003**. The Controller has held:

> '..... Even though substantial updated information on the corresponding application filed in foreign countries were expected to be available like the information in JP and USA, the same was not informed to the Indian Patent Office. I view this irregularity by patentee as violation of provision as required under Section 8 of Patents Act. **I conclude that such a ground of opposition is validly established by the opponent'.**
>
> [Refer decision 1119/MUMNP/2003]

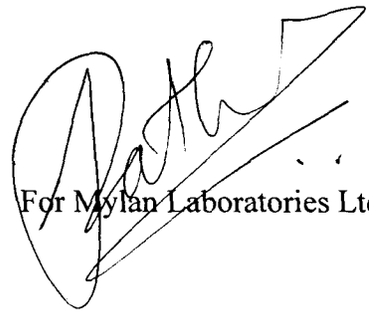
13 ***PRAYERS:***

The Opponents' arguments are based on the specification and claims, as uploaded on IPAIR. The Opponent now prays for the following:

- That the Controller take the present Opposition on record;
- Reject the claims of the present application, *in toto*;
- Leave to file further evidence and additional grounds, if necessary;
- Revert with arguments, additional evidence and additional grounds, should the Applicant choose to amend the claims;
- Grant of hearing to the Opponent;
- Allow the Opponent to inspect all the statements made by Applicant under S.8; and
- Grant such additional relief as the Controller may deem fit.

Dated: this 10th day of June, 2013

Opponent



For Mylan Laboratories Ltd

To:
The Controller of Patents
The Patent Office, Delhi

Exhibit 1

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
PATENT OFFICE
INTELLECTUAL PROPERTY BUILDING
Plot No. 32, Sector-14,Dwarka
New Delhi - 110 078

Tel No. (091)(011) 28034304-06,22
Fax No. 011 28034301,28034302
E-mail : delhi-patent@nic.in
Web Site : www.ipindia.nic.in

Date : 20/03/2013

Letter No.:-CHEM/2013/

To,
ANAND & ANAND,
ADVOCATES,
B-41, NIZAMUDDIN EAST NEW DELHI-110013,INDIA

SUB : **Examination Report**

APPLICATION NUMBER	:	6733/DELNP/2007
DATE OF FILING	:	30/08/2007
DATE OF REQUEST FOR EXAMINATION	:	20/02/2009
DATE OF PUBLICATION	:	21/09/2007

With reference to the RQ No. 1472/RQ-DEL/2009 Dated 20/02/2009 in the above mentioned

a) application for Grant of Patent , Examination has been conducted under Section 12 and 13 of the Patents Act 1970 , The following objections are hereby communicated

b) Objections :

1 Claims 6 to 13 are not clear since the matter for which protection is sought is not clearly defined. It attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. Claim 1 is also not clear as the inclusion of dosage form in the preamble without further elaboration thereof induces a lack of clarity, as the pharmaceutical dosage form generally implies multiple constituents.

Claims 1-13 fall u/s 3(d) of the Patents (Amended) Act, 2005 as the claims define new form/new use of known substance(as cited by the prior art documents as described in para 1 of the report).

Applicant has not showed any surprising effect or significant efficacy to prove better efficacy or
2 comparison data over the prior art. Claim 14 is directed to a method of treatment hence is not allowable under section 3(i) of Indian Patents Act. Claims 1-13 fall u/s 3(e) of the Patents (Amended) Act, 2005 as the said claims defines a mere admixture resulting only in the aggregation of the properties of the components thereof. It is not clear if the combined agents act together to provide a technical effect that is greater than just the sum of the two or more agents alone, or whether the combination is in fact a mere juxtaposition with no interaction of the agents.

Subject matter of claims 1-14 lacks novelty and inventive step in view of documents;
D1-WO01/34119
D2-US2001/051721
D3-US20030104063
D4-US4801460
D5-US5073379
D6-US5456923
D7-US5741519
D8-US6143328
D9-WO2004032903

Document D1 discloses pharmaceutical compositions comprising a solid dispersion of lopinavir and ritonavir in combination. The two compounds are in the formulation in an amorphous form (due to the presence a crystallization inhibitor, such as PVP). Furthermore, said compositions are administered to mammals for the treatment of an HIV infection. In view of the disclosure in D1, the present claims are not considered novel. Document D2 discloses that lopinavir is administered in combination with ritonavir in a ratio of 4:1. D2 further discloses that if more than about 75% of the maximum allowable solvent is removed, amorphous lipinavir is obtained (page 7, lines 1 -3). Document D3 discloses a pharmaceutical composition which comprises of a dispersion of a low solubility drug in combination with a concentration enhancer polymer. This document also teaches that the composition may
3 comprise the drug in amorphous or crystalline form and the dispersions of the drug and the matrix may be made by known processes. The polymers as disclosed in D3 are the same as the instant application. Document D4 teaches a process for preparation of solid pharmaceuticals form. D4 teaches that the use of a N-vinyl pyrrolidone polymer is advantageous in obtaining the desired release profiles and clearly states that the object of achieving control release of an active compound may be easily achieved when the glass transition temperature(Tg) is greater than 120degreeC and that preferably the Tg is between 60 degree to 130 degree C. Document D5 teaches the pharmaceutical mixture comprises an active compound alongwith excipients with copolymers of NVP and such that the mixture has a Tg of 60 to 130 degree C. Document D6 discloses a method of manufacturing a solid dispersion and solid dispersions are meant for enhancing the solubility of drugs and for controlling the rate of release from the dosage form. Document D7 teaches a process of producing compositions of active substances in a polymer matrix. This document clearly states that molecular dispersion of an active substance in water soluble polymer may be used effectively to maintain the dissolution and absorption. Document D8 discloses solid dispersion of a pharmaceutical product. Though the active ingredient is different from that of instant application, the principle herein is the same. D8 also teaches that the use of a surface active agent can help in adjusting the release rate. Document D9 discloses(example 1, col.6) a formulation as disclosed in specification. The above said documents teach the same as claimed in the instant application and therefore considered prejudicial to the novelty and inventive step of the subject-matter of the said claims. In light of the above claims do

not constitute an invention u/s 2(1)j of Indian Patent Act as amended.

4 The due Power of Authority with prescribed stamp duty and the particulars of the case should be filed.

5 Form-3 filed on dated 01/07/2010 can not be taken on record as the same not filed within prescribed time limit u/r 12 of Indian Patent Rules.

6 Pages of complete specification should be renumbered.

7 The claim part of the Completed Specification should commence with phrase; "We claim".

8 Drawing should be filed as per rule 15 of the Indian Patent Rules.

9 Details regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, 2003, in respect of same or substantially the same invention filed in all the major Patent offices along with appropriate translation where applicable, should be submitted within a period of Six months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.

10 Details regarding application for Patents which may be filed outside India from time to time for the same or substantially the same invention should be furnished within Six months from the date of filing of the said application under clause(b) of sub section(1) of secton 8 and rule 12(1) of Indian Patent Act.

c) You are requested to comply with the objections by filing your reply by way of explanation and/or amendments within 12 months from the date of issue of FER failing which you application will be treated as "Deemed to have been abandoned" under section 21(1) of the Act. The last Date is 20/03/2014.

d) You are advised to file your reply at the earliest so that the office can further proceed with application and complete the process within the prescribed period.

(Hardev Karar)

Asst. Controller of Patents & Designs

NOTE : All Communications to be sent to the Controller of Patents at INTELLECTUAL PROPERTY BUILDING Plot No. 32, Sector-14,Dwarka New Delhi - 110 078.

Back Close

Exhibit 2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34119 A2

(51) International Patent Classification[7]: A61K 9/14

(21) International Application Number: PCT/US00/31072

(22) International Filing Date:
10 November 2000 (10.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/438,994 12 November 1999 (12.11.1999) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: KRILL, Steven, K.; 5133 Pembrook Court, Gurnee, IL 60031 (US). FORT, James, J.; 2700 Leafield Terrace, Midlothian, VA 23113 (US). LAW, Devalina; 835C Country Club Drive, Libertyville, IL 60048 (US). SCHMITT, Eric, A.; 310 Evergreen Court, Libertyville, IL 60048 (US). QIU, Yihong; 6118 Honeysuckle Lane, Gurnee, IL 60031 (US).

(74) Agents: SICKERT, Dugal, S. et al.; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

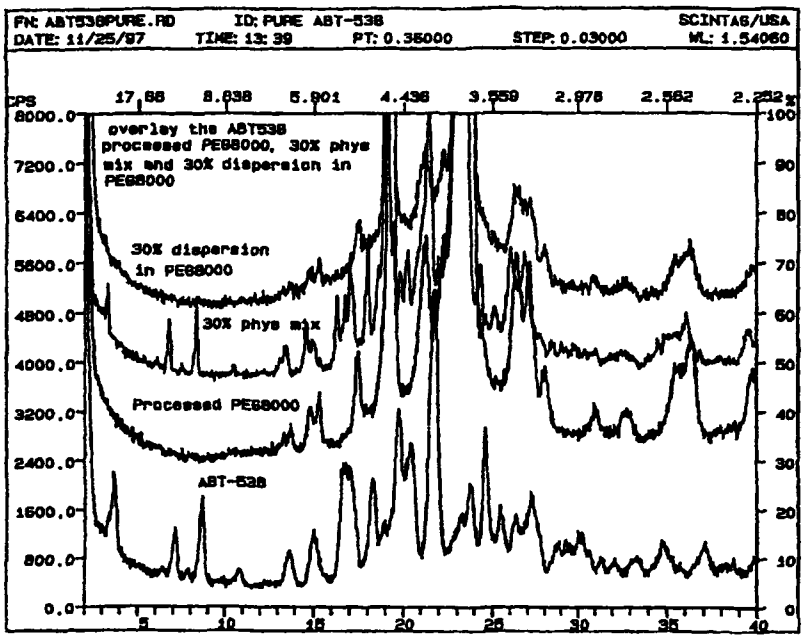
(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION



(57) Abstract: A pharmaceutical composition is disclosed which comprises a solid dispersion of a pharmaceutical compound in a water soluble carrier, such as polyethylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone or hydroxypropylmethylcellulose. The solid dispersion may optionally be encapsulated in hard gelatin capsules, compressed into a tablet, or may be granulated wiht a pharmaceutically acceptable granulating agent. Also disclosed are methods of making said solid dispersion and methods of treatment employing said solid dispersion.

WO 01/34119 A2

INHIBITORS OF CRYSTALLIZATION IN A SOLID DISPERSION

Technical Field of the Invention

The instant invention relates to the fields of pharmaceutical and organic chemistry, and provides novel solid dispersion pharmaceutical formulations which demonstrate an inhibition of crystallization.

Background of the Invention

One measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength, and first pass effect. Aqueous solubility is one of the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally

identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable solid dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

An alternative dosage form is a solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Sciences*, *60*, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by

mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions.

Retroviral protease inhibiting compounds are useful for inhibiting HIV proteases *in vitro* and *in vivo*, and are useful for inhibiting HIV (human immunodeficiency virus) infections and for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability. Examples of HIV protease inhibiting compounds include

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl]-amino-1,6-diphenylhexane (ABT-378);

N-(2(R)-hydroxy-1 (S)-indanyl)-2(R)-phenylmethyl -4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcar boxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS) -isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*])-N^1 [3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

VX-478; DMP-323; DMP-450; AG1343(nelfinavir);

BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or combinations thereof.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug.

Polyethylene glycol (PEG) solid dispersion formulations are generally known to improve the dissolution and bioavailability of many compounds. However, Aungst *et al.* has recently demonstrated that this was unable to improve the bioavailability of an HIV protease inhibitor with a cyclic urea structural backbone, called DMP 323

(Aungst *et al.*, *International Journal of Pharmaceutics*, *156*, 79 (1997)).

In addition, some drugs tend to form crystals when placed in solution, which can be problematic during formulation.

Polyvinylpyrrolidone (PVP) is known to inhibit crystallization of drugs (Yohioka, M. et al., J. Pharm. Sci., 84, 983, 1995). However, prior to the instant invention, the incorporation of PVP into a second polymer matrix, such as polyethylene glycol, has never been established.

U.S. 4,610,875 teaches a process for the preparation of a stable pharmaceutical dipyridamole composition containing PVP.

U.S. 4,769,236 teaches a process for the preparation of a stable pharmaceutical composition with a high dissolution rate in the gastrointestinal tract containing PVP, wherein the pharmaceutical agent is hydroflumethiazide, dipyridamole, hydrochlorothiazide, cyclothiazide, cyclopenthiazide, polythiazide, methyldopa, spironolactone, quinidine, cyanidol, metronidazole, ibuprofen, naproxen, erythromycin, glaphenin, furosemide, suloctidil, nitrofurantoin, indomethacin, flavoxate,

phenobarbitol, cyclandelate, ketoprofen, natridrofuryl, or triamterene.

Thus, it would be a significant contribution to the art to provide a stable solid dispersion pharmaceutical formulation which demonstrates a lack of crystallization.

Summary of the Invention

The instant invention provides a stable solid dispersion pharmaceutical formulation comprising a pharmaceutical compound, a water soluble carrier, such as polyehtylene glycol (PEG), and a crystallization inhibitor, such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

Also provided by the instant invention is a pharmaceutical composition comprising a stable solid dispersion as described above with additional pharmaceutically acceptable carriers, diluents, or excipients.

Additionally provided by the instant invention is a method for preparing a stable solid dispersion as described above.

The instant invention still further provides methods of treatment comprising administering an effective amount of a stable solid dispersion as described above to a mammal in need of such treatment.

Brief Description of the Figures

Figure 1 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated within PEG alone.

Figure 2 illustrates the PXD patterns showing that Amorphous ABT-538 can be isolated with a PVP/PEG matrix.

Figure 3 illustrates the DSC thermograms of PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 4 illustrates the DSC thermograms of PVP/PEG, ABT-538, a physical mixture of the two and a solid dispersion. The absence of ABT-538 melting in the dispersion confirms the above PXD data showing amorphous ABT-538 present in the dispersion.

Figure 5 illustrates the effect of PEG or PVP on the crystallization rate of amorphous ritonavir. The heat of fusion was used to calculate percent crystallized. In the presence of PVP the crystallization rate is slower.

Figure 6 illustrates the inhibition of crystallization using PVP.

Figure 7 illustrates PXD patterns of ABT-538 dispersions with and without PVP stored at 50°C. The data

demonstrate the improved physical stability of amorphous ABT-538 on storage.

Figure 8 illustrates PXD patterns of fenofibrate dispersions with and without PVP.

Figure 9 illustrates PXD patterns of fenofibrate dispersions with and without PVP and PEG.

Figure 10 illustrates PXD patterns of fenofibrate dispersions with and without PEG.

Figure 11 illustrates PXD patterns of fenofibrate dispersions with and without 10% PVP and PEG.

Figure 12 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 13 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Figure 14 illustrates PXD patterns of griseofulvin dispersions with and without PEG.

Figure 15 illustrates PXD patterns of griseofulvin dispersions with and without PEG and PVP.

Detailed Description of the Invention

This invention pertains to the preparation of solid dispersion systems for pharmaceuticals which demonstrate a lack of crystallization.

The invention involves dispersion in a hydrophilic matrix of pharmaceuticals which exhibit poor aqueous solubility. The intent of such a formulation is to improve the aqueous dissolution properties and ultimately achieve improved bioavailability. Typically, the intent of such systems is to generate a dispersion of amorphous (high energy) drug within the matrix. The presence of the high energy drug form usually improves the dissolution rate. However, these systems are not often physically stable. The drug can crystallize over time, causing the loss of the desired properties and reduced shelf-life. The current invention enhances the physical stability of such formulations, thereby making this type of formulation more feasible.

In the instant invention, PEG 8000 is used as the hydrophilic matrix. Also employed in this formulation is polyvinylpyrrolidone (PVP), which is an example of a hydrophilic, amorphous polymer, and is used to inhibit crystallization. Other hydrophilic, amorphous polymers

include hydroxypropylmethylcellulose (HPMC), or other pharmaceutically acceptable hydrophilic, amorphous polymers. Specifically, PVP PF 17 is used within the PEG matrix to inhibit the crystallization of the drug of interest. A range of 1%-95% (w/w) of PVP can be employed, with a range of 1%-15% (w/w) being preferred.

The benefits of incorporating PVP into the PEG matrix are two fold. Firstly, processing PVP can be difficult due to its hygroscopicity. Secondly, when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug. Another benefit of adding PVP is an increase in amorphous volume of the polymer matrix where drugs may reside. Since polyethylene glycols tend to be highly crystalline, this increase in amorphous volume could be important for fast dissolution. PVP has the added advantage of having a high Tg, which imparts stabilization of amorphous regions by reducing mobility. Therefore, this invention affords the benefits of the PEG properties in a dispersion along with those of PVP.

A solid (molecular) dispersion comprising an HIV protease inhibiting compound may be prepared by dissolving or dispersing the HIV protease inhibiting compound in a sufficient amount of an organic solvent followed by

dispersion into a suitable water soluble carrier. Suitable organic solvents include pharmaceutically acceptable solvents such as methanol, ethanol, or other organic solvents in which the protease inhibitor is soluble. Suitable water soluble carriers include polymers such as polyethylene glycol (PEG), pluronics, pentaeythritol, pentaeythritol tetraacetate, polyoxyethylene stearates, poly-ε-caprolactone, and the like.

The organic solvent (preferably ethanol) may then be evaporated away, leaving the drug dispersed/dissolved in the molten matrix, which is then cooled. The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus improving the bioavailability of a drug exhibiting dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the HIV protease inhibiting compound.

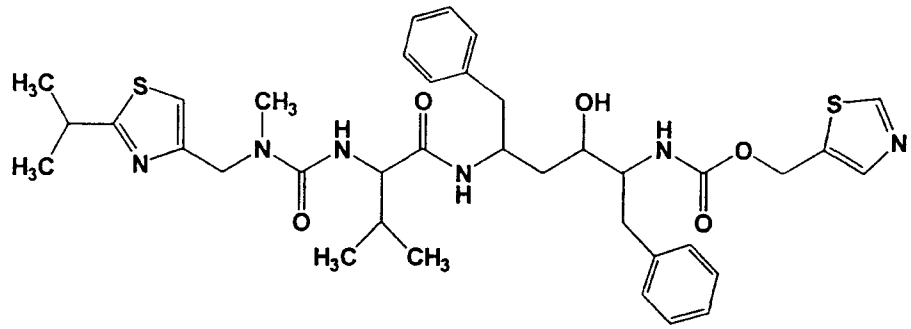
Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, and the like, that might be needed to prepare a capsule or tablet.

The resulting composition comprising the pharmaceutical compound may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into capsules, or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The composition can be used to improve the oral bioavailability and solubility of said HIV protease inhibiting compound.

Total daily dosing of the pharmaceutical compound may be administered to a human in single or divided doses in amounts, for example, from 0.001 to 1000 mg/kg body weight daily, but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of

submultiples thereof to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

One type of pharmaceutical compound that may be employed in the practice of the present invention is an HIV protease inhibitor. An example of an HIV protease inhibitor is ABT-538 (ritonavir), the chemical structure of which is represented hereinbelow as a compound of formula I

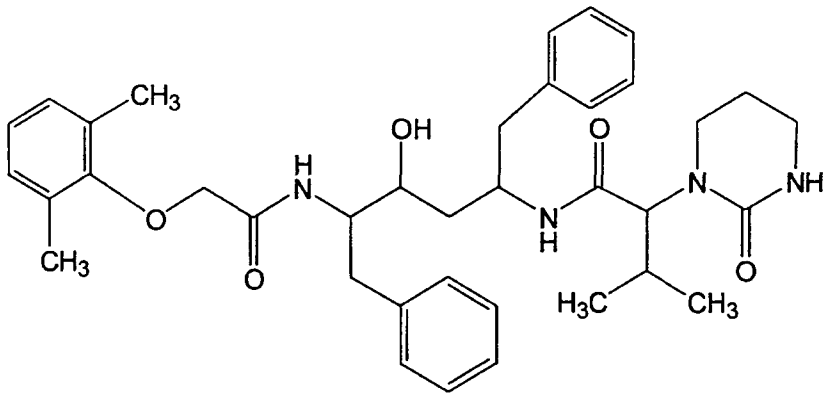


I

A compound of formula I is an HIV protease inhibitor marketed by Abbott Laboratories under the tradename Norvir®, with the common name ritonavir [(2S,3S,5S)-5-(N-(N-((N-

methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane]. This and other compounds as well as methods for preparing same are disclosed in U.S. Patent Nos. 5,648,497 and 5,541,206, the disclosures of which are herein incorporated by reference.

Additional HIV protease inhibitors which may be formulated into a solid dispersion of the instant invention include compounds of formula II



II

A compound of formula II is known as ABT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane). This and other compounds, as well as methods for preparing same, are identified in U.S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference.

Other types of pharmaceutical compounds which may be employed in the practice of the present invention include but are not limited to antibacterial agents, antifungal agents such as griseofulvin, chemotherapeutic agents, agents for treating hyperlipidemia such as fenoifibrate, and the like.

The following Examples are provided to further illustrate the present invention.

EXAMPLES

Equipment:

DSC

DSC measurements were made using a Mettler DSC 30 unit. Samples (4-7mg) were sealed in standard 40 μl aluminum crucibles with a single hole punched in the lids. An empty crucible of the same type was used as a reference.

X-ray Powder Diffraction Analysis

An X-ray powder diffraction (XPD) pattern was obtained with a Scintag® XDS 2000 θ/θ diffraction system equipped with a 2 kW normal focus X-ray tube and a liquid nitrogen cooled germanium solid state detector.

Isothermal Calorimetry (TAM)

The recrystallization reactions of 30% ABT-538 in PEG or PEG:PVP (95:5) solid dispersions were monitored via isothermal calorimetry (Thermometric 2277 Calorimeter) at 40 °C. Since crystallization is an exothermic process, a positive power output indicates

crystallization. The magnitude of the power output at any time is proportional to the rate of crystallization. XPD was used to confirm crystallization.

HPLC

The potency values of all the dispersions as well as the dissolution sample concentrations were determined via HPLC.

The effect of PVP on the crystallization rate of the drug in each dispersion system (drug with polymer) was investigated with the appropriate experimental technique. The results of these studies are provided in Figures 1-15.

Three pharmaceuticals of different properties were employed to demonstrate the general applicability of the instant invention. These compounds are identified in Table 1 below:

Table 1

Model Compounds

Property/Compound	ABT-538	Fenofibrate	Griseofulvin
MW (g/mole)	720.96	360.84	352.77
T_m (°C)	124	79	218.13
T_g (°C)	45.8	-21.7	91

Example 1

Dispersion Preparations

A. Ritonavir (ABT-538) Dispersion Preparation:

The samples were prepared by dissolving ABT-538 in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 75 °C. The PEG 8000 was added to the hot alcohol solution with continual swirling until the PEG melted. The flask was then attached to a rotary evaporator, immersed in the water bath (75 °C) under vacuum for 15 minutes to remove the ethanol. After the majority of ethanol had evaporated, the flask was immersed in an ice

bath for 15 minutes. The contents of the flask were then vacuum dried at room temperature overnight to remove residual alcohol. The dispersion was removed from the flask, gently ground, and sized to 40-100 mesh size. The drug loads used for these dispersions were 10, 20 and 30% w/w.

B. ABT-378 Dispersion Preparation:

The solid dispersion of 30% ABT-538 in 95:5 PEG8000:PVP was prepared by dissolving the ABT-538 and PVP 17 PF in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The remainder of the process was as described above. A 30% ABT-538 dispersion in 85:15 PEG8000:PVP was also prepared similarly as were dispersions of 10 or 20% PVP 17PF in PEG 8000 without drug.

C. Fenofibrate Dispersion Preparation:

15% Fenofibrate in PEG 8000:

Both fenofibrate and PEG 8000 were sized to 40-100 mesh prior to mixing with a spatula on weighing paper. The mixture was then added to a 25 ml beaker and heated to 85°C in a water bath until the all the material had

melted. The molten solution was then poured onto a chilled X-ray sample holder to rapidly solidify the solution. The solid sample was immediately used to monitor the crystallization rate via X-ray powder diffraction.

15% Fenofibrate in 90:10 PEG 8000:PVP:

Fenofibrate (40-100 mesh) was added to the 90:10 PEG 8000:PVP control dispersion (see above) which was also sized to 40-100 mesh and mixed with spatula on a piece of weighing paper. The mixture was then processed as described above for the 15% fenofibrate dispersion in PEG 8000.

D. Griseofulvin Dispersion Preparation:

15% griseofulvin in PEG 8000:

Both griseofulvin and PEG 8000 were sized to 40-100 mesh prior to mixing on a weighing paper with a spatula. The sample was then added to an 4 ml stainless steel vessel which was sealed under a N_2 atmosphere. The vessel was then immersed into an oil bath maintained at 180°C. The sample was occasionally shaken to mix the molten contents. After 5 minutes the vessel was immersed into a

liquid N_2 bath for 30 minutes. The contents of the vessel were removed, gently ground and sized to 40-100 mesh.

15% griseofulvin in 80:20 PEG 8000:PVP:

This dispersion was prepared in a similar manner as describe above for the 15% griseofulvin in PEG 8000 dispersion using the 80:20 PEG8000:PVP control dispersion.

E. Results:

ABT-538:

Figure 1 shows the X-ray powder diffraction (XPD) pattern of ABT-538, processed PEG 8000, a physical mixture of the two components and the 30% solid dispersion. A similar plot is shown in Figure 2 with PVP incorporated into the matrix. It is apparent from these figures that ABT-538 is not crystalline within either matrix. Figure 3 shows the DSC thermograms of ABT-538, PEG8000, the 30% physical mixture and the dispersion. A similar plot is seen in Figure 4 for the PEG:PVP dispersion. The endotherm associated with drug melting can clearly be discerned from the other components. Thus, it is possible to follow the kinetics of ABT-538

crystallization via DSC measurements. Crystallization kinetics were determined by heating the samples to 85°C, holding them isothermally for predetermined times followed by heating through the melting transition temperature of ABT-538. The heats of fusion were determined and ratioed against the heat of fusion of the drug melting in the physical mixture, giving the fraction crystallized. The percent crystallized as a function of isothermal (85°C) hold time is shown in Figure 5. It is clear from this experiment that the presence of PVP within the matrix suppresses the crystallization rate of ABT-538.

The crystallization rate was also followed via the heat associated with crystallization of ABT-538 using a isothermal calorimetry. The shapes and magnitudes of the crystallization peaks in Figure 6 indicate that ABT-538 crystallizes more readily in the PEG matrix as compared to the PEG:PVP matrix. This stabilizing effect of PVP is also reflected in the times required for complete crystallization (time to reach baseline) which were <10 hours for PEG and >30 hours for PEG:PVP (95:5). These data support the previous DSC results.

An additional study was performed with a dispersion containing 15% PVP. The samples were held at 50°C (above

the T_g of ABT-538) and X-ray diffraction patterns were measured over time to monitor for the appearance of crystalline ABT-538. Figure 7 shows that in the presence of PVP, crystalline ABT-538 is not present after 272 hours, while in PEG8000 alone crystalline drug is detected at 233 hours (and before, data not shown).

Fenofibrate:

Figure 8 shows the XPD patterns of PEG 8000, fenofibrate, a 15% physical mixture and the 15% fenofibrate solid dispersion. The figure illustrates that the fenofibrate is X-ray-amorphous within the matrix. A similar plot with the XPD patterns for the 15% fenofibrate dispersion in a 90:10 PEG 8000:PVP matrix is presented in Figure 9. Again, the fenofibrate is amorphous. Upon storage at 25°C, the fenofibrate begins to crystallize in the PEG 8000 matrix within 1 hour (Figure 10). Additional crystallization follows upto 12 hours, when the experiment was terminated. In the presence of PVP (Figure 11), the fenofibrate does not crystallize in the timeframe of the experiment. This clearly demonstrates the inhibitory effects of PVP on crystallization within the PEG 8000 matrix.

Griseofulvin:

Similar XPD patterns for the griseofulvin dispersion in PEG 8000 and 80:20 PEG 8000:PVP matrices are shown in Figures 12 and 13, respectively. In both instances, amorphous griseofulvin is isolated within the respective matrices. The XPD rate of crystallization experiments show that after one hour at 25°C, griseofulvin begins to crystallize (Figure 14). However, in the presence of PVP (Figure 15), crystallization is not observed even after 15 hours under the same conditions. This again demonstrates the inhibitory effects of PVP amorphous drug crystallization within a PEG matrix.

E. Conclusions:

The data presented demonstrate that PVP incorporated within a hydrophilic matrix, such as PEG 8000, inhibits crystallization of drug molecules having varying physicochemical properties. Thus, the instant invention has a broad application to development of viable solid dispersion formulations where the high energy amorphous (non-crystalline) form of a drug is desired.

Example 2

Stability of Dispersion in Molten PEG 8000

The stability of the dispersion of ABT-538 in PEG 8000 in the molten state at 70 °C was examined. Individual approximately 5 mg quantities of the dispersion (aged for 6 weeks at room temperature) were placed in 4 ml glass vials. These vials, with the exception of the initial time point, were placed in a 70 °C oven which was sampled at pre-determined intervals, chilled in ice water and placed in the freezer until HPLC analysis. After all samples were collected, they were analyzed for ABT-538 content by HPLC. The HPLC system consisted of a Hitachi AS 4000 autosampler, SP 8800 ternary pump, Applied Biosystems 783 detector, and PE Nelson Data acquisition system. Other chromatographic details included a Regis Little Champ 5 cm C-18 column, a mobile phase consisting of an aqueous solution of 0.1% trifluoroacetic acid in 10 mM aqueous tetramethyl ammonium perchlorate (TMAP)/acetonitrile/methanol (55/40/5). The flow rate was 1 ml/minute, the wavelength of detection was 205 nm, and the injection volume was 100 µl. Standard curves of peak area of ABT-538 vs.

concentration in the range of interest were compared with experimentally obtained area counts.

Example 3

Protocol For Oral Bioavailability Studies

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) are fasted overnight prior to dosing, but are permitted water *ad libitum*. Each dog receives a 100 μg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog receives a single solid dosage form corresponding to a 5 mg/kg dose of the drug. The dose is followed by approximately 10 milliliters of water. Blood samples are obtained from each animal prior to dosing and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug administration. The plasma is separated from the red cells by centrifugation and frozen (- 30 °C) until analysis. The concentrations of parent drug is determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve is calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition is calculated by comparing the area under the curve after oral dosing to

that obtained from a single intravenous dose. Each capsule or capsule composition is evaluated in a group containing at least six dogs. The values reported are averages for each group of dogs.

5

WE CLAIM:

1. A pharmaceutical composition comprising a solid dispersion of a pharmaceutical compound, a water soluble carrier, and a crystallization inhibitor selected from the group consisting of polyvinylpyrrolidone (PVP) and hydroxypropylcellulose (HPMC).

2. The composition of Claim 1 wherein said water soluble carrier is polyethylene glycol (PEG).

3. The composition of Claim 1 wherein said pharmaceutical compound is an HIV protease inhibitor dissolved in an organic solvent.

4. The composition of Claim 3 wherein said organic solvent is ethanol.

5. The composition of Claim 3 wherein said HIV protease inhibitor is 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

6. The composition of Claim 3 wherein said HIV protease inhibitor is (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane (ABT-378).

7. The composition of Claim 3 wherein said HIV protease inhibitor is a combination of 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

8. The composition of Claim 2 wherein said solid dispersion is encapsulated in a hard gelatin capsule.

9. The composition of Claim 2 wherein said solid dispersion is compressed into a tablet.

10. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected

from the group consisting of pharmaceutically acceptable surfactants and antioxidants.

11. The composition of Claim 1 wherein said pharmaceutical compound is fenofibrate.

12. The composition of Claim 1 wherein said pharmaceutical compound is griseofulvin.

13. A method of preparing a composition of Claim 1 which comprises:

a) dissolving a pharmaceutical compound inhibitor into an organic solvent to form a solution;

b) adding a water soluble carrier to said solution to form a mixture;

c) adding PVP to said mixture of step b);

d) optionally flash evaporating said solvent;

e) optionally drying the resulting residue remaining after evaporation;

f) optionally grinding and sieving the solid dispersion to obtain a resultant product.

14. The method of Claim 13 additionally comprising encapsulating the solid dispersion in a hard gelatin capsule.

15. The method of Claim 13 additionally comprising compressing said solid dispersion into a tablet.

16. The method of Claim 13 wherein said pharmaceutical compound is an HIV protease inhibitor.

17. The method of Claim 16 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

18. The method of Claim 13 wherein said solvent is ethanol.

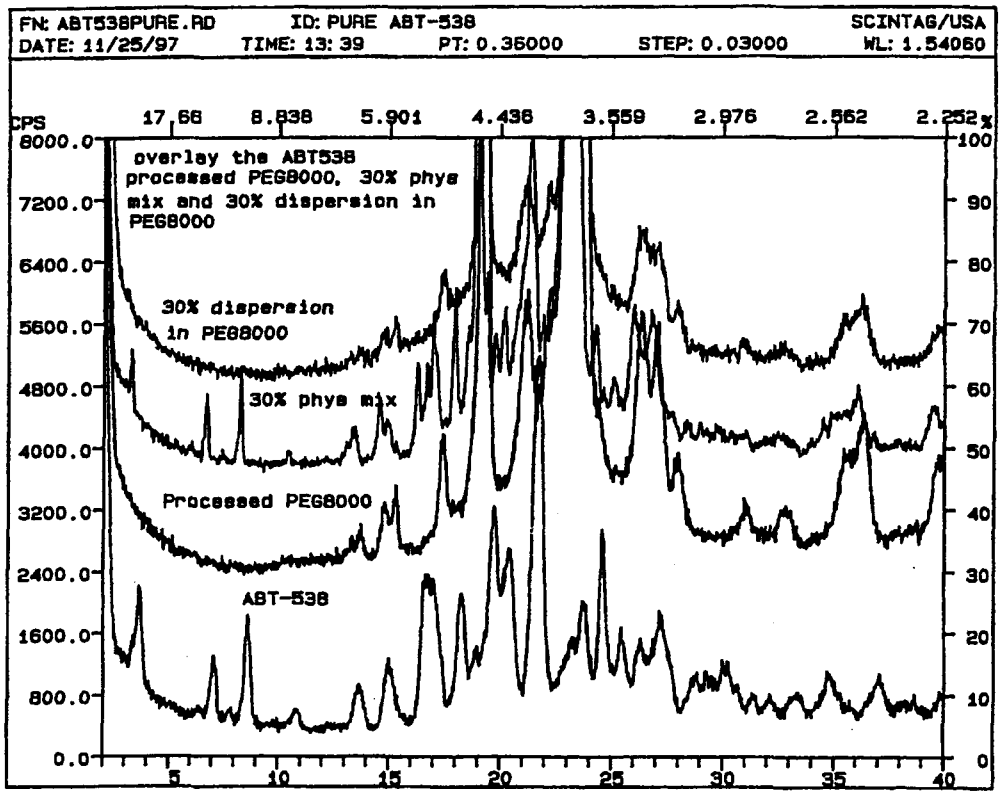
19. The method of Claim 13 wherein said water soluble carrier is polyethylene glycol (PEG).

20. A method of treating an HIV infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is an HIV protease inhibitor.

21. The method of Claim 20 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S, 3S, 5S)-2-(2,6)-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

22. A method of treating hyperlipidemia comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is fenofibrate.

23. A method of treating a fungal infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment, wherein said pharmaceutical compound is griseofulvin.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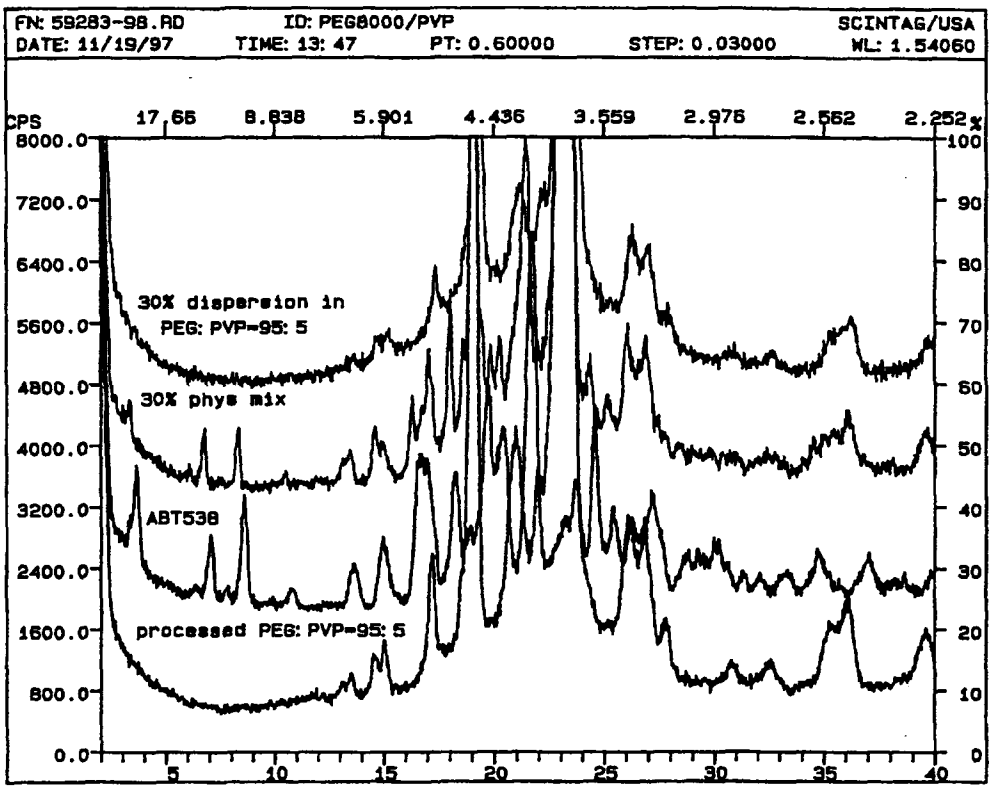
8.838
5.901
4.436
3.559
2.976
2.562
2.252
%
overlay the ABT538 processed PEG8000, 30% phys mix and 30% dispersion in PEG8000
30% dispersion in PE88000
30% phys mix
Processed PEG8000
ABT-538
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
5
10
15
20
25
30
35
40

Figure 1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2.976
2.562
2.252
Å
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
30% dispersion in
PEG: PVP-95: 5
30% phys mix
ABT538
processed PEG: PVP-95: 5
5
10
15
20
25
30
35
40

Figure 2

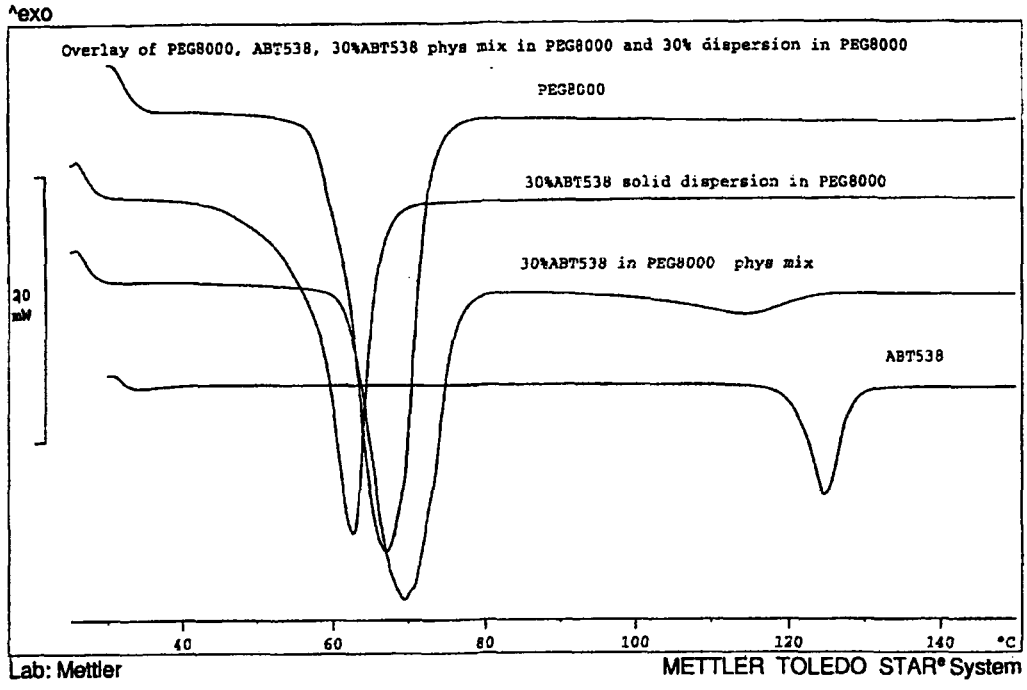
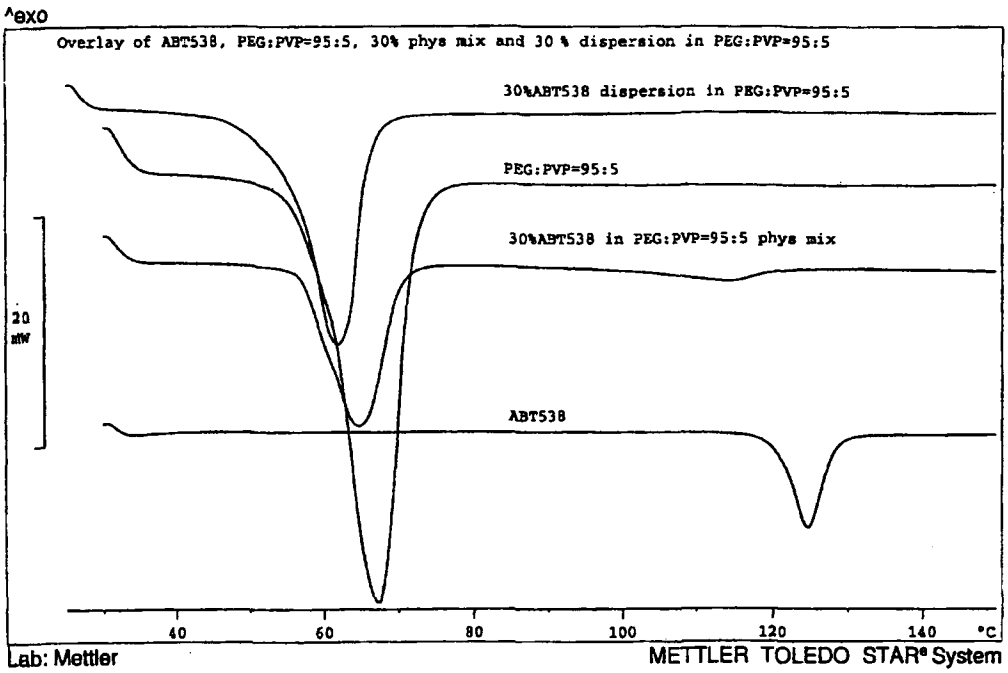

^exo
Overlay of PEG8000, ABT538, 30%ABT538 phys mix in PEG8000 and 30% dispersion in PEG8000
PEG8000
30%ABT538 solid dispersion in PEG8000
30%ABT538 in PEG8000 phys mix
ABT538
20
mW
40
60
80
100
120
140
°C
Lab: Mettler
METTLER TOLEDO STAR° System

Figure 3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Overlay of ABT538, PEG:PVP=95:5, 30% phys mix and 30 % dispersion in PEG:PVP=95:5
30%ABT538 dispersion in PEG:PVP=95:5
PEG:PVP=95:5
30%ABT538 in PEG:PVP=95:5 phys mix
ABT538
20 mW
40
60
80
100
120
140
°C
Lab: Mettler
METTLER TOLEDO STAR System

Figure 4

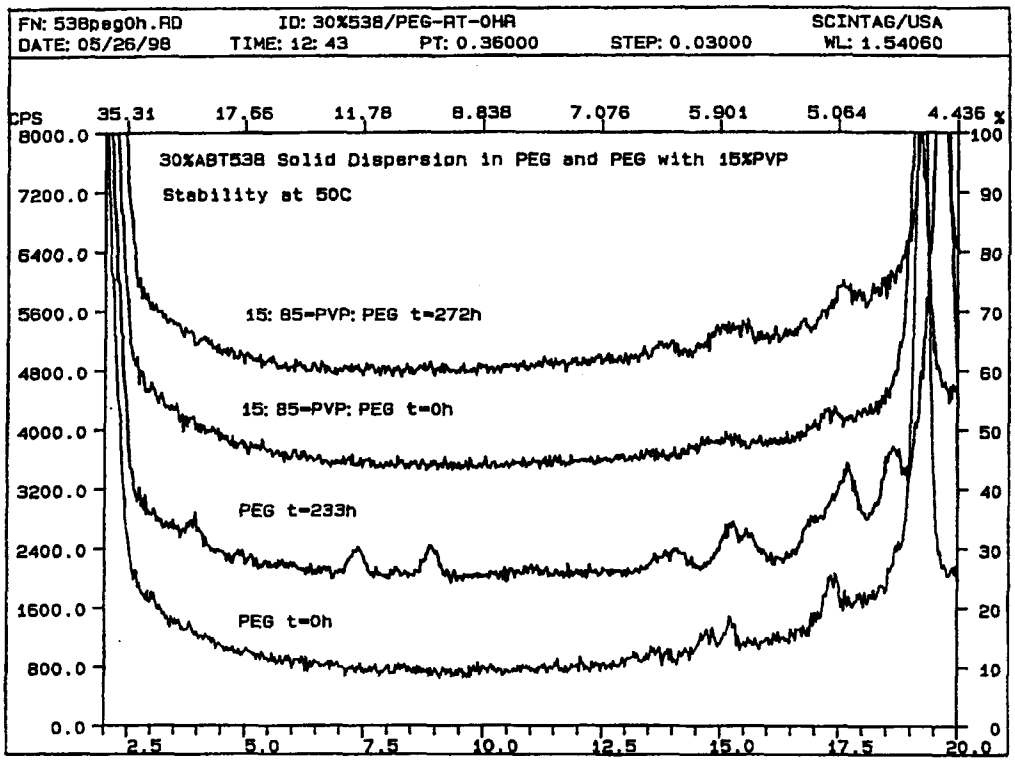
Missing at the time of publication

Figure 5

ABT-538 Isothermal Calorimetry (40°C)

Missing at the time of publication

Figure 6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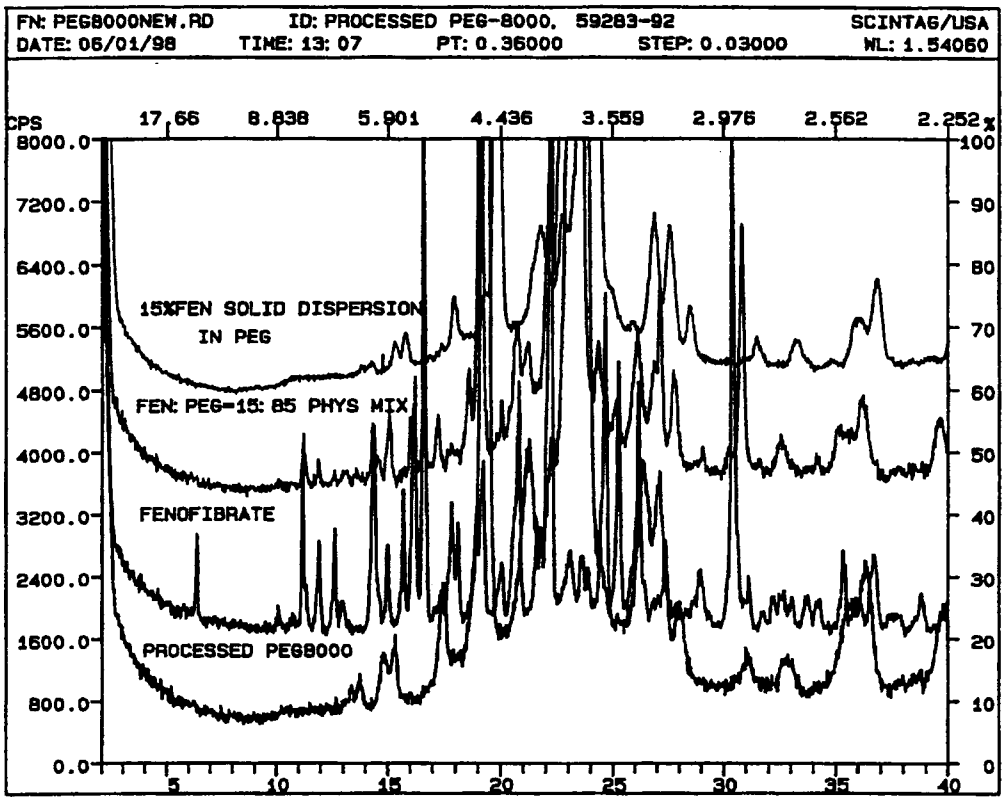
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
30%ABT538 Solid Dispersion in PEG and PEG with 15%PVP
Stability at 50C
15: 85-PVP: PEG t=272h
15: 85-PVP: PEG t=0h
PEG t=233h
PEG t=0h
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 7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4.436
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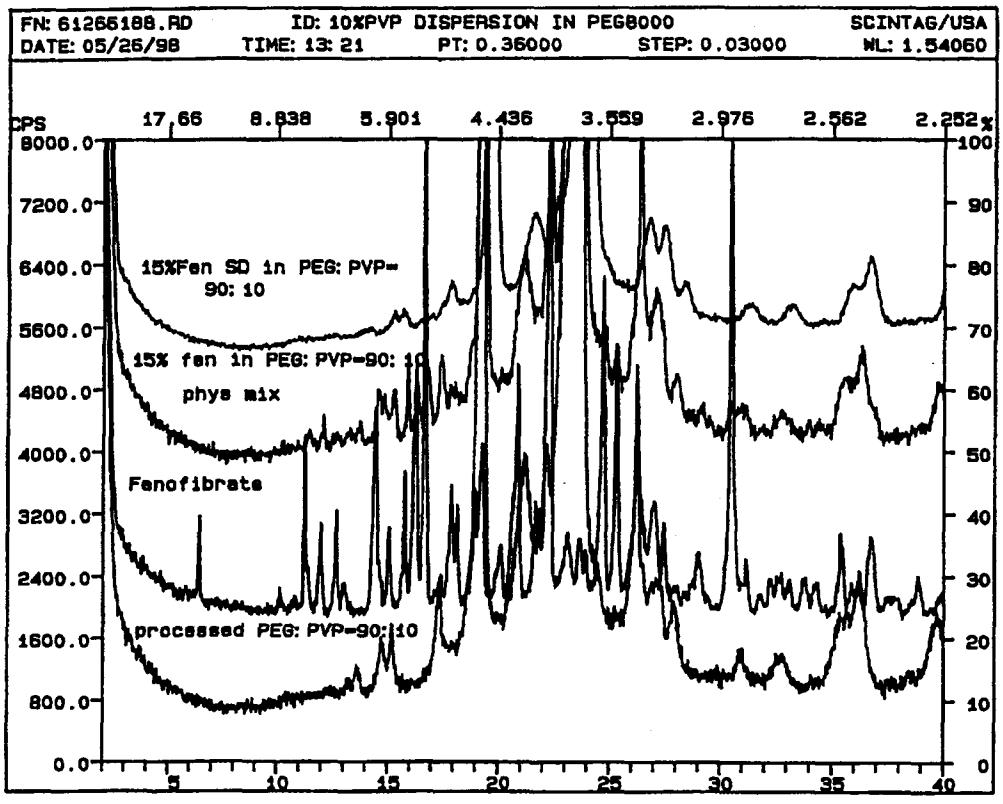
2.976
2.562
2.252
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
5
10
15
20
25
30
35
40
15%FEN SOLID DISPERSION IN PEG
FEN: PEG=15: 85 PHYS MIX
FENOFIBRATE
PROCESSED PEG8000

Figure 8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8.838
5.901
4.436
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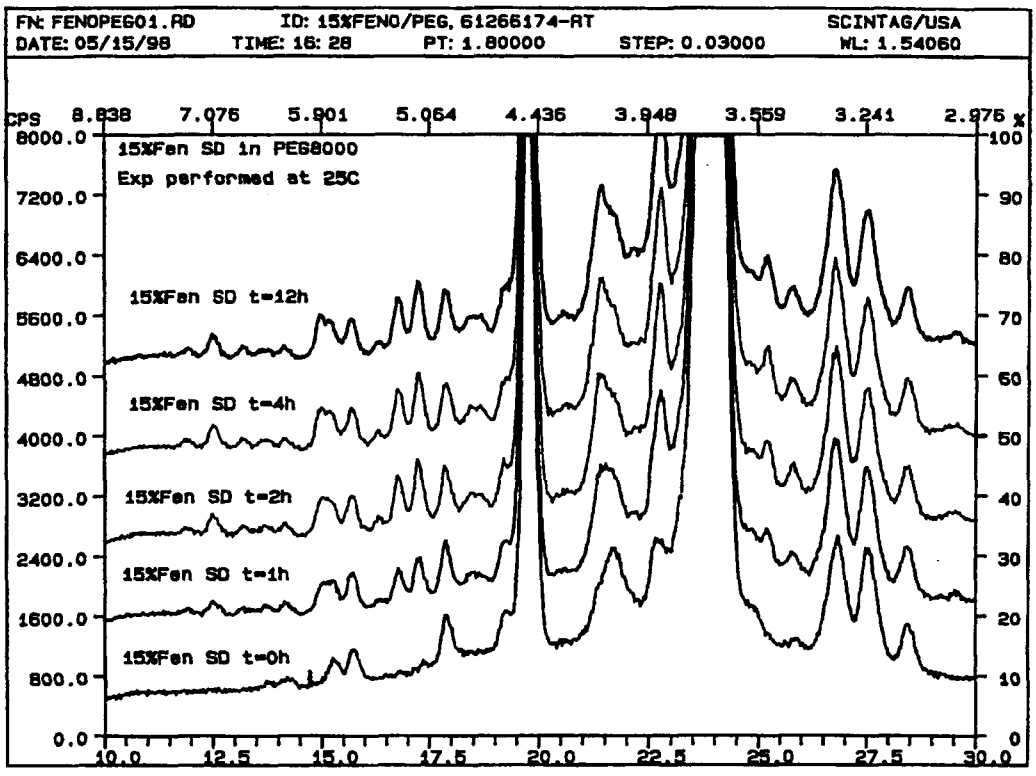
2.976
2.562
2.252
%
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
5
10
15
20
25
30
35
40
15%Fen SD in PEG: PVP= 90: 10
15% fen in PEG: PVP=90: 10
phys mix
Fenofibrate
processed PEG: PVP=90: 10

Figure 9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5.064
4.436
3.948
3.559
3.241
2.975
%
8000.0
7200.0
6400.0
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4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Fen SD in PEG8000
Exp performed at 25C
15%Fen SD t=12h
15%Fen SD t=4h
15%Fen SD t=2h
15%Fen SD t=1h
15%Fen SD t=0h
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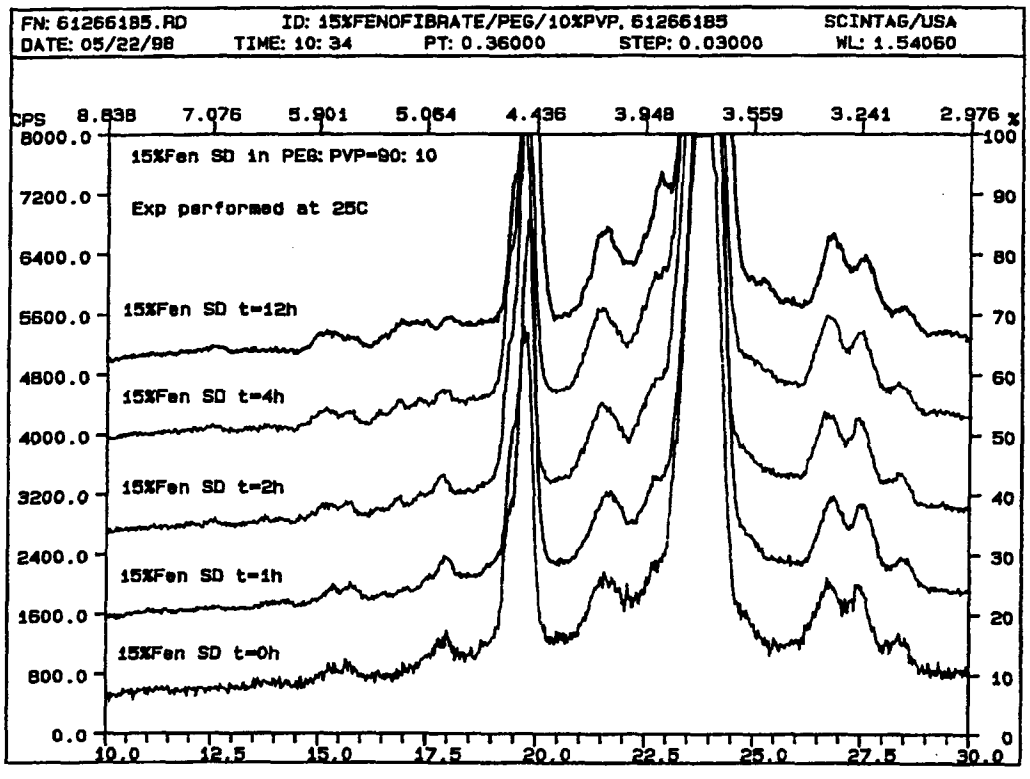
15.0
17.5
20.0
22.5
25.0
27.5
30.0

Figure 10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4.436
3.948
3.559
3.241
2.976
%
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7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
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Exp performed at 25C
15%Fen SD t=12h
15%Fen SD t=4h
15%Fen SD t=2h
15%Fen SD t=1h
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15.0
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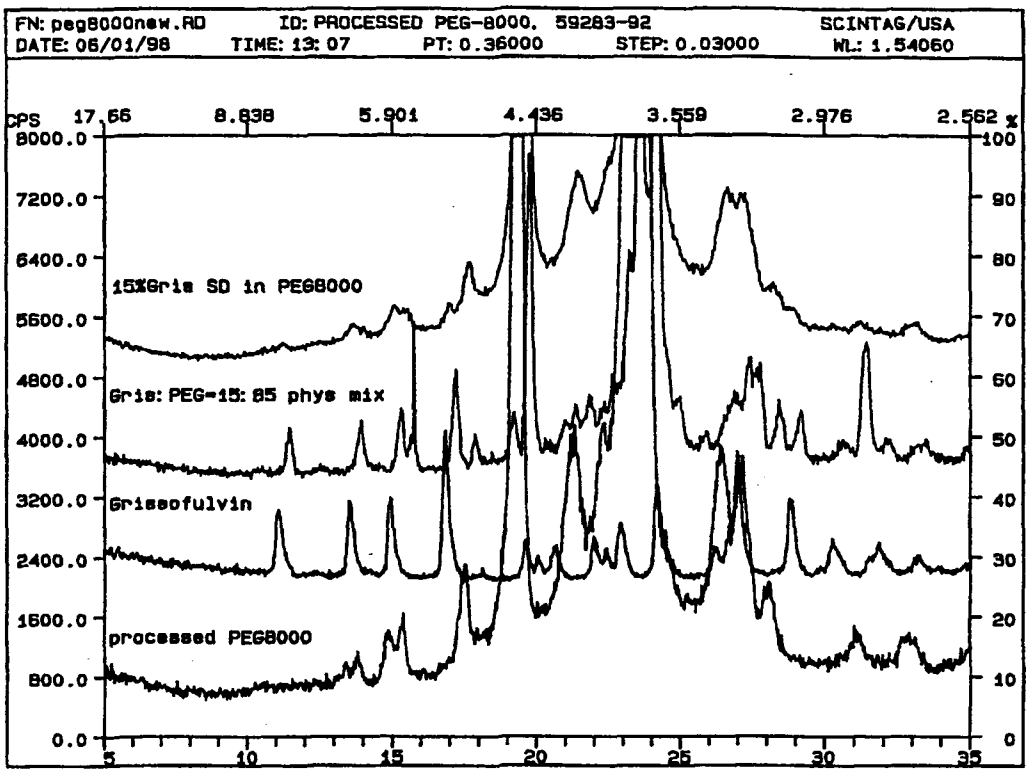
20.0
22.5
25.0
27.5
30.0

Figure 11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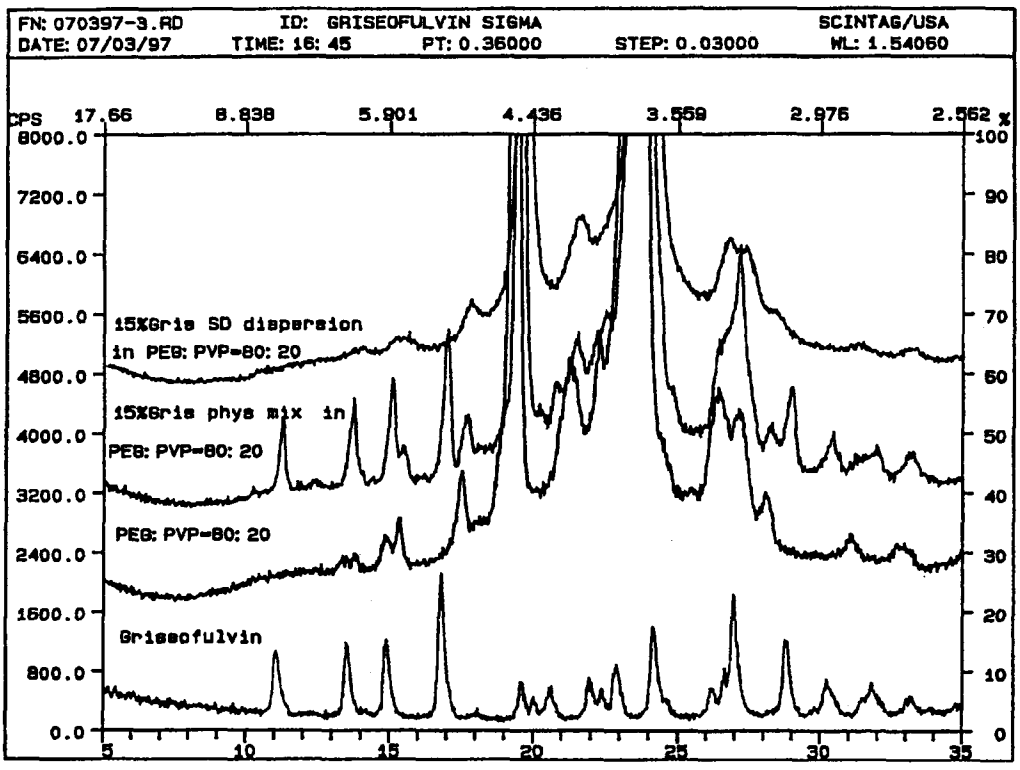
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
800.0
0.0
100
90
80
70
60
50
40
30
20
10
0
15%Gris SD in PEG8000
Gris: PEG-15: 85 phys mix
Griseofulvin
processed PEG8000
5
10
15
20
25
30
35

Figure 12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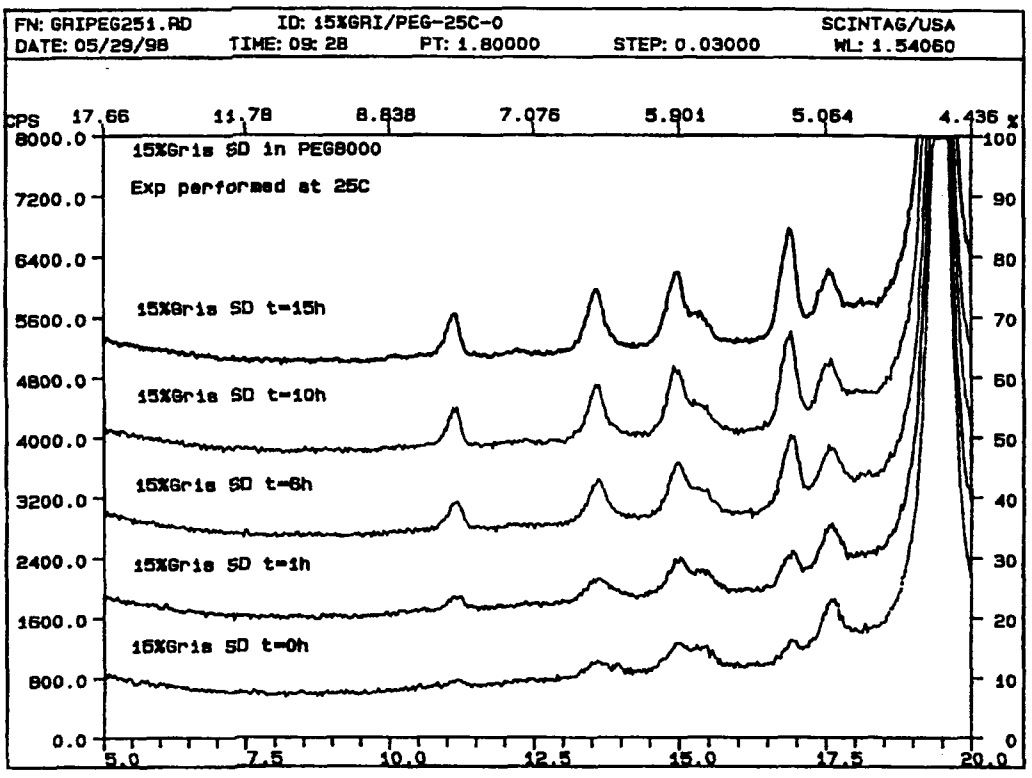
80
70
60
50
40
30
20
10
0
15%Gris SD dispersion
in PEG: PVP=80: 20
15%Gris phys mix in
PEG: PVP=80: 20
PEG: PVP=80: 20
Griseofulvin
5
10
15
20
25
30
35

Figure 13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CPS
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11.78
8.838
7.076
5.901
5.064
4.436
%
15%Gris SD in PEG8000
Exp performed at 25C
15%Gris SD t=15h
15%Gris SD t=10h
15%Gris SD t=6h
15%Gris SD t=1h
15%Gris SD t=0h
8000.0
7200.0
6400.0
5600.0
4800.0
4000.0
3200.0
2400.0
1600.0
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100
90
80
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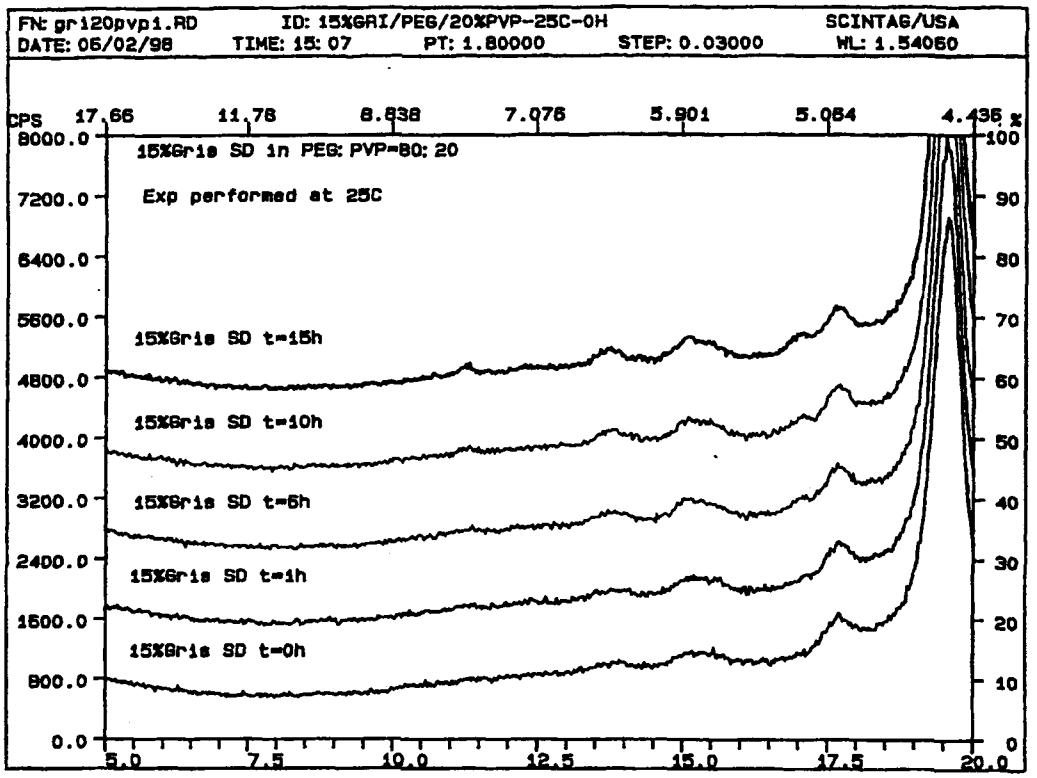
5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 14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WL: 1.54060
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11.78
8.838
7.076
5.901
5.064
4.436
%
15%Gris SD in PEG: PVP=80: 20
Exp performed at 25C
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15%Gris SD t=10h
15%Gris SD t=5h
15%Gris SD t=1h
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4800.0
4000.0
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800.0
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100
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80
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20
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5.0
7.5
10.0
12.5
15.0
17.5
20.0

Figure 15

Exhibit 3

Volker Bühler

Kollidon®

Polyvinylpyrrolidone for the pharmaceutical industry

BASF Aktiengesellschaft
Fine Chemicals
D-67056 Ludwigshafen

BASF

March 1998
(4th edition)

Table 71: Sugar-coating suspension with Kollidon 30

Sucrose	2130 g
Titanium dioxide	45 g
Kollidon 30	15 g
Colour lake (Sicovit®)	12 g
Lutrol F 68 (= Poloxamer 188)	3 g
Water	870 g

Apart from its use in traditional sugar coating, Kollidon 30 makes it possible to automate the sugar coating process. Table 72 gives a suitable formulation.

Table 72: Suspension for automatic sugar coating [231]

Sucrose	76 g
Kollidon 30	8 g
Titanium dioxide	9 g
Calcium carbonate	9 g
Talc	29 g
Colorant (Sicovit)	q.s.
Glycerol	4 g
Water	63 g

40 kg of tablet cores with a weight of 420 mg were sprayed with 25 kg of the above suspension in a conventional coating pan under the following conditions:

Spray phase:	5 s
Interval:	10 min
Drying phase (warm air):	10 min
Total coating time:	16 h

2.4.4.2 Film coatings

The properties given in Table 70 for Kollidon 25 and Kollidon 30 are also useful in the film-coating of tablets and hard gelatin capsules [281].

The glass transition temperatures (Tg) of the soluble Kollidon grades lie between 90 °C and 185 °C, depending on their molecular weight and on their moisture content [524]. Tg values of 155 °C and 168 °C have been measured for dried Kollidon 25 and Kollidon 30 [485].

Kollidon 90 F is only seldom used for film coating (see Table 73). Its most important properties here are film formation, adhesion promotion [276], pigment dispersion and the improvement of the solubility of other film-forming agents and of the final coating in water [100].

A disadvantage of the Kollidon grades in film-coating is their hygroscopicity (see Section 2.2.5). This is why they are normally never used as the sole

Exhibit 4

US006599528B1

(12) **United States Patent**
Rosenberg et al.

(10) **Patent No.: US 6,599,528 B1**
(45) **Date of Patent: Jul. 29, 2003**

(54) **MECHANICALLY STABLE PHARMACEUTICAL PRESENTATIONS FORM CONTAINING LIQUID OR SEMISOLID SURFACE-ACTIVE SUBSTANCES**

(75) Inventors: **Jörg Rosenberg**, Ellerstadt (DE); **Gunther Berndl**, Herxheim (DE); **Bernd Liepold**, Mannheim (DE); **Jörg Breitenbach**, Mannheim (DE)

(73) Assignee: **Abbott GmbH & Co. KG**, Ludwigshafen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/936,349**

(22) PCT Filed: **Mar. 17, 2000**

(86) PCT No.: **PCT/EP00/02381**

§ 371 (c)(1),
(2), (4) Date: **Sep. 11, 2001**

(87) PCT Pub. No.: **WO00/57854**

PCT Pub. Date: **Oct. 5, 2000**

(30) **Foreign Application Priority Data**

Mar. 25, 1999 (DE) 199 13 692

(51) **Int. Cl.**[7] **A61K 9/48**; A61K 9/20
(52) **U.S. Cl.** **424/451**; 424/464
(58) **Field of Search** 424/451, 464

(56) **References Cited**

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5,834,472	A	11/1998	Sangekar et al.	514/252

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Voigt "Pharmazeutische Technologie" (1993) pp. 80–85.

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Primary Examiner—Carlos Azpuru
(74) *Attorney, Agent, or Firm*—Keil & Weinkauf

(57) **ABSTRACT**

The present invention relates to mechanically stable pharmaceutical presentations for oral administration, comprising in addition to one or more active ingredients and at least one melt-processable matrix-forming excipient more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C.

6 Claims, No Drawings

MECHANICALLY STABLE PHARMACEUTICAL PRESENTATIONS FORM CONTAINING LIQUID OR SEMISOLID SURFACE-ACTIVE SUBSTANCES

BACKGROUND OF THE INVENTION

The present invention relates to mechanically stable pharmaceutical presentations for oral administration, comprising in addition to one or more active ingredients and at least one melt-processable matrix-forming excipient more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C. A process for producing such forms has also been found.

The production of pharmaceutical preparations by the melt extrusion process is known per se. Thus, the process described, for example, in EP-A 240 904 or EP-A 240 906 makes it possible, by a specific selection and defined mixtures of the excipients employed, to control specifically the properties of the formulations to be produced.

For example, it is possible to produce, by selecting suitable matrix polymers, preparations which release the active ingredient continuously over a lengthy period. On the other hand, it may be desirable, for example in the case of analgesics, for the active ingredient to dissolve rapidly and be released quickly. The melt extrusion process has proven to be suitable for producing rapid release and slow release formulations.

A basic requirement is, however, that the active ingredient is able to dissolve sufficiently in the aqueous medium in the digestive tract. Absorption of the active ingredient is possible only if it is in dissolved form, because only dissolved active ingredients can cross the intestinal wall. Active ingredients of low solubility may therefore not be absorbed sufficiently and, associated with this, have a low bioavailability.

[redacted]

However, the use of solid dispersions has a beneficial effect on the bioavailability of the active ingredient only if the active ingredient can also undergo rapid absorption. However, if the absorption process is slow, the active ingredient of low solubility recrystallizes in the aqueous medium of the intestinal lumen because a supersaturated solution of active ingredient may be produced on dissolution of the drug form. For this reason, the bioavailabilities which can be achieved even with solid dispersions are often unsatisfactory.

The absorption of the active ingredient is often insufficient also because the active ingredient is released too slowly from the tablet. Absorption of most active ingredients into the blood circulation takes place in the upper sections of the small intestine, i.e. relatively soon after passing through the stomach. Active ingredients which have not been

adequately solubilized on reaching this region of the small intestine can be absorbed to only a limited extent.

It is therefore crucial for achieving optimal absorption rates, especially of active ingredients of low solubility which readily crystallize, to achieve rapid and sufficiently long-lasting solubilization in the aqueous medium of the digestive tract without recrystallization occurring.

The addition of surface-active substances is appropriate for this. The addition of surface-active substances to formulations of active ingredients of low solubility is generally known per se.

U.S. Pat. No. 5,834,472 discloses, for example, that the bioavailability of an antifungal agent can be improved by using a nonionic surface-active substance.

However, since most surface-active substances are liquid or semisolid at room temperature, the preparations produced to date are usually oily liquids or semisolids used to fill hard or soft gelatin capsules. However, in the case of soft gelatin capsules, interactions between excipients and the gelatin shell of the capsule are frequent and lead to leakage from the capsule.

[redacted]

It is an object of the present invention to find mechanically stable solid formulations for oral use which can be used in particular for rapid and nevertheless long-lasting solubilization of active ingredients of low solubility after they have been liberated from the drug form.

BRIEF SUMMARY OF THE INVENTION

We have found that this object is achieved by the pharmaceutical formulations defined at the outset, and a process for producing them.

DETAILED DESCRIPTION OF THE INVENTION

The active ingredients which can be used are in principle all human and veterinary pharmaceutical substances, and active ingredients used in food supplements.

[redacted]

to CNS-active substances or dihydropyrimidine derivatives.

It is possible in particular to formulate active ingredients of low solubility or low bioavailability according to the invention. Low solubility means that the solubility in an aqueous medium is less than 1 mg/ml. Such active ingredients are also referred to in USP XXII, page 8, as scarcely soluble or practically insoluble.

Examples of active ingredients of low solubility are esuprone, nifedipine, ciclosporin or Taxol.

[redacted]

Examples of suitable surface-active substances are saturated and unsaturated polyglycolized glycerides, semisyn-

thetic glycerides, fatty acid esters or ethers of fatty alcohols as long as they have the properties stated above.

The corresponding sorbitan fatty acid esters or ethoxylated sorbitan fatty acid esters are particularly suitable, such as, for example, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene 20 sorbitan monooleate, polyoxyethylene 20 sorbitan tristearate, polyoxyethylene 20 sorbitan trioleate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 4 sorbitan monolaurate or polyoxyethylene 4 sorbitan monooleate. Also suitable are macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether.

Particular preference is given to polyoxyethylene glycerol ricinoleate 35, polyoxyethylene glycerol trihydroxystearate 40, PEG 660 12-hydroxystearate (polyglycol ester of 12-hydroxystearic acid (70 mol%) with 30 mol% ethylene glycol).

The surface-active substances are present in the preparations in amounts of more than 10% by weight based on the total weight of the preparation, and up to 40% by weight, preferably 15 to 25% by weight and particularly preferably 20 to 25% by weight.

The preparations according to the invention also comprise at least one melt-processable matrix excipient. Particularly suitable matrix-forming excipients are water-soluble pharmaceutically acceptable polymers or sugar alcohols or mixtures thereof as long as they can be melted without decomposition.

[redacted]

Also suitable are polyvinyl alcohol or polyvinyl acetate, which may also be partially hydrolyzed, or acrylate polymers of the Eudragit type.

Also suitable are cellulose derivatives such as hydroxyalkylcelluloses, for example hydroxypropylcellulose, or, if slower release is required, hydroxyalkylalkylcelluloses which swell in water, for example hydroxypropylmethylcellulose (HPMC), preferably with degrees of methoxy substitution in the region of 22% and degrees of hydroxypropoxy substitution in the region of 8%, particularly preferably HPMC types with viscosities of 4000 mPas, 15,000 mPas or 100,000 mPas, measured at 20° C. in 2% by weight aqueous solution. Also suitable are HPMC types with degrees of methoxy substitution in the range from 28 to 29% and degrees of hydroxypropoxy substitution in the range from 5 to 8.5%.

Likewise suitable are meltable sugar alcohols such as, for example, sorbitol, maltitol, isomalt, mannitol, xylitol, erythritol or mixtures thereof. Maltitol, mannitol, xylitol or isomalt is preferred.

Suitable matrix-forming polymers are also polyethylene glycols with molecular weights in the range from 1000 to 20,000,000 Dalton, preferably 4000 to 10,000 Dalton.

The preparations may additionally contain conventional pharmaceutical excipients such as flavorings, antioxidants, silicas, release agents or dyes in the amounts usual therefor.

[redacted]

[redacted]

Depending on the composition, the processing generally takes place at temperatures from 40° C. to 260° C., preferably 50 to 200° C.

The starting materials can be fed into the extruder or kneader singly or as premix. They are preferably added in the form of powdered or granulated premixes. Thus, the liquid or oily surface-active substance can previously be mixed with another starting material to give free-flowing granules. Addition of the surface-active substance in liquid form, for example by liquid pumps, which are preferably heated in the case of semisolid substances, is likewise possible.

It is also possible first to dissolve the active substance in the surface-active substance, and then to granulate this mixture with the polymer. In this case, the active ingredient must not itself melt.

It may also be advisable for temperature-sensitive active ingredients first to melt the other starting materials and only then to add the active ingredient.

The starting materials are accordingly processed together to form a melt, which is processed by input of mechanical energy, in particular in the form of shear forces, to a homogeneous composition.

The homogenous melt is then extruded through a die or a breaker plate and subjected to shaping. This can take place by pelletizing the extrudate by usual techniques, for example using rotating knives or compressed air, to result in pellets or granules. The shaping can also take place as described in EP-A 240 906, by the extrudate being passed between two counter-rotating calender rolls and being shaped directly to tablets. It is likewise possible to pass the melt through the open extruder head and, after solidification, further process where appropriate by grinding or by suitable granulation equipment such as roll mills or compacting units.

Granules or pellets can then be processed to tablets in conventional tablet presses. It is also possible for the preparations which have been initially obtained by calendering already in the form of mechanically stable tablets to be subjected to a grinding process and then to be compressed to tablets in a conventional way. If required, the tablets can then be provided with a conventional coating.

It is surprisingly possible according to the invention to obtain tablets which, despite a high proportion of liquid or semisolid surface-active substances, have good mechanical stability and are not prone to be tacky or to soften. The good dimensional stability of the preparations makes it unnecessary, according to the invention, to use them for filling capsules.

The resulting drug forms comprise the active ingredient embedded amorphously. The preferred result is solid dispersions in which the active ingredient is in the form of a molecular dispersion. The drug forms according to the invention make it possible for even active ingredients of low solubility to be sufficiently solubilized and stably dispersed in aqueous medium.

The preparations according to the invention form, after dissolving in aqueous medium, in particular at pH 1, for at least one hour a stable solubilizate or a stable dispersion, in which the active ingredient is preferably not in crystalline form.

EXAMPLE 1

50 g of a powdered mixture of 40% by weight of esuprone, 35% by weight of polyvinylpyrrolidone K 17

(PVP) and 25% by weight of polyoxyethylene glycerol trihydroxystearate 40 as surface-active substance were produced by initially producing a powdered premix of esupron and the PVP, into which the surface-active substance was mixed at 20° C. until homogeneous granules resulted.

EXAMPLE 2

The granules obtained in Example 1 were kneaded at a temperature of 100° C. in a heatable kneader (supplied by Haake) to a homogeneous melt. After cooling to 20° C., the melt was solid and was broken into small fragments.

EXAMPLE 3

250 g of the granules obtained in Example 1 were stirred into 50 ml of water at room temperature. There was formation after a few minutes of a cloudy suspension from which crystalline esuprone sedimented.

EXAMPLE 4

The melt granules obtained in Example 2 were stirred into water in analogy to Example 3. After only a few minutes an opalescent solution formed, and no esuprone had separated out of this even after one hour.

We claim:

1. A mechanically stable pharmaceutical presentation for oral administration, comprising one or more active ingredients, at least one melt-processable matrix-forming excipient selected from the group consisting of homo- and copolymers of N-vinylpyrrolidone, acrylate polymers and cellulose derivatives, and more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C., obtainable by mixing the starting materials in the melt without addition of solvents and subsequently shaping.

2. A preparation as claimed in claim 1, comprising from 15 to 25% by weight of surface-active substance.

3. A preparation as claimed in claim 1, comprising a surface-active substance with an HLB of from 10 to 15.

4. A preparation as claimed in claim 1, comprising a surface-active substance with a drop point in the range from 20 to 40° C.

5. A preparation as claimed in claim 1, comprising macrogol glycerol hydroxystearate, polyoxyethylene ricinoleate 35 or PEG 660 12-hydroxystearate as surface-active substance.

6. A process for producing mechanically stable pharmaceutical presentations as claimed in claim 1 by a melt process, which comprises processing one or more active ingredients, at least one melt-processable matrix-forming excipient and more than 10 and up to 40% by weight of a surface-active substance with an HLB of from 2 to 18, which is liquid at 20° C. or has a drop point in the range from 20 to 50° C., in the melt to a homogeneous mixture, and shaping the latter to presentations.

* * * * *

Exhibit 5

(12) STANDARD PATENT (11) Application No. **AU 2003283261 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Method for producing solid galenic formulations using a crosslinked non-thermoplastic carrier

(51) International Patent Classification(s)
A61K 9/16 (2006.01) ***A61K 31/513*** (2006.01)
A61K 9/20 (2006.01)

(21) Application No: **2003283261** (22) Date of Filing: **2003.10.09**

(87) WIPO No: **WO04/032903**

(30) Priority Data

(31) Number	(32) Date	(33) Country
102 47 037.5	**2002.10.09**	**DE**

[redacted]

(71) Applicant(s)
Abbott GmbH & Co. KG

(72) Inventor(s)
Rosenberg, Jorg;Magerlein, Markus;Berndl, Gunther

(74) Agent / Attorney
Watermark Patent & Trademark Attorneys, Level 2 302 Burwood Road, Hawthorn, VIC, 3122

(56) Related Art
US 2002/012706
EP 960620

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
22. April 2004 (22.04.2004)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2004/032903 A3

(51) Internationale Patentklassifikation[7]: A61K 9/16, 31/513

(21) Internationales Aktenzeichen: PCT/EP2003/011205

(22) Internationales Anmeldedatum:
9. Oktober 2003 (09.10.2003)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
102 47 037.5 9. Oktober 2002 (09.10.2002) DE

(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von US)*: **ABBOTT GMBH & CO. KG** [DE/DE]; Max-Planck-Ring 2, 65205 Wiesbaden (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder *(nur für US)*: **ROSENBERG, Jörg** [DE/DE]; Bruchstr. 29, 67158 Ellerstadt (DE). **BERNDL, Gunther** [DE/DE]; Am Dörrling 7, 67273 Herxheim (DE). **MÄGERLEIN, Markus** [DE/DE]; Eichendorffstrasse 8, 68167 Mannheim (DE).

(74) Anwälte: **KINZEBACH, Werner** usw.; Reitstötter, Kinzebach & Partner (GbR), Sternwartstrasse 4, 81679 München (DE).

(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 11. November 2004

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: METHOD FOR PRODUCING SOLID GALENIC FORMULATIONS USING A CROSSLINKED NON-THERMOPLASTIC CARRIER

(54) Bezeichnung: HERSTELLUNG VON FESTEN DOSIERUNGSFORMEN UNTER VERWENDUNG EINES VERNETZTEN NICHT-THERMOPLASTISCHEN TRÄGERS

(57) Abstract: The invention concerns a method for producing solid galenic formulations which consists in: forming a processable paste comprising a) 50 to 99.4 wt. % of at least one non-thermoplastic carrier, b) 0.5 to 30 wt. % of at least an adjuvant selected among thermoplastic polymers, lipids, sugar alcohols and solubilizing agents, c) 0.1 to 49.5 wt. % of at least one active principle, at a temperature not less than the softening temperature of the adjuvant but rising to at least 70 °C; then in cooling the resulting paste. Said solid galenic formulations quickly disintegrate in an aqueous medium.

(57) Zusammenfassung: Beschrieben wird ein Verfahren zur Herstellung fester Dosierungsformen, bei dem man eine formbare Masse, die a) 50 bis 5 99,4 Gew.-% wenigstens eines nicht-thermoplastischen Trägers, b) 0,5 bis 30 Gew.-% wenigstens eines unter thermoplastischen Polymeren, Lipiden, Zuckeralkoholen, Zuckeralkoholderivaten und Solubilisatoren ausgewählten Adjuvans und c) 0,1 bis 49,5 Gew.-% wenigstens eines Wirkstoffs umfasst, bei einer Temperatur bei 10 oder oberhalb des Erweichungspunkts des Adjuvans, mindestens jedoch 70 °C, bildet und anschließend abkühlt. Die Dosierungsformen zerfallen in wässriger Umgebung rasch.

WO 2004/032903 A3

M/42135-PCT

Preparation of solid dosage forms using a crosslinked nonthermoplastic carrier

Description

The present invention relates to a process for producing fast-release solid dosage forms.

The production of solid dosage forms by melt extrusion, i.e. a process in which a melt of a polymeric binder and of an active ingredient is extruded, and the extrudate is shaped to the desired drug form, is known, see, for example, EP-A 240 904, EP-A 240 906, EP-A 337 256 and EP-A 358 105. This process permits the preparation of slightly soluble active ingredients in the form of solid solutions. The active ingredient is present in the solid solutions in amorphous form and can therefore be absorbed more easily than the crystalline active ingredient. However, the dissolution of the dosage form and the release of the active ingredient takes place only at the surface of the dosage form. In many cases, however, rapid disintegration of the dosage form is desired.

EP-B 0078430 discloses a process for producing fast-release pharmaceutical preparations comprising dihydropyridine, polyvinylpyrrolidone and insoluble carriers such as crosslinked polyvinylpyrrolidone, where the active ingredient and the polyvinylpyrrolidone are dissolved in an organic solvent, and the solution is granulated with the carrier. This process cannot, however, be directly applied to other slightly soluble active ingredients because a suitable physiologically tolerated solvent does not exist for all active ingredients and/or complete removal of the solvent is impossible or possible only in a troublesome manner.

GB 2 153 676 proposes the loading of water-insoluble

polymers such as crosslinked polyvinylpyrrolidone with an active ingredient by mixing the polymer with the active ingredient and heating to the melting point of the active ingredient. This procedure has the disadvantage that many active ingredients cannot be melted without decomposition.

EP-A 0 446 753 discloses the loading of crosslinked polymers with an active ingredient by treating the polymer with a solution of the active ingredient, or grinding the polymer and the active ingredient with high energy input. The process has the disadvantage that it cannot be carried out continuously.

DE-A 44 13 350 describes slow-release matrix pellets consisting of an active ingredient, 5 to 50% by weight of a water-insoluble polymer such as ethylcellulose, 5 to 45% by weight of a lipophilic component, 3 to 40% by weight of a gel former such as hydroxypropylcellulose, and where appropriate formulation aids. The slow-release matrix pellets can be produced by melt extrusion.

It is an object of the invention to indicate a universally applicable process which allows dosage forms with rapid release in particular of slightly soluble active ingredients to be produced without the need to use organic solvents or to melt the active ingredient.

The present invention therefore relates to a process for producing solid dosage forms, in which a moldable composition which comprises

a) 50 to 99.4% by weight, preferably 60 to 80% by weight, of at least one crosslinked nonthermoplastic carrier,

b) 0.5 to 30% by weight, preferably 5 to 20% by weight, of at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and

c) 0.1 to 49.5% by weight, preferably 5 to 25% by weight, of at least one active ingredient,

is formed at a temperature at or above the softening point of the adjuvant, but at least 70°C, preferably 100 to 180°C, and subsequently cooled.

In preferred embodiments, the composition comprises

a) 50 to 90% by weight, preferably 60 to 80% by weight, of at least one crosslinked nonthermoplastic carrier,

b1) 5 to 30% by weight, preferably 7 to 15% by weight, of at least one thermoplastic polymer,

b2) 0.5 to 20% by weight, preferably 5 to 10% by weight, of at least one solubilizer,

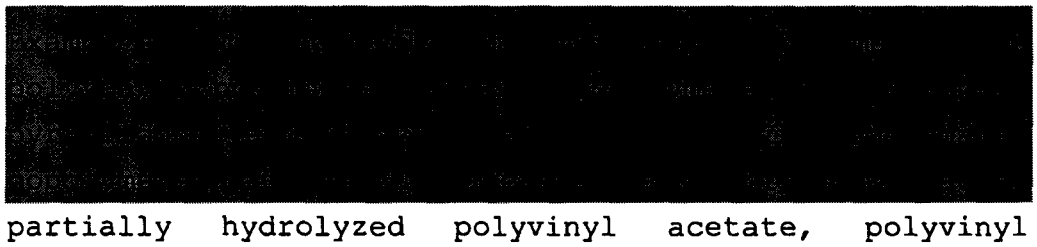
c) 0.1 to 45.5% by weight, preferably 5 to 25% by weight, of at least one active ingredient.

The crosslinked nonthermoplastic carrier acts as disintegrant which brings about rapid disintegration of the dosage form in an aqueous environment such as gastric juice. It is surprisingly possible to produce the dosage forms, which comprise a predominant proportion of a crosslinked nonthermoplastic carrier, in the absence of solvents through a process similar to melt extrusion if particular adjuvants are additionally used. "Adjuvant" or "adjuvants" mean excipients which remain in the dosage form and are not merely added during production and are removed again in a later

processing step.

The crosslinked nonthermoplastic carrier is a natural, semisynthetic or fully synthetic polymer which is crosslinked to a degree of crosslinking such that it has no thermoplastic properties. It is usually insoluble in water but swellable in water. The nonthermoplastic carrier is preferably selected from crosslinked polyvinylpyrrolidone and crosslinked sodium carboxymethylcellulose. Crosslinked polyvinylpyrrolidone is most preferred. Suitable products are described for example in the US Pharmacopeia (USP NF).

Besides the active ingredient and the crosslinked nonthermoplastic carrier, there is also employed in the process of the invention at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers.



partially hydrolyzed polyvinyl acetate, polyvinyl alcohol, polyhydroxyalkylacrylates, polyhydroxyalkylmethacrylates, polyacrylates and polymethacrylates (Eudragit types), copolymers of methyl methacrylate and acrylic acid, polyethylene glycols, alkylcelluloses, especially methylcellulose and ethylcellulose, hydroxyalkylcelluloses, especially hydroxypropylcellulose (HPC), hydroxyalkylalkylcelluloses, especially hydroxypropylmethylcellulose (HPMC), cellulose esters such as

cellulose phthalates, in particular cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and

[redacted]

pyrrolidone with Fikentscher K values of from 12 to 100, preferably 17 to 30, or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA), such as, for example, a copolymer of 60% by weight VP and 40% by weight VA.

The thermoplastic polymers preferably have a softening temperature of from 60 to 180°C, in particular 70 to 130°C.

Suitable sugar alcohols are sorbitol, xylitol, mannitol, maltitol; a suitable sugar alcohol derivative is isomalt.

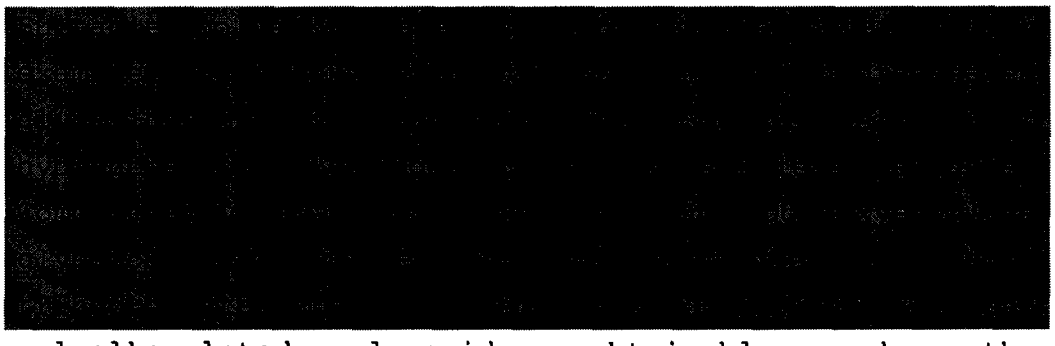
Suitable lipids are fatty acids such as stearic acid; fatty alcohols such as cetyl or stearyl alcohol; fats such as animal or vegetable fats; waxes such as carnauba wax; or mono- and/or diglycerides or phosphatides, especially lecithin. The fats preferably have a melting point of at least 50°C. Triglycerides of C_{12}, C_{14}, C_{16} and C_{18} fatty acids are preferred.

[redacted]

or fatty acid esters of polyalkylene glycols; or polyalkoxylated ethers of fatty alcohols. A fatty acid chain in these compounds usually comprises 8 to 22 carbon atoms. The polyalkylene oxide blocks comprise on average from 4 to 50 alkylene oxide units, preferably ethylene oxide units, per molecule.

Suitable sorbitan fatty acid esters are sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan tristearate, sorbitan trioleate, sorbitan monostearate, sorbitan monolaurate or sorbitan monooleate.

Examples of suitable polyalkoxylated sorbitan fatty acid esters are polyoxyethylene(20)sorbitan monolaurate, polyoxyethylene(20)sorbitan monopalmitate, polyoxyethylene(20)sorbitan monostearate, polyoxyethylene(20)sorbitan monooleate, polyoxyethylene(20)sorbitan tristearate, polyoxyethylene(20)sorbitan trioleate, polyoxyethylene(4)-sorbitan monostearate, polyoxyethylene(4)sorbitan monolaurate or polyoxyethylene(4)sorbitan monooleate.



polyalkoxylated glycerides obtainable under the proprietary names Gelucire® and Labrafil® from Gattefosse, e.g. Gelucire® 44/14 (lauroyl macrogol 32 glycerides prepared by transesterification of hydrogenated palm kernel oil with PEG 1500), Gelucire® 50/13 (stearoyl macrogol 32 glycerides prepared by transesterification of hydrogenated palm oil with PEG 1500) or Labrafil M1944 CS (oleoyl macrogol 6 glycerides prepared by transesterification of apricot kernel oil with PEG 300).

A suitable fatty acid ester of polyalkylene glycols is for example PEG 660 hydroxystearic acid (polyglycol ester of 12-hydroxystearic acid (70 mol%) with 30 mol% ethylene glycol).

Suitable polyalkoxylated ethers of fatty alcohols are for example macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether

Besides these, it is possible additionally to use conventional pharmaceutical excipients, the total amount of which may be up to 20% by weight based on the dosage form. These include:

extenders or fillers such as lactose, cellulose, silicates or silica,

lubricants such as magnesium stearate and calcium stearate, sodium stearyl fumarate,

colorants such as azo dyes, organic or inorganic pigments or colorants of natural origin,

stabilizers such as antioxidants, light stabilizers, hydroperoxide destroyers, radical scavengers, stabilizers against microbial attack.

Active ingredients mean for the purposes of the invention all substances with a desired physiological effect on the human or animal body or plants. They are in particular active pharmaceutical ingredients. The amount of active ingredient per dose unit may vary within wide limits. It is usually chosen so that it is sufficient to achieve the desired effect. Combinations of active ingredients can also be employed. Active ingredients for the purposes of the invention are also vitamins and minerals. Vitamins include the vitamins of the A group, or the B group, by which are meant besides B_1, B_2, B_6 and B_{12} and nicotinic acid and nicotinamide also compounds having vitamin B properties such as, for example, adenine, choline, pantothenic acid, biotin, adenylic acid, folic acid, orotic acid, pangamic acid, carnitine, p-aminobenzoic acid, myo-inositol and lipoic

acid, and vitamin C, vitamins of the D group, E group, F group, H group, I and J groups, K group and P group. Active ingredients for the purposes of the invention also include peptide therapeutics and proteins. Plant treatment agents include for example vinclozolin, epoxiconazole and quinmerac.

The process of the invention is suitable, for example, for processing the following active ingredients:

acebutolol, acetylcysteine, acetylsalicylic acid, acyclovir, albrazolam, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclomethasone, benserazide, benzalkonium hydrochloride, benzocaine, benzoic acid, betamethasone, bezafibrate, biotin, biperidene, bisoprolol, bromazepam, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefachlor, cefalexin, cefatroxil, cefazolin, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, celedilin, chloramphenicol, chlorhexidine, chlorpheniramine, chlortalidone, choline, cyclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clevulanic acid, clomibramine, clonazepam, clonidine, clotrimazole, codeine, cholestyramine, cromoglycic acid, cyanocobalamin, cyproterone, desogestrel, dexamethasone, dexpanthenol, dextromethorphan, dextropropoxiphen, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, dihydroergotoxin, diltiazem, diphenhydramine, dipyridamole, dipyrone, disopyramide, domperidone, dopamine, doxycycline, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, Eucalyptus Globulus, famotidine, felodipine,

fenofibrate, fenofibric acid, fenoterol, fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, furosemide, gallopamil, gemfibrozil, gentamicin, Gingko Biloba, glibenclamide, glipizide, clozapine, Glycyrrhiza glabra, griseofulvin, guaifenesin, haloperidol, heparin, hyaluronic acid, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, ipratropium hydroxide, ibuprofen, imipenem, indomethacin, insulin, iohexol, iopamidol, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, ketotifen, ketoconazole, ketoprofen, ketorolac, labatalon, lactulose, lecithin, levocarnitine, levodopa, levoglutamide, levonorgestrel, levothyroxine, lidocaine, lipase, lipramine, lisinopril, loperamide, lorazepam, lovastatin, medroxyprogesterone, menthol, methotrexate, methyldopa, methylprednisolone, metoclopramide, metoprolol, miconazole, midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamin mixtures or combinations and mineral salts, N-methylephedrine, naftidrofuryl, naproxen, neomycin, nicardipine, nicergoline, nicotinamide, nicotine, nicotinic acid, nifedipine, nimodipine, nitrazepam, nitrendipine, nizatidine, norethisterone, norfloxacin, norgestrel, nortriptyline, nystatin, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, phenobarbital, phenoxifylline, phenoxymethylpenicillin, phenylephrine, phenylpropanolamine, phenytoin, piroxicam, polymyxin B, povidone-iodine, pravastatin, prazepam, prazosin, prednisolone, prednisone, promocriptine, propafenone, propranolol, proxyphylline, pseudoephedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin, salicylic acid, simvastatin, somatropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulfasalazine, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline,

terfenadine, tetracycline, theophylline, thiamine, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide, triamteren, trimethoprim, troxerutin, uracil, valproic acid, vancomycin, verapamil, vitamin E, volinic acid, zidovudine.

The process is particularly suitable for active ingredients having a solubility in water at 25°C of less than 1 mg/ml. Such active ingredients are also referred to according to USP XXII, page 8, as scarcely soluble or practically insoluble.

The solid dosage forms are produced by producing, at an elevated temperature, i.e. a temperature at or above the softening point of the adjuvant, but at least 70°C, a moldable cohesive composition of the components, which is subsequently cooled, where appropriate after a shaping step. The time for which the components are exposed to the elevated temperature is preferably less than 5 minutes, in particular less than 3 minutes, for each of the components.

The mixing of the components and the formation of the moldable composition can take place in various ways. The mixing can take place before, during and/or after the heating of one or all of the components of the composition, although it is not expedient to heat the crosslinked nonthermoplastic carrier in the absence of the thermoplastic components of the composition. For example, the components can first be mixed and then heated to form the moldable composition. However, they can also be mixed and heated simultaneously. The moldable composition is frequently also homogenized in order to obtain a highly dispersed distribution of the active ingredient. In the case of sensitive active ingredients, preferably the adjuvant(s) is (are) initially melted in the presence of the nonthermoplastic carrier and then the active ingredient

is admixed.

The heating takes place in an apparatus usual for this purpose. Heatable extruders or kneaders are particularly suitable, such as mixer/kneader reactors (e.g. ORP, CRP, AP, DTB supplied by List or Reactotherm supplied by Krauss-Maffei or Ko-kneader supplied by Buss), trough mixers and internal mixers or rotor/stator systems (e.g. Dispax supplied by IKA). The residence time of the composition in the extruder is preferably less than 5 minutes, in particular less than 3 minutes.

Extruders which can be employed are single-screw machines, intermeshing screw machines or else multi-screw extruders, especially twin screw extruders, corotating or counter-rotating and, where appropriate, equipped with kneading disks. Twin screw extruders of the ZSK series from Werner & Pfleiderer are particularly preferred.

The charging of the extruder or kneader takes place continuously or batchwise according to the design thereof in a conventional way. Powdered components can be fed in freely, e.g. via a weigh feeder. Plastic compositions can be fed in directly from an extruder or fed in via a gear pump, which is particularly advantageous for high viscosities and high pressures. Liquid media can be metered in via a suitable pumping unit.

The resulting composition is doughy or pasty. It is usually subjected to a shaping. It is possible in this way to produce a large number of shapes, depending on the tool and mode of shaping. For example, on use of an extruder the extrudate can be shaped between a belt and a roll, between two belts or between two rolls, as described in EP-A-358 105, or by calendering in a

calender with two molding rolls, see, for example, EP-A-240 904. Small-particle granules can be obtained for example by extrusion and hot or cold cut of the extrudate. The cooled compositions can then also be ground to a powder and subsequently compressed to tablets in a conventional way. It is possible in this case also to use tableting aids such as colloidal silica, calcium hydrogen phosphate, lactose, microcrystalline cellulose, starch or magnesium stearate.

The invention is illustrated in more detail by the following examples.

Examples

Example 1

A mixture of 20.83% by weight of active ingredient (lopinavir), 68.17% by weight of crosslinked polyvinylpyrrolidone (Kollidon CL), 7.00% by weight of polyoxyethylene glycerol trihydroxystearate 40 (Cremophor® RH-40) and 1.00 by weight of Aerosil 200 was processed in a twin screw extruder (18 mm screw diameter) at a material temperature of 120°C. The Cremophor® RH-40 had previously been mixed at room temperature with the powdered Kollidon CL with stirring or kneading to give free-flowing granules, to which the active ingredient and the Aerosil 200 were then admixed. 1.5 kg/h of this mixture were then fed via a weigh feeder into the extruder. A hot moldable composition in the form of a white extrudate emerged from the extruder head and then hardened after cooling. The cooled extrudates (with a thickness of about 10 mm) disintegrated in water within a few minutes.

Example 2

Pieces of the extrudate obtained in example 1 were ground in a laboratory mill (from Retsch) and, after addition of 12% by weight of calcium hydrogen phosphate and 1% by weight of Aerosil 200 (colloidal silica), compressed in an eccentric press (Fette E 1) to oblong tablets. The tablets showed a disintegration time of a few minutes in a disintegration test (complying with DAB) in 0.1 M hydrochloric acid at 37°C.

Example 3 (comparative example)

Example 1 was repeated but with use of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate (Kollidon VA-64) instead of Kollidon CL. A translucent extrudate emerged from the extruder head and formed a hard brittle composition after cooling. The extrudates dissolved in water only after several hours.

Example 4 (comparative example)

Pieces of the extrudate obtained in example 3 were ground in analogy to example 2 and compressed with the stated excipients to oblong tablets. The disintegration time of the tablets in a disintegration test (complying with DAB) was more than 3 hours.

Example 5

A mixture of 20.83% by weight of active ingredient (lopinavir), 61.17% by weight of crosslinked polyvinylpyrrolidone (Kollidon CL), 10.00% by weight of N-vinylpyrrolidone/vinyl acetate 60/40 copolymer (Kollidon VA-64), 7.00% by weight of Cremophor RH-40 and 1.00 by weight of Aerosil 200 was processed in analogy to example 1. A hot moldable composition in the form of a white extrudate emerged from the extruder head and hardened after cooling. The cooled extrudates

disintegrated in water in a few minutes.

Example 6

A mixture of 20.83% by weight of active ingredient (lopinavir), 51.17% by weight of crosslinked polyvinylpyrrolidone (Kollidon CL), 20.00% by weight of N-vinylpyrrolidone/vinyl acetate 60/40 copolymer (Kollidon VA-64), 7.00% by weight of Cremophor RH-40 and 1.00 by weight of Aerosil 200 was processed in analogy to example 1. A hot moldable composition in the form of a yellowish white extrudate emerged from the extruder head and hardened after cooling. The cooled extrudates disintegrated in water in a few minutes.

Example 7

A mixture of 20.83% by weight of active ingredient (lopinavir) , 61.17% by weight of crosslinked polyvinylpyrrolidone (Kollidon CL), 10.00% by weight of N-vinylpyrrolidone/vinyl acetate 60/40 copolymer (Kollidon VA-64), 7.00% by weight of sorbitan monopalmitate (Span 40) and 1.00% by weight of Aerosil 200 was processed in analogy to example 1. A hot moldable composition in the form of a yellowish white extrudate emerged from the extruder head and hardened after cooling. The cooled extrudates disintegrated in water in a few minutes.

Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

We claim:

1. A process for producing solid dosage forms, in which a moldable composition which comprises

a) 50 to 99.4% by weight of at least one crosslinked nonthermoplastic carrier,

b) 0.5 to 30% by weight of at least one adjuvant selected from thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and

c) 0.1 to 49.5% by weight of at least one active ingredient,

is formed at a temperature at or above the softening point of the adjuvant, but at least 70°C, and subsequently cooled.

2. The process according to claim 1, where the composition comprises

a) 50 to 90% by weight of at least one crosslinked nonthermoplastic carrier,

b1) 5 to 30% by weight of at least one thermoplastic polymer,

b2) 0.5 to 20% by weight of at least one solubilizer,

c) 0.1 to 45.5% by weight of at least one active ingredient.

3. The process according to claim 1 or 2, where the crosslinked nonthermoplastic carrier is selected from crosslinked polyvinylpyrrolidone and crosslinked sodium carboxymethylcellulose.

2003283261 29 Apr 2008

4. The process according to any one of the preceding claims, where the thermoplastic polymer is a homo- or copolymer of vinylpyrrolidone.

5. The process according to any one of the preceding claims, where the sugar alcohol is selected from sorbitol, xylitol, mannitol, maltitol and the sugar alcohol derivative isomalt.

6. The process according to any one of the preceding claims, where the lipid is selected from fatty acids, fatty alcohols, fats, waxes, mono- and diglycerides and phosphatides.

7. The process according to any one of the preceding claims, where the solubilizer is selected from sorbitan fatty acid esters, polyalkoxylated fatty acid esters and polyalkoxylated ethers of fatty alcohols.

8. The process according to any one of the preceding claims, where the active ingredient has a solubility in water at 25°C of less than 1 mg/ml.

9. The process according to any one of the preceding claims, where the cooled composition is comminuted and compressed to the dosage form.

10. A process substantially as hereinbefore described with reference to the examples.

Exhibit 6

FORM 2

The Patents Act, 1970
(39 of 1970)
&
The Patent Rules, 2003
COMPLETE SPECIFICATION
(See section 10 and rule 13)

"SOLID PHARMACEUTICAL DOSAGE FORM"

Abbott Laboratories, a company incorporated in USA having its Registered Office at Dept. 377 Bldg AP6A-1, 100 Abbott Park Road, Abbott Park, IL 60064-6008 (USA).

The following specification particularly describes the invention and the manner in which it is to be performed

Original

339/MUMNP/2006

SOLID PHARMACEUTICAL DOSAGE FORM

The present invention is directed to a solid pharmaceutical dosage form comprising at least one HIV protease inhibitor, and a process for preparing same.

The virus causing acquired immunodeficiency syndrome (AIDS) is known by different names, including T-lymphocyte virus III (HTLV-III) or lymphadenopathy-associated virus (LAV) or AIDS-related virus (ARV) or human immunodeficiency virus (HIV). Up until now, two distinct families have been identified, i. e., HIV-1 and HIV-2.

One of the critical pathways in a retroviral life cycle is the processing of polyprotein precursors by aspartic protease. For instance with the HIV virus the gag-pol protein is processed by HIV protease. The correct processing of the precursor polyproteins by the aspartic protease is required for the assembly of infectious virions, thus making the aspartic protease an attractive target for antiviral therapy. In particular for HIV treatment, the HIV protease is an attractive target.

A measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength and first pass effect. Aqueous solubility is one of the most important of these factors. Unfortunately, HIV protease inhibiting compounds typically are characterized by having poor aqueous solubility.

For a variety of reasons, such as patient compliance and taste masking, a solid dosage form is usually preferred over a liquid dosage form. In most instances however, oral solid dosage forms of a drug provide a lower bioavailability than oral solutions of the drug.

There have been attempts to improve the bioavailability provided by solid dosage forms by forming solid solutions of the drug. The term "solid solution" defines a system in a solid state wherein the drug is molecularly dispersed throughout a matrix such that the system is chemically and physically uniform or homogenous throughout. Solid solutions are preferred physical systems because the components therein readily form liquid solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of the components from a crystalline or microcrystalline solid phase. If, however, the drug absorption in the gastrointestinal tract is slow the drug released from the solid solution may result in a high supersaturation and precipitate in the aqueous fluids of the gastrointestinal tract.

There is a continuing need for the development of improved oral solid dosage forms for HIV protease inhibitors which have suitable oral bioavailability and stability and which do not necessitate high vehicle volumes.

The present invention provides a solid pharmaceutical dosage form comprising a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant. In one embodiment, the pharmaceutically acceptable water-soluble polymer has a glass transition temperature (Tg) of at least about 50 °C.

The term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed evenly throughout the other component or components. For example, the active ingredient or combination of active ingredients is dispersed in a matrix comprised of the pharmaceutically acceptable water-soluble polymer(s) and pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles, typically of less than 1 μm in diameter, of one phase dispersed in another phase. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called a

"solid solution" or a "glassy solution". A glassy solution is a homogeneous, glassy system in which a solute is dissolved in a glassy solvent. Glassy solutions and solid solutions of HIV protease inhibitors are preferred physical systems. These systems do not contain any significant amounts of active ingredients in their crystalline or microcrystalline state, as evidenced by thermal analysis (DSC) or X-ray diffraction analysis (WAXS).

In one embodiment of the present invention, the pharmaceutical dosage form is comprising from about 5 to about 30 % by weight of the total dosage form (preferably from about 10 to about 25 % by weight of the total dosage form) of an HIV protease inhibitor or a combination of HIV protease inhibitors, from about 50 to about 85 % by weight of the total dosage form (preferably from about 60 to about 80 % by weight of the total dosage form) of a water-soluble polymer (or any combination of such polymers), from about 2 to about 20 % by weight of the total dosage form (preferably from about 3 to about 15 % by weight of the total dosage form) of the surfactant (or combination of surfactants), and from about 0 to about 15 % by weight of the total dosage form of additives.

HIV protease inhibiting compounds suitable for use in the present invention include for example, but are not limited thereto:

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3hydroxyhexane (ritonavir);

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]-amino-1,6-diphenylhexane (ABT-378; lopinavir);

N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-tbutylamide;

[1S-[1R-(R-),2S*])-N[1] [3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

amprenavir (VX-478); DMP-323; DMP-450; AG1343 (nelfinavir);

atazanavir (BMS 232,632);

tipranavir;

palinavir;

TMC-114;

RO033-4649;

fosamprenavir (GW433908);

P-1946;

BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or combinations thereof.

In one embodiment, ritonavir (Abbott Laboratories, Abbott Park, IL, USA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention. This and other compounds as well as methods for preparing same are disclosed in U. S. Patent Nos. 5,542,206 and 5,648,497, the disclosures of which are herein incorporated by reference. In a further embodiment, the present invention provides a dosage form wherein said HIV protease inhibitor is ritonavir or a combination of ritonavir and at least one other HIV protease inhibitor, the dosage form showing a dose-adjusted AUC of ritonavir plasma concentration in dogs of at least about 9 μg.h/ml/100 mg.

In another embodiment, lopinavir (Abbott Laboratories, Abbott Park, IL, USA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention. This and other compounds, as well as methods for preparing same, are identified in U. S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference. In a further embodiment, the present invention provides a dosage form wherein said HIV protease inhibitor is lopinavir or a combination of lopinavir and at least one other HIV protease inhibitor, the dosage form showing a dose-adjusted AUC of lopinavir plasma concentration in

dogs of at least about 20 μg.h/ml/100 mg (preferably at least about 22.5 μg.h/ml/100 mg, most preferred at least about 35 μg.h/ml/100 mg).

In yet another embodiment, nelfinavir mesylate (marketed under the tradename Viracept by Agouron Pharmaceuticals, Inc. in La Jolla, CA) is an HIV protease inhibitor which may be formulated into the dosage form of the invention.

The dosage forms of the present invention exhibit a release and absorption behaviour that is characterized by high attainable AUC, high attainable C_{max} (maximum plasma concentration), and low T_{max} (time to reach maximum plasma concentration).

In still another embodiment, the present invention provides a dosage form wherein said HIV protease inhibitor is a combination of ritonavir and lopinavir, the dosage form showing a dose-adjusted AUC of ritonavir plasma concentration in dogs of at least about 9 μg.h/ml/100 mg and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg (preferably at least about 22.5 μg.h/ml/100 mg, most preferred at least about 35 μg.h/ml/100 mg).

The term "AUC" means "Area Under the Curve" and is used in its normal meaning, i. e. as the area under the plasma concentration-time curve from 0 to 24 hours, where the dosage form has been administered orally to dogs (beagle) under non-fasting conditions. "Non-fasting condition" means that the dogs receive a nutritionally balanced daily ration during the pre-test period and the whole test period. The AUC has units of concentration times time. Once the experimental concentration-time points have been determined, the AUC may conveniently be calculated, e.g. by a computer program or by the trapezoidal method. All AUC data herein were dose adjusted to the 100 mg dose level. For the purposes herein, the AUC is determined within a dose range where the AUC increases proportionally with dose. Administration of 50 mg ritonavir or 200 mg lopinavir, respectively, to dogs is considered suitable for determining the AUC values as used herein.

The dosage forms according to the invention are characterized by an excellent stability and, in particular, exhibit high resistance against recrystallization or decomposition of the active ingredient(s). Thus, upon storage for 6 weeks at 40 °C and 75% humidity (e.g., when kept in high density polyethylene (HDPE) bottles without desiccant), the dosage forms according to the present invention usually do not exhibit any sign of crystallinity (as evidenced by DSC or WAXS analysis) and contain at least about 98 % of the initial active ingredient content (as evidenced by HPLC analysis).

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant. In one embodiment, the dosage form is comprising at least one surfactant having an hydrophilic lipophilic balance (HLB) value of from about 4 to about 10, preferably from about 7 to about 9. The HLB system (Fiedler, H.B., Encylopedia of Excipients, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values und hydrophilic substances receiving higher HLB values. Surfactants having an HLB value of from about 4 to about 10 suitable for use in the present invention include for example, but are not limited thereto:

polyoxyethylene alkyl ethers, e.g. polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether; polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether;

polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate;

alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (Lauroglycol®);

sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; or

sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalmitate (Span® 40), or sorbitan stearate, or

mixtures of one or more thereof.

The sorbitan mono fatty acid esters are preferred, with sorbitan mono laurate and sorbitan monopalmitate being particularly preferred.

Besides the surfactant having an HLB value of from about 4 to about 10, the dosage form may comprise additional pharmaceutically acceptable surfactants such as polyoxyethylene castor oil derivates, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethylenglycol 40 hydrogenated castor oil (Cremophor® RH 40) or polyethylenglycol 60 hydrogenated castor oil (Cremophor® RH 60); or block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, Poloxamer® 407 (BASF Wyandotte Corp.); or a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), polyoxyethylene (20) sorbitan monolaurate (Tween® 20).

Where such additional surfactants are used, the surfactant having an HLB value of from about 4 to about 10 generally accounts for at least about 50 % by weight, preferably at least about 60 % by weight, of the total amount of surfactant used.

The water-soluble polymer employed in the present invention has a Tg of at least about 50 °C, preferably at least about 60°C, most preferred from about 80 °C to about 180

°C. Methods for determining Tg values of the organic polymers are described in "Introduction to Physical Polymer Science", 2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992. The Tg value can be calculated as the weighted sum of the Tg – values for homopolymers derived from each of the individual monomers, i.e., that make up the polymer: $Tg = \Sigma W_i X_i$ where W is the weight percent of monomer i in the organic polymer, and X is the Tg value for the homopolymer derived from monomer i. Tg values for the homopolymers may be taken from "Polymer Handbook", 2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by John Wiley & Sons, Inc., 1975.

Water-soluble polymers having a Tg as defined above allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable so that the solid dispersions may be used as dosage forms without further processing or be compacted to tablets with only a small amount of tabletting aids.

The water-soluble polymer comprised in the dosage form is a polymer that preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of about 1 to about 5000 mPa.s. more preferably of about 1 to about 700 mPa.s, and most preferred of about 5 to about 100 mPa.s. Water-soluble polymers suitable for use in the present invention include for example, but are not limited thereto:

homopolymers and copolymers of N-vinyl lactams, escpecially homopolymers and copolymers of N-vinyl pyrrolidone, e.g. polyvinylpyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate,

cellulose esters and cellulose ethers, in particular methylcellulose and ethylcellulose, hydroxyalkylcelluloses, in particular hydroxypropylcellulose, hydroxyalkylalkylcelluloses, in particular hydroxypropylmethylcellulose, cellulose phthalates or succinates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate or hydroxypropylmethylcellulose acetate succinate;

high molecular polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide,

polyacrylates and polymethacrylates such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates),

polyacrylamides,

vinyl acetate polymers such as copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"),

polyvinyl alcohol,

oligo- and polysaccharides such as carrageenans, galactomannans and xanthan gum, or mixtures of one or more thereof..

Of these, homopolymers or copolymers of N-vinyl pyrrolidone, in particular a copolymer of N-vinyl pyrrolidone and vinyl acetate, are preferred. A particularly preferred polymer is a copolymer of about 60 % by weight of the copolymer, N-vinyl pyrrolidone and about 40 % by weight of the copolymer, vinyl acetate.

The dosage forms of the invention may contain at least one conventional additive, such as flow regulators, lubricants, bulking agents (fillers) and disintegrants. In general, the additive is contained in an amount of about 0.01 to about 15 % by weight relative to the weight of the dosage form.

Various methods can be used for manufacturing the solid dosage forms according to the invention. These methods comprise the preparation of a solid solution of the HIV protease inhibitor or the combination of HIV protease inhibitors in a matrix of the water-soluble

polymer and the surfactant, and shaping into the required tablet form. Alternatively, the solid solution product may be subdivided to granules, e.g. by grinding or milling, and the granules may subsequently be compacted to tablets.

Various techniques exist for preparing solid solutions including melt-extrusion, spray-drying and solution-evaporation with melt-extrusion being preferred.

The melt-extrusion process comprises the steps of preparing a homogeneous melt of the HIV protease inhibitor or the combination of HIV protease inhibitors, the water-soluble polymer and the surfactant, and cooling the melt until it solidifies. "Melting" means a transition into a liquid or rubbery state in which it is possible for one component to get embedded homogeneously in the other. Typically, one component will melt and the other components will dissolve in the melt thus forming a solution. Melting usually involves heating above the softening point of the water-soluble polymer. The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. Usually, the melt is homogenized in order to disperse the active ingredients efficiently. Also, it may be convenient first to melt the water-soluble polymer and then to mix in and homogenize the active ingredients.

Usually, the melt temperature is in the range of about 70 to about 250 °C, preferably from about 80 to about 180 °C, most preferred from about 100 to about 140 °C.

The active ingredients can be employed as such or as a solution or dispersion in a suitable solvent such as alcohols, aliphatic hydrocarbons or esters. Another solvent which can be used is liquid carbon dioxide. The solvent is removed, e.g. evaporated, upon preparation of the melt.

Various additives may be included in the melt, for example flow regulators such as colloidal silica; lubricants, fillers, disintegrants, plasticizers, stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

The melting and/or mixing takes place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or else multiscrew extruders, preferably twin screw extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

The melt ranges from pasty to viscous. Shaping of the extrudate conveniently is carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. A broad range of tablet forms can be attained by using rollers with different forms of depressions. Alternatively, the extrudate is cut into pieces, either before (hot-cut) or after solidification (cold-cut).

Optionally, the resulting solid solution product is milled or ground to granules. The granules may then be compacted. Compacting means a process whereby a powder mass comprising the granules is densified under high pressure in order to obtain a compact with low porosity, e.g. a tablet. Compression of the powder mass is usually done in a tablet press, more specifically in a steel die between two moving punches. Where a solid dosage form of the invention comprises a combination of more than one HIV protease inhibitor (or a combination of an HIV protease inhibitor with one or more other active ingredients) it is of course possible to separately prepare solid solution products of the individual active ingredients and to blend the milled or ground products before compacting.

At least one additive selected from flow regulators, disintegrants, bulking agents (fillers) and lubricants is preferably used in compacting the granules. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the granules which are liberated

separate from one another. Suitable disintegrants are crosslinked polymers such as crosslinked polyvinyl pyrrolidone and crosslinked sodium carboxymethylcellulose. Suitable bulking agents (also referred to as "fillers") are selected from lactose, calcium hydrogenphosphate, microcrystalline cellulose (Avicell®), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, polyvinyl alcohol.

Suitable flow regulators are selected from highly dispersed silica (Aerosil®), and animal or vegetable fats or waxes.

A lubricant is preferably used in compacting the granules. Suitable lubricants are selected from polyethylene glycol (e.g., having a Mw of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

Various other additives may be used, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

Dosage forms according to the invention may be provided as dosage forms consisting of several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer. Multilayer forms have the advantage that two active ingredients which are incompatible with one another can be processed, or that the release characteristics of the active ingredient(s) can be controlled. For example, it is possible to provide an initial dose by including an active ingredient in one of the outer layers, and a maintenance dose by including the active ingredient in the inner layer(s). Multilayer tablets types may be produced by compressing two or more layers of granules. Alternatively, multilayer dosage forms may be produced by a process known as "coextrusion". In essence, the process comprises preperation of at least two different melt compositions as explained above, and passing these molten compositions into a joint coextrusion die. The shape of the coextrusion die depends on the

required drug form. For example, dies with a plain die gap, called slot dies, and dies with an annular slit are suitable.

In order to faciliate the intake of such a dosage form by a mammal, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. If desired, the film-coat may be an enteric coat. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. a Tween® type, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. The film coat usually accounts for less than about 5 % by weight of the dosage form.

The exact dose and frequency of administration depends on the particular condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art.

Exemplary compositions of the present invention for combined administration of ritonavir/ lopinavir are shown below in Table 1, and the values are % by weight.

Table 1.

Ritonavir	18	4.17	4.17
Lopinavir	– 22.5 in total	16.67	16.67

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40)	65 – 75	71.16	70.12
Span 20 (Sorbitan monolaurate)	4 – 10	7.0	5.02
Cremophor RH40 (polyoxyethyleneglycerol oxystearate)	0 – 10	-	3.02
Colloidal silica	0 - 3	1.0	1.0

Exemplary compositions of the invention for administration of ritonavir only are shown below in Table 2. The values are % by weight.

Ritonavir	18 – 22.5	20.8
Lopinavir	-	-
Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40)	60 – 75	63.15
Span 20 (Sorbitan monolaurate)	5 –15 in total	-
Cremophor RH40 (polyoxyethyleneglycerol oxystearate)		10.00
PEG 6000	0 – 8	5.00
Colloidal silica	0 – 3	1.04

The above compositions are processed by melt extrusion. The resulting extrudates may be used as such or milled and compressed into tablets, preferably by the use of suitable tabletting aids such as sodium stearyl fumarate, colloidal silica, lactose, isomalt, calcium silicate, and magnesium stearate, cellulose or calcium hydrogenphosphate.

The following examples will serve to further illustrate the invention without limiting it.

Protocol for the oral bioavailability studies

Dogs (beagle dogs, mixed sexes, weighing approximately 10 kg) received a balanced diet with 27 % fat and were permitted water ad libitum. Each dog received a 100 μg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. A single dose corresponding to about 200 mg lopinavir, about 50 mg ritonavir, or about 200 mg lopinavir and about 50 mg ritonavir, respectively, was administered to each dog. The dose was followed by approximately 10 milliliters of water. Blood samples were obtained from each animal prior to dosing and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after drug administration. The plasma was separated from the red cells by centrifugation and frozen (-30 °C) until analysis. Concentrations of HIV protease inhibitors were determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The area under the curve (AUC) was calculated by the trapezoidal method over the time course of the study. Each dosage form was evaluated in a group containing 8 dogs; the values reported are averages for each group of dogs.

Comparative example

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 78.17 parts by weight) was mixed with ritonavir (4.16 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.0 part by weight). The powdery mixture was then fed into a twin-screw

extruder (screw diameter 18 mm) at a rate of 2.0 kg/h and a melt temperature of 133 °C. The clear, fully transparent melt was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1080 mg were thus obtained. DSC and WAXS analysis did not reveal any evidence of crystalline drug material in the formulation.

The dose-adjusted AUC in dogs was 0.52 µg.h/ml/100 mg for ritonavir and 4.54 µg.h/ml/100 mg for lopinavir. This example shows that solid solutions of HIV protease inhibitors without added surfactant yield a very poor bioavailabilty.

Example 1

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 68.17 parts by weight) was blended with Cremophor RH40 (polyoxyethyleneglycerol oxystearate; 10.00 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (4.17 parts by weight), lopinavir (16.67 parts by weight) and colloidal silica (1.00 parts by weight). The powdery mixture was then fed into a Leistritz Micro 18 twin-screw extruder at a rate of 2.3 kg/h and a melt temperature of 126 °C. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material (86.49 parts by weight) was blended in a bin blender with lactose monohydrate (6.00 parts by weight), crosslinked PVP (6.00 parts by weight), colloidal silica (1.00 part by weight) and magnesium stearate (0.51 parts by weight). The powdery blend was compressed to tablets of 1378.0 mg on a Fette E 1 single punch tablet press. The tablets were then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry, available from Colorcon) at a temperature of 60 °C.

The dose-adjusted AUC in dogs was 0.60 µg.h/ml/100 mg for ritonavir and 7.43 µg.h/ml/100 mg for lopinavir. This example shows that inclusion of a surfactant into solid solutions of HIV protease inhibitors improves the bioavailabilty attained.

Example 2

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 853.8 parts by weight) was blended with Span 20 (Sorbitan monolaurate; 83.9 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight), lopinavir (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1120 mg were thus obtained.

The dose-adjusted AUC in dogs was 10.88 µg.h/ml/100 mg for ritonavir and 51.2 µg.h/ml/100 mg for lopinavir. This example shows that inclusion of a surfactant having an HLB of 4 to 10 into solid solutions of HIV protease inhibitors markedly improves the bioavailability attained.

Example 3

Example 2 was repeated, however, the extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled to a particle size of about 250 µm, using a high impact universal mill. The milled material was blended in a bin blender with sodium stearyl fumarate (12.3 parts by weight) and colloidal silica (8.0 parts by weight) for 20 min. The powdery blend was compressed on a rotary tablet machine with 3 punches (6500 tablets/h). The tablets were then film-coated in a coating pan by spraying an aqueous dispersion for film coating (Opadry) at a temperature of 60 °C.

The dose-adjusted AUC in dogs was 14.24 µg.h/ml/100 mg for ritonavir and 52.2 µg.h/ml/100 mg for lopinavir.

Example 4

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 841.3 parts by weight) was blended with Cremophor RH40 (polyoxyethyleneglycerol oxystearate; 36.2 parts by weight), Span 20 (Sorbitan monolaurate; 60.2 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight), lopinavir (200 parts by weight) and colloidal silica (12 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 114 °C. The extrudate was fed to a calender with two counter-rotating rollers having mutually matching cavities on their surfaces. Tablets of 1120 mg were thus obtained.

The dose-adjusted AUC in dogs was 10.96 µg.h/ml/100 mg for ritonavir and 46.5 µg.h/ml/100 mg for lopinavir. This example shows that a combination of a surfactant having an HLB of 4 to 10 and a further surfactant can successfully be used.

Example 5

Example 4 was repeated, however, the extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled to a particle size of about 250 µm, using a high impact universal mill. The milled material was blended in a bin blender with sodium stearylfumarate (13.9 parts by weight), colloidal silica (7.0 parts by weight), isomalt DC100 (159.4 parts by weight) and calcium silicate (7.0 parts by weight) for 20 min. The blend was compressed and film-coated as described in example 1.

The dose-adjusted AUC in dogs was 10.38 µg.h/ml/100 mg for ritonavir and 42.7 µg.h/ml/100 mg for lopinavir.

Example 6

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 683.3 parts by weight) was blended with Span 40 (sorbitan monopalmitate; 67.2 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with lopinavir (200 parts by

weight) and colloidal silica (9.6 parts by weight). The powdery mixture was then fed into a twin-screw extruder (screw diameter 18 mm) at a rate of 2.1 kg/h and a melt temperature of 119 °C. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material was blended in a bin blender with sodium stearylfumarate (7.9 parts by weight), colloidal silica (11.3 parts by weight), isomalt DC100 (129.1 parts by weight) and sodium dodecyl sulfate (15.6 parts by weight). The blend was compressed and film-coated as described in example 1.

Tablets corresponding to 200 mg lopinavir were coadministered to dogs together with 50 mg ritonavir. The dose-adjusted AUC of lopinavir was 38.8 μg.h/ml/100 mg.

Example 7

Copovidone (N-vinyl pyrrolidone/vinyl acetate copolymer 60:40; 151.5 parts by weight) was blended with Cremophor RH40 (24 parts by weight) and PEG 6000 (12 parts by weight) in a Diosna high-shear mixer. The resulting granules were mixed with ritonavir (50 parts by weight) and colloidal silica (2.4 parts by weight). The powdery mixture was then fed into a twin-screw extruder and was melt-extruded. The extrudate was cut into pieces and allowed to solidify. The extruded pieces were milled using a high impact universal mill. The milled material was blended in a bin blender with colloidal silica (1.4 parts by weight), isomalt DC100 (31.9 parts by weight) and calcium silicate (4.2 parts by weight). The blend was compressed and film-coated as described in example 1.

The dose-adjusted AUC in dogs was 9.98 μg.h/ml/100 mg.

We claim:

1. A solid pharmaceutical dosage form which comprises a solid dispersion of at least one HIV protease inhibitor and at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, said pharmaceutically acceptable water-soluble polymer having a Tg of at least about 50 °C.

2. The dosage form of claim 1 comprising a glassy solution or solid solution of said HIV protease inhibitor.

3. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant has an HLB value of from about 4 to about 10.

4. The dosage form of claim 1, wherein said pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about10 and at least one further pharmaceutically acceptable surfactant.

5. The dosage form of Claim 1 wherein said pharmaceutically acceptable surfactant is a sorbitan fatty acid ester.

6. The dosage form of Claim 1 which comprises, relative to the weight of the dosage form, from about 5 to about 30 % by weight of said HIV protease inhibitor, from about 50 to about 85 % by weight of said water-soluble polymer, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.

7. The dosage form of claim 1, wherein said HIV protease inhibitor is selected from the group consisting of: 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir); (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir); N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(l-(4-(3-

pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4t-butylamide;
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;
[1S-[1R-(R-),2S*])-N'-[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;
amprenavir (VX-478); DMP-323; DMP-450; AG1343 (nelfinavir);
atazanavir (BMS 232,632)
tipranavir
palinavir
TMC-114
RO033-4649
fosamprenavir (GW433908)
P-1946,
BMS 186,318; SC-55389a; BILA 1096 BS; U-140690,
or combinations thereof.

8. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

9. The dosage form of Claim 8 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least about 9 μg.h/ml/100 mg.

10. The dosage form of Claim 1 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)-amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl]amino-1,6-diphenylhexane (lopinavir).

11. The dosage form of claim 10 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg.

12. The dosage form of claim 1 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl] amino-1,6-diphenylhexane (lopinavir).

13. The dosage form of claim 12 which shows a dose-adjusted AUC, in dogs under non-fasting conditions, of ritonavir plasma concentration of at least 9 about μg.h/ml/100 mg and a dose-adjusted AUC of lopinavir plasma concentration of at least about 20 μg.h/ml/100 mg.

14. The solid dosage form of Claim 1 wherein said water-soluble polymer has a Tg of from about 80 to about 180 °C.

15. The solid dosage form of Claim 1 wherein said water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

16. The solid dosage form of Claim 1 wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

17. The solid dosage form of Claim 1 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

18. The solid dosage form of Claim 1 which contains, upon storage for about 6 weeks at about 40 °C and about 75% humidity, at least about 98 % of the initial content of HIV protease inhibitor.

19. A method of preparing a solid dosage form of claim 1 which comprises:
    i. preparing a homogeneous melt of said HIV protease inhibitor(s), said water-soluble polymer(s) and said surfactant(s), and
    ii. allowing the melt to solidify to obtain a solid dispersion product.

20. The method of claim 19 additionally comprising grinding said solid dispersion product and compressing said solid dispersion product into a tablet.

21. A method of treating an HIV infection comprising administering the solid dosage form of claim 1 to a mammal in need of such treatment.

22. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

a homopolymer of N-vinyl pyrrolidone; and

a sorbitan fatty acid ester.

23. The solid dosage form of Claim 22 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

24. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir);

a copolymer of N-vinyl pyrrolidone; and

a sorbitan fatty acid ester.

25. The solid dosage form of Claim 24 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

26. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir);

a copolymer of N-vinyl pyrrolidone and vinyl acetate; and

a sorbitan fatty acid ester.

27. The solid dosage form of Claim 26 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

28. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) from about 5 % to about 30 % by weight of the dosage form;

a homopolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

29. The solid dosage form of Claim 28 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

30. The solid dosage form of claim 29 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

31. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir) from about 5 % to about 30 % by weight of the dosage form;

a copolymer of N-vinyl pyrrolidone from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

32. The solid dosage form of Claim 31 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

33. The solid dosage form of claim 32 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight.

34. A solid pharmaceutical dosage form comprising,

(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(l-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir) present in an amount from about 5 % to about 30 % by weight of the dosage form;

a copolymer of N-vinyl pyrrolidone and vinyl acetate from about 50 % to about 85 % by weight of the dosage form; and

a sorbitan fatty acid ester from about 2 % to about 20 % by weight of the dosage form.

35. The solid dosage form of Claim 34 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

36. The solid dosage form of claim 35 wherein the at least one additive is present in an amount from about 0 % to about 15 % by weight of the dosage form.

37. A method of treating an HIV infection comprising administering the solid dosage form of any one of claims 22-36 to a mammal in need of such treatment.

1-3-06

(C. M. MANIAR)

Exhibit 7

KALETRA®

(lopinavir/ritonavir) tablets
(lopinavir/ritonavir) oral solution

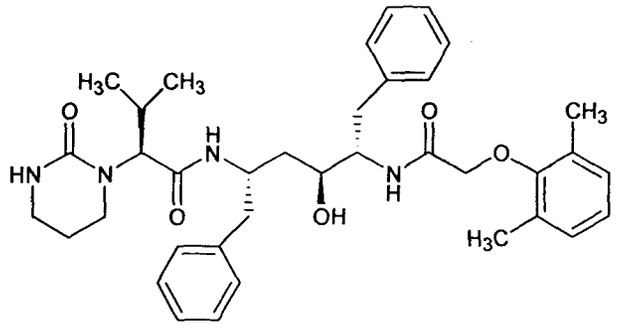
R_x only

Tear at perforation to dispense patient information.

DESCRIPTION

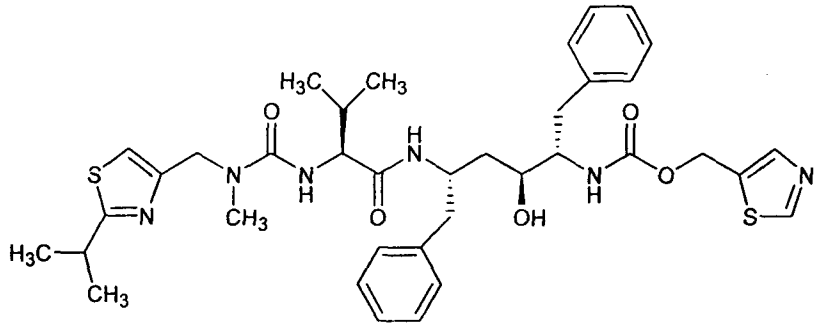
KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is

$C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

KALETRA film-coated tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene 3350, yellow ferric oxide E172, and polysorbate 80.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA oral solution contains 42.4% alcohol (v/v).

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral Activity *In Vitro*

The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006-0.017 μg/mL, 1 μg/mL = 1.6 μM) and ranged from 4-11 nM (0.003-0.007 μg/mL) against several HIV-1 clinical isolates (n = 6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65-289 nM (0.04-0.18 μg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to KALETRA in antiretroviral treatment naïve patients has not yet been characterized. In a Phase III study of 653 antiretroviral treatment naïve patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV > 400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. No evidence of resistance to KALETRA was observed in 37 evaluable KALETRA-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable

nelfinavir-treated patients. The selection of resistance to KALETRA in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to KALETRA has been noted to emerge in patients treated with other protease inhibitors prior to KALETRA therapy. In Phase II studies of 227 antiretroviral treatment naïve and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (> 400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. The assessment of these mutational patterns is under study.

Cross-resistance – Preclinical Studies

Varying degrees of cross-resistance have been observed among HIV protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed > 4-fold reduced susceptibility to nelfinavir (n = 13) and saquinavir (n = 4), displayed < 4-fold reduced susceptibility to lopinavir. Isolates with > 4-fold reduced susceptibility to indinavir (n = 16) and ritonavir (n = 3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more

protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies – Antiviral Activity of KALETRA in Patients with Previous Protease Inhibitor Therapies

The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naïve patients with HIV RNA > 1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). In this study, patients were initially randomized to receive one of two doses of KALETRA in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC_{50} values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the wild-type EC_{50}. Fifty-five percent (31/56) of these baseline isolates displayed a > 4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold. Table 1 shows the 48 week virologic response (HIV RNA < 400 and < 50 copies) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in the study (957) described above. Because this was a select patient population and the sample size was small, the data depicted in Table 1 do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically significant breakpoints for KALETRA.

Table 1. HIV RNA Response at Week 48 by Baseline KALETRA Susceptibility and by Number of Protease Inhibitor-associated Mutations[1]

Lopinavir susceptibility[2] at baseline	HIV RNA < 400 copies/mL (%)	HIV RNA < 50 copies/mL (%)
< 10 fold	25/27 (93%)	22/27 (81%)
> 10 and < 40 fold	11/15 (73%)	9/15 (60%)
≥ 40 fold	2/8 (25%)	2/8 (25%)
Number of protease inhibitor mutations at baseline		
Up to 5	21/23 (91%)[3]	19/23 (83%)
> 5	17/27 (63%)	14/27 (52%)

1 *Lopinavir susceptibility was determined by recombinant phenotypic technology performed by* Virologic; genotype also performed by Virologic.

2 *Fold change in susceptibility from wild type.*

3 Thirteen of the 23 patient isolates contained PI mutations at positions 82, 84, and/or 90.

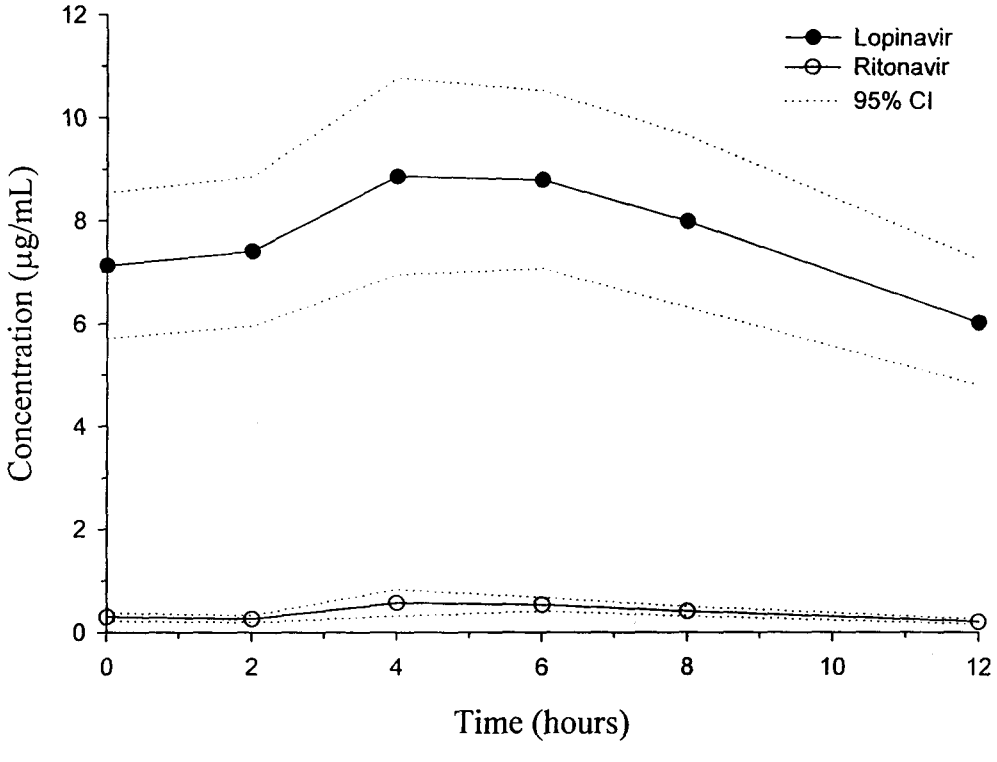
There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA 400/100 mg twice-daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice-daily. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg twice-daily with food for 3 weeks from a pharmacokinetic study in HIV-infected adult subjects (n = 19).

Figure 1. Mean Steady-state Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 19)



Absorption

In a pharmacokinetic study in HIV-positive subjects (n = 19), multiple dosing with 400/100 mg KALETRA twice-daily with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the

morning dose was 7.1 ± 2.9 μg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 μg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 μg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg KALETRA tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability.

Effects of Food on Oral Absorption

KALETRA tablets

No clinically significant changes in C_{max} and AUC were observed following administration of Kaletra tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA tablets with a moderate fat meal (500 – 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of KALETRA tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9%, but not C_{max}. Therefore, Kaletra tablets may be taken with or without food.

KALETRA oral solution

Relative to fasting, administration of KALETRA oral solution with a moderate fat meal (500 – 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 80 and 54%, respectively. Relative to fasting, administration of KALETRA oral solution with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by

130% and 56%, respectively. To enhance bioavailability and minimize pharmacokinetic variability KALETRA oral solution should be taken with food.

Distribution

At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg KALETRA twice-daily, and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 ± 5.75 L/hr (mean ± SD, n = 19).

Once-Daily Dosing

The pharmacokinetics of once-daily KALETRA have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. KALETRA 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once-daily regimen. Multiple dosing of 800/200 mg KALETRA once-daily for 4 weeks with food (n = 24) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 11.8 ± 3.7 μg/mL, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 3.2 ± 2.1 μg/mL and minimum concentration within a dosing interval was 1.7 ± 1.6 μg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 μg•h/mL.

Special Populations

Gender, Race and Age

Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pediatric Patients

The pharmacokinetics of KALETRA oral solution 300/75 mg/m^2 twice-daily and 230/57.5 mg/m^2 twice-daily have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 twice-daily regimen without nevirapine and the 300/75 mg/m^2 twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine). KALETRA once-daily has not been evaluated in pediatric patients.

The mean steady-state lopinavir AUC, C_{max}, and C_{min} were 72.6 ± 31.1 μg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 μg/mL, respectively after KALETRA oral solution 230/57.5 mg/m^2 twice-daily without nevirapine (n = 12), and were 85.8 ± 36.9 μg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 μg/mL, respectively, after 300/75 mg/m^2 twice-daily with nevirapine (n

= 12). The nevirapine regimen was 7 mg/kg twice-daily (6 months to 8 years) or 4 mg/kg twice-daily (> 8 years).

Renal Insufficiency

Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment

Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of KALETRA 400/100 mg twice-daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment (n = 12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-infected subjects with normal hepatic function (n = 12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Caution should be exercised when administering KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment (see **PRECAUTIONS**).

Drug-drug Interactions

See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS – Drug Interactions**.

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS**).

KALETRA does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 2 (effect of other drugs on lopinavir) and Table 3 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 10 in **PRECAUTIONS**.

Table 2. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug

(See PRECAUTIONS – Table 10 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with Co-administered drug-/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	750 BID, 10 d	400/100 capsule BID, 21 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 QD, 4 d	400/100 capsule BID,	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)

		14 d				
Efavirenz[1]	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 QHS, 9 d	600/150 tablet BID, 10 d with efavirenz 600 mg QHS compared to 400/100 BID alone	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Fosamprenavir[2]	700 BID plus ritonavir 100 BID, 14 d	400/100 capsule BID, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BID, 10 d	400/100 capsule BID, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BID, steady-state (> 1 yr)[3]	400/100 capsule BID, steady-state	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk[4]	(> 1 yr) 300/75 mg/m^2 oral solution BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 capsule BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)

Rifampin	600 QD, 10 d	400/100 capsule BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 QD, 14 d	800/200 capsule BID, 9 d[5]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 QD, 14 d	400/400 capsule BID, 9 d[6]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of KALETRA and rifampin is not recommended. (See **PRECAUTIONS** – Table 9 and Table 10)	
Ritonavir[3]	100 BID, 3-4 wk	400/100 capsule BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir[7]	300 mg QD, 14 d	400/100 capsule BID, 14 d	24	NC†	NC†	NC†

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

1 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

2 Data extracted from the fosamprenavir package insert.

3 Study conducted in HIV-positive adult subjects.

4 Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.

5 Titrated to 800/200 BID as 533/133 BID x 1 d, 667/167 BID x 1 d, then 800/200 BID x 7 d, compared to 400/100 BID x 10 days alone.

6 Titrated to 400/400 BID as 400/200 BID x 1 d, 400/300 BID x 1 d, then 400/400 BID x 7 d, compared to 400/100 BID x 10 days alone.

7 Data extracted from the tenofovir package insert.

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

† NC = No change.

Table 3. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA

(See PRECAUTIONS – Table 10 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	750 BID, 10 d combo vs. 1200 BID, 14 d alone	400/100 capsule BID, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Desipramine[2]	100 single dose	400/100 capsule BID, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A
Efavirenz	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Fosamprenavir[3]	700 BID plus ritonavir 100 BID, 14 d	400/100 capsule BID, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[1]	600 BID, 10 d combo nonfasting vs. 800 TID, 5 d alone fasting	400/100 capsule BID, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 capsule BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nelfinavir[1]	1000 BID, 10 d combo vs.	400/100 capsule BID,	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)

M8 metabolite	1250 BID, 14 d alone	21 d		2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 capsule BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 QD, 10 d; combo vs. 300 QD, 10 d; alone	400/100 capsule BID, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-*O*-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-*O*-desacetyl rifabutin[4]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Tenofovir[5]	300 mg QD, 14 d	400/100 capsule BID, 14 d	24	NC†	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

1 Ratio of parameters for amprenavir, indinavir, and nelfinavir, are not normalized for dose.

2 Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

3 Data extracted from the fosamprenavir package insert.

4 Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.

5 Data extracted from the tenofovir package insert.

* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.

N/A = Not available.

† NC = No change.

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 144-204 weeks duration.

Once-daily administration of KALETRA is not recommended in therapy-experienced patients.

When initiating treatment with KALETRA in therapy-naïve patients, it should be noted that the incidence of diarrhea was greater for KALETRA capsules once-daily compared to KALETRA capsules twice-daily in Study 418 (57% vs. 35% - events of all grades and probably or possibly related to drug; 16% vs. 5% - events of at least moderate severity and probably or possibly related to drug) (see **CLINICAL PHARMACOLOGY**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**).

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA twice-daily + stavudine + lamivudine compared to nelfinavir three-times-daily + stavudine + lamivudine

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg twice-daily) plus stavudine and lamivudine versus nelfinavir (750 mg three-times-daily) plus stavudine and lamivudine in 653 antiretroviral treatment naïve patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD_4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 2.6 to 6.8 log_{10} copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 4.

Table 4. Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	KALETRA+d4T+3TC (N = 326)	Nelfinavir+d4T+3TC (N = 327)
Responder[1]	75%	62%
Virologic failure[2]	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons[3]	10%	8%

1 Patients achieved and maintained confirmed HIV RNA < 400 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through Week 48, including patients who discontinued subsequent to virologic failure, was 17% in the KALETRA arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA < 400 copies/mL (75% vs. 62%, respectively) and HIV RNA < 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in Table 5.

Table 5. Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA +d4T+3TC			Nelfinavir +d4T+3TC		
	< 400 copies/mL[1]	< 50 copies/mL[2]	n	< 400 copies/mL[1]	< 50 copies/mL[2]	n
< 30,000	74%	71%	82	79%	72%	87
≥ 30,000 to < 100,000	81%	73%	79	67%	54%	79
≥ 100,000 to < 250,000	75%	64%	83	60%	47%	72
≥ 250,000	72%	60%	82	44%	33%	89

1 Patients achieved and maintained confirmed HIV RNA < 400 copies/mL through Week 48.

2 Patients achieved HIV RNA < 50 copies/mL at Week 48.

Through 48 weeks of therapy, the mean increase from baseline in CD_4 cell count was 207 cells/mm^3 for the KALETRA arm and 195 cells/mm^3 for the nelfinavir arm.

Study 418: KALETRA once-daily + tenofovir DF + emtricitabine compared to KALETRA twice-daily + tenofovir DF + emtricitabine

Study 418 was an ongoing, randomized, open-label, multicenter trial comparing treatment with KALETRA 800/200 mg once-daily plus tenofovir DF and emtricitabine versus KALETRA 400/100 mg twice-daily plus tenofovir DF and emtricitabine in 190 antiretroviral treatment naïve patients. Patients had a mean age of 39 years (range: 19 to 75), 54% were Caucasian, and 78% were male. Mean baseline CD_4 cell count was 260 cells/mm^3 (range: 3 to 1006 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range: 2.6 to 6.4 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 6.

Table 6. Outcomes of Randomized Treatment Through Week 48 (Study 418)

Outcome	KALETRA QD + TDF + FTC (n = 115)	KALETRA BID + TDF + FTC (n = 75)
Responder[1]	71%	65%
Virologic failure[2]	10%	9%
Rebound	6%	5%
Never suppressed through Week 48	3%	4%
Death	0%	1%
Discontinued due to an adverse event	12%	7%
Discontinued for other reasons[3]	7%	17%

1 Patients achieved and maintained confirmed HIV RNA < 50 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Through 48 weeks of therapy, 71% in the KALETRA once-daily arm and 65% in the KALETRA twice-daily arm achieved and maintained HIV RNA < 50 copies/mL (95%

confidence interval for the difference, -7.6% to 19.5%). Mean CD_4 cell count increases at Week 48 were 185 cells/mm^3 for the KALETRA once-daily arm and 196 cells/mm^3 for the KALETRA twice-daily arm.

Patients with Prior Antiretroviral Therapy

Study 888: KALETRA twice-daily + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 is a randomized, open-label, multicenter trial comparing treatment with KALETRA (400/100 mg twice-daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD_4 cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 7.

Table 7. Outcomes of Randomized Treatment Through Week 48 (Study 888)

Outcome	KALETRA + nevirapine + NRTIs (n = 148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n = 140)
Responder[1]	57%	33%
Virologic failure[2]	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons[3]	14%	13%

1 Patients achieved and maintained confirmed HIV RNA < 400 copies/mL through Week 48.
2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.
3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the investigator-selected protease inhibitor(s) arm with HIV RNA < 400 copies/mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in CD_4 cell count was 111 cells/mm^3 for the KALETRA arm and 112 cells/mm^3 for the investigator-selected protease inhibitor(s) arm.

Other Studies

Study 720: KALETRA twice-daily + stavudine + lamivudine

Study 765: KALETRA twice-daily + nevirapine + NRTIs

Study 720 (patients without prior antiretroviral therapy) and study 765 (patients with prior protease inhibitor therapy) are randomized, blinded, multi-center trials evaluating treatment with KALETRA at up to three dose levels (200/100 mg twice-daily [720 only], 400/100 mg twice-daily, and 400/200 mg twice-daily). In Study 720, all patients

switched to 400/100 mg twice-daily between Weeks 48-72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD_4 cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/mm^3, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) log_{10} copies/mL, respectively.

Through 204 weeks of treatment in study 720, the proportion of patients with HIV RNA < 400 (< 50) copies/mL was 71% (70%) [n = 100], and the corresponding mean increase in CD_4 cell count was 440 cells/mm^3. Twenty-eight patients (28%) discontinued the study, including 9 (9%) discontinuations due to adverse events and 1 (1%) death. Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in CD_4 cell count was 212 cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

CONTRAINDICATIONS

KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 8.

Table 8. Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/Hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about medicines that should NOT be taken with KALETRA.
This statement is included on the product's bottle label.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics** – *Drug-drug Interactions*, **CONTRAINDICATIONS – Table 8: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS – Table 9: Drugs That Should Not Be Co-administered With KALETRA** and **Table 10: Established and Other Potentially Significant Drug Interactions).**

Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS – Drug Interactions** and the complete prescribing information for sildenafil, tadalafil, and vardenafil.)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the

CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

Concomitant use of KALETRA and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of KALETRA and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see **PRECAUTIONS – Drug Interactions**).

Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS – Lipid Elevations**). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased (see **CLINICAL PHARMACOLOGY** – *Hepatic Impairment).* Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be

considered in these patients, especially during the first several months of KALETRA treatment.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see **Microbiology**).

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS – Table13 and Table 14**). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS – Table 10: Established and Other**

Potentially Significant Drug Interactions for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis) which may necessitate further evaluation and treatment.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: **"ALERT: Find out about medicines that should NOT be taken with KALETRA."** A Patient Package Insert (PPI) for KALETRA is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

KALETRA tablets can be taken at the same time as didanosine without food. Patients taking didanosine should take didanosine one hour before or two hours after KALETRA oral solution.

Patients receiving sildenafil, tadalafil, or vardenafil should be advised that they may be at an increased risk of associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA tablets may be taken with or without food. KALETRA oral solution should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 10. Established and Other Potentially Significant Drug Interactions**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism

appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with KALETRA.

KALETRA does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 10. Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with KALETRA are included in **Table 9. Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 9. Drugs That Should Not Be Co-administered With KALETRA

Drug Class: Drug Name	Clinical Comment
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents. (See Table 9 for further details).
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 10. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

See **CLINICAL PHARMACOLOGY** for Magnitude of Interaction – Table 2 and Table 3

Concomitant Drug Class: Drug Name	**Effect on Concentration of lopinavir or Concomitant Drug**	**Clinical Comment**
	HIV-Antiviral Agents	
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ Lopinavir	KALETRA should not be administered once-daily in combination with efavirenz or nevirapine. (see **DOSAGE AND ADMINISTRATION**.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		KALETRA tablets can be administered simultaneously with didanosine without food. For KALETRA oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ Tenofovir	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for tenofovir-associated adverse events.
HIV-Protease Inhibitor: amprenavir*	↑ Amprenavir (amprenavir 750 mg BID + KALETRA produces ↑ AUC, similar C_{max}, ↑ C_{min}, relative to amprenavir 1200 mg BID ↓ Lopinavir	KALETRA should not be administered once-daily in combination with amprenavir. (see **DOSAGE AND ADMINISTRATION**).
HIV-Protease Inhibitor: Fosamprenavir/ritonavir	↓ Amprenavir ↓ Lopinavir	An increased rate of adverse events has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.

HIV-Protease Inhibitor: indinavir*	↑ Indinavir (indinavir 600 mg BID + KALETRA produces similar AUC, ↓ C_{max}, ↑ C_{min} relative to indinavir 800 mg TID	Decrease indinavir dose to 600 mg BID, when co-administered with KALETRA 400/100 mg BID (see **CLINICAL PHARMACOLOGY** – Table 3). KALETRA once-daily has not been studied in combination with indinavir.
HIV-Protease Inhibitor: nelfinavir*	↑ Nelfinavir (nelfinavir 1000 mg BID + KALETRA produces similar AUC, similar C_{max}, ↑ C_{min} relative to nelfinavir 1250 mg BID) ↑ M8 metabolite of nelfinavir ↓ Lopinavir	KALETRA should not be administered once-daily in combination with nelfinavir. (see **DOSAGE AND ADMINISTRATION**).
HIV-Protease Inhibitor: saquinavir*	↑ Saquinavir	The saquinavir dose is 1000 mg BID, when co-administered with KALETRA 400/100 mg BID. KALETRA once-daily has not been studied in combination with saquinavir.
HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. KALETRA should not be administered once-daily in combination with carbamazepine, phenobarbital, or phenytoin.

Antidepressant: trazodone	↑ Trazodone	Concomitant use of trazodone and KALETRA may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole, voriconazole	↑ Ketoconazole ↑ Itraconazole Voriconazole effect is unknown.	High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole with KALETRA has not been studied. However, administration of voriconazole with ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%. The effect of lower ritonavir doses on voriconazole is not known at this time. Until data are available, voriconazole should not be administered to patients receiving KALETRA.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.

Antimycobacterial: Rifampin	↓ Lopinavir	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg QD, with KALETRA 800/200 mg BID or KALETRA 400/100 mg + ritonavir 300 mg BID. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a ≥ grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone. (See **CLINICAL PHARMACOLOGY** for magnitude of interaction – Table 2).
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Disulfiram/metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*	↑ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.

Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Inhaled Steroid: fluticasone	↑ Fluticasone	Concomitant use of fluticasone propionate and KALETRA may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadministration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect (see **WARNINGS**)
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.

* See **CLINICAL PHARMACOLOGY** for Magnitude of Interaction – Table 2 and Table 3.

Other Drugs

Drug interaction studies reveal no clinically significant interaction between KALETRA and desipramine (CYP2D6 probe), pravastatin, stavudine or lamivudine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure (based on $AUC_{0\text{-}24hr}$ measurement) at the recommended dose of 400/100 mg KALETRA twice-daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA twice-daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo*

assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily).

Pregnancy

Pregnancy Category C

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve (44%) and experienced (56%)

pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naïve patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD_4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA < 400 copies/mL was 80% for antiretroviral naïve patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD_4 cell count was 404 cells/mm^3 for antiretroviral naïve and 284 cells/mm^3 for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naïve patient prematurely discontinued secondary to an adverse event attributed to KALETRA, while one antiretroviral experienced patient prematurely discontinued secondary to an HIV-related event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 oral solution twice-daily regimen without nevirapine and the 300/75 mg/m^2 oral solution twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine). KALETRA once-daily has not been evaluated in pediatric patients.

ADVERSE REACTIONS

Adults

Treatment-Emergent Adverse Events

KALETRA has been studied in 891 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 5.8% in KALETRA-treated and 4.9% in nelfinavir-treated patients in Study 863. The incidence of diarrhea was greater for KALETRA capsules once-daily compared to KALETRA capsules twice-daily in Study 418 (see Table 11 and **INDICATIONS AND USAGE**).

Treatment-Emergent clinical adverse events of moderate or severe intensity in ≥ 2% of patients treated with combination therapy for up to 48 weeks (Phase III) and for up to 204 weeks (Phase I/II) are presented in Table 11. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS.**

Table 11. Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

	Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (204 Weeks)
	KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA 800/200 mg QD + TDF + FTC (N=115)	KALETRA 400/100 mg BID + TDF + FTC (N=75)	KALETRA BID[2] + d4T + 3TC (N=100)
Body as a Whole					
Abdominal Pain	4%	3%	3%	3%	10%
Asthenia	4%	3%	0%	0%	9%
Headache	2%	2%	3%	3%	7%
Cardiovascular System					
Vein distended	0%	0%	0%	0%	2%
Digestive System					
Anorexia	1%	<1%	<1%	1%	2%
Diarrhea	16%	17%	16%	5%	27%
Dyspepsia	2%	<1%	0%	1%	5%
Flatulence	2%	1%	2%	1%	4%
Nausea	7%	5%	9%	8%	16%
Vomiting	2%	2%	3%	4%	6%
Metabolic and Nutrition					
Weight loss	1%	<1%	0%	0%	2%
Musculoskeletal					
Myalgia	1%	1%	0%	0%	2%
Nervous System					
Depression	1%	2%	1%	0%	0%
Insomnia	2%	1%	0%	0%	2%
Libido decreased	<1%	<1%	0%	1%	2%
Paresthesia	1%	1%	0%	0%	2%
Respiratory					
Bronchitis	0%	0%	0%	0%	2%
Skin and Appendages					
Rash	1%	2%	1%	0%	4%
Urogenital					

Hypogonadism male	0%	0%	0%	0%	2%
Amenorrhea	0%	0%	4.5%	0%	0%

[1] Includes adverse events of possible, probable, or unknown relationship to study drug.

[2] Includes adverse event data from dose group I (200/100 mg BID [N=16] and 400/100 mg BID [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

Table 12. Percentage of Patients with Selected Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥2% of Adult Protease Inhibitor-Experienced Patients

	Study 888 (48 Weeks)		Study 957[2] and Study 765[3] (84-144 Weeks)
	KALETRA 400/100 mg BID + NVP + NRTIs (N=148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)	KALETRA BID + NNRTI + NRTIs (N=127)
Body as a Whole			
Abdominal Pain	2%	2%	4%
Asthenia	3%	6%	9%
Chills	2%	0%	0%
Fever	2%	1%	2%
Headache	2%	3%	2%
Cardiovascular			
Hypertension	0%	0%	2%
Digestive System			
Anorexia	1%	3%	0%
Diarrhea	7%	9%	23%
Dyspepsia	1%	1%	2%
Dysphagia	2%	1%	0%
Flatulence	1%	2%	2%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Metabolic and Nutritional			
Weight loss	0%	1%	3%
Musculoskeletal			
Myalgia	1%	1%	2%
Nervous System			
Depression	1%	2%	2%
Insomnia	0%	2%	2%
Paresthesia	1%	0%	2%
Skin and Appendages			
Rash	2%	1%	2%

1 Includes adverse events of possible, probable, or unknown relationship to study drug.

2 Includes adverse event data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients receiving KALETRA in combination with NRTIs and efavirenz.

3 Includes adverse event data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving KALETRA in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with KALETRA and of at least moderate intensity are listed below by body system.

Body as a Whole

Allergic reaction, back pain, chest pain, chest pain substernal, cyst, drug interaction, drug level increased, face edema, flu syndrome, hypertrophy, infection bacterial, malaise, and viral infection.

Cardiovascular System

Atrial fibrillation, cerebral infarct, deep thrombophlebitis, deep vein thrombosis, migraine, palpitation, postural hypotension, thrombophlebitis, varicose vein, and vasculitis.

Digestive System

Cholangitis, cholecystitis, constipation, dry mouth, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, hemorrhagic colitis, hepatitis, increased appetite, jaundice, mouth ulceration, pancreatitis, periodontitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System

Cushing's syndrome, diabetes mellitus, and hypothyroidism.

Hemic and Lymphatic System

Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders

Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight gain.

Musculoskeletal System

Arthralgia, arthrosis and bone necrosis.

Nervous System

Abnormal dreams, agitation, amnesia, anxiety, apathy, ataxia, confusion, convulsion, dizziness, dyskinesia, emotional lability, encephalopathy, facial paralysis, hypertonia, nervousness, neuropathy, peripheral neuritis, somnolence, thinking abnormal, tremor, and vertigo.

Respiratory System

Asthma, dyspnea, lung edema, pharyngitis, rhinitis, and sinusitis.

Skin and Appendages

Acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, seborrhea, skin benign neoplasm, skin discoloration, skin ulcer, and sweating.

Special Senses

Abnormal vision, eye disorder, otitis media, taste loss, taste perversion, and tinnitus.

Urogenital System

Abnormal ejaculation, breast enlargement, gynecomastia, kidney calculus, nephritis, and urine abnormality.

Post-marketing Experience

The following adverse reactions have been reported during post-marketing use of KALETRA. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to KALETRA exposure.

Body as a Whole

Redistribution/accumulation of body fat has been reported (see **PRECAUTIONS – Fat Redistribution**).

Cardiovascular

Bradyarrhythmias.

Skin and Appendages

Stevens Johnson Syndrome and erythema multiforme

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 13 and Table 14.

Table 13. Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Antiretroviral-Naïve Patients

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (204 Weeks)
Variable	**Limit[1]**	**KALETRA 400/100 mg BID + d4T +3TC (N=326)**	**Nelfinavir 750 mg TID + d4T + 3TC (N=327)**	**KALETRA 800/200 mg QD + TDF + FTC (N=115)**	**KALETRA 400/100 mg BID + TDF + FTC (N=75)**	**KALETRA BID + d4T + 3TC (N=100)**
Chemistry	**High**					
Glucose	**>250 mg/dL**	2%	2%	3%	1%	4%
Uric Acid	**>12 mg/dL**	2%	2%	0%	3%	3%
SGOT/ AST	**>180 U/L**	2%	4%	5%	3%	9%
SGPT/ ALT	**>215 U/L**	4%	4%	4%	3%	9%
GGT	**>300 U/L**	N/A	N/A	N/A	N/A	6%
Total Cholesterol	**>300 mg/dL**	9%	5%	3%	3%	22%
Triglycerides	**>750 mg/dL**	9%	1%	5%	4%	22%
Amylase	**>2 x ULN**	3%	2%	7%	5%	4%
Hematology	**Low**					
Neutrophils	**0.75 x 10^9/L**	1%	3%	5%	1%	5%

[1] ULN = upper limit of the normal range; N/A = Not Applicable.

Table 14. Grade 3-4 Laboratory Abnormalities Reported in ≥2% of Adult Protease Inhibitor-Experienced Patients

		Study 888 (48 Weeks)		Study 957[2] and Study 765[3] (84-144 Weeks)
Variable	**Limit[1]**	**KALETRA 400/100 mg BID + NVP + NRTIs (N=148)**	**Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)**	**KALETRA BID + NNRTI + NRTIs (N=127)**
Chemistry	**High**			
Glucose	**>250 mg/dL**	1%	2%	5%
Total Bilirubin	**>3.48 mg/dL**	1%	3%	1%
SGOT/AST	**>180 U/L**	5%	11%	8%
SGPT/ALT	**>215 U/L**	6%	13%	10%
GGT	**>300 U/L**	N/A	N/A	29%
Total Cholesterol	**>300 mg/dL**	20%	21%	39%
Triglycerides	**>750 mg/dL**	25%	21%	36%
Amylase	**>2 x ULN**	4%	8%	8%
Chemistry	**Low**			
Inorganic Phosphorus	**<1.5 mg/dL**	1%	0%	2%
Hematology	**Low**			
Neutrophils	**0.75 x 10^9/L**	1%	2%	4%

[1] ULN = upper limit of the normal range; N/A = Not Applicable.

[2] Includes clinical laboratory data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.

[3] Includes clinical laboratory data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

Pediatrics

Treatment-Emergent Adverse Events

KALETRA has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Taste aversion, vomiting, and diarrhea were the most commonly reported drug related adverse events of any severity in pediatric patients treated with combination therapy including KALETRA for up to 48 weeks in Study 940. A total of 8 children experienced

moderate or severe adverse events at least possibly related to KALETRA. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in ≥ 2% of children enrolled.

Laboratory Abnormalities

The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 15.

Table 15. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients

Variable	Limit[1]	KALETRA BID+ RTIs (N = 100)
Chemistry	High	
Sodium	> 149 mEq/L	3%
Total Bilirubin	≥ 3.0 x ULN	3%
SGOT/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%
Total Cholesterol	> 300 mg/dL	3%
Amylase	> 2.5 x ULN	7%[2]
Chemistry	Low	
Sodium	< 130 mEq/L	3%
Hematology	Low	
Platelet Count	$< 50 \times 10^9$/L	4%
Neutrophils	$< 0.40 \times 10^9$/L	2%

1 ULN = upper limit of the normal range.

2 Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

OVERDOSAGE

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with KALETRA is limited. Treatment of overdose with KALETRA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with KALETRA. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

KALETRA tablets may be taken with or without food.

KALETRA oral solution must be taken with food.

KALETRA tablets should be swallowed whole and not chewed, broken, or crushed.

The recommended oral dose of KALETRA is as follows: (Please also refer to **INDICATIONS AND USAGE** and **ADVERSE REACTIONS**)

Adults

Therapy-Naïve Patients

- KALETRA tablets 400/100 mg (2 tablets) twice-daily with or without food.
- KALETRA oral solution 400/100 mg (5.0 mL) twice-daily taken with food.
- KALETRA tablets 800/200 mg (4 tablets) once-daily taken with or without food.
- KALETRA oral solution 800/200 mg (10 mL) once-daily taken with food.

Therapy-Experienced Patients

- KALETRA tablets 400/100 mg (2 tablets) twice-daily taken with or without food.

- KALETRA oral solution 400/100 mg (5.0 mL) twice-daily taken with food.

Once-daily administration of KALETRA is not recommended in therapy-experienced patients.

Concomitant therapy: Efavirenz, nevirapine, fosamprenavir or nelfinavir

- KALETRA 400/100 mg tablets can be used twice-daily in combination with these drugs with no dose adjustment in antiretroviral-naïve patients.
- A dose increase of KALETRA tablets to 600/150 mg (3 tablets) twice-daily may be considered when used in combination with efavirenz, nevirapine, fosamprenavir without ritonavir, or nelfinavir in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).
- A dose increase of KALETRA oral solution to 533/133 mg (6.5 mL) twice-daily taken with food is recommended when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

Increasing the dose of KALETRA tablets to 600/150 mg (3 tablets) twice-daily coadministered with efavirenz significantly increased the lopinavir plasma concentrations approximately 35% and ritonavir concentrations approximately 56% to 92% compared to KALETRA tablets 400/100 mg twice-daily without efavirenz (see **CLINICAL PHARMACOLOGY– *Drug-drug Interactions* Table 2 and/or PRECAUTIONS – Table 10**).

KALETRA tablets and oral solution should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

Pediatric Patients

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to < 15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice-daily taken with food, up to a

maximum dose of 400/100 mg in children > 40 kg (5.0 mL or 2 tablets) twice-daily. KALETRA once-daily has not been evaluated in pediatric patients. **It is preferred that the prescriber calculate the appropriate milligram dose for each individual child ≤ 12 years old and determine the corresponding volume of solution or number of tablets.** However, as an alternative, the following table contains dosing guidelines for KALETRA oral solution based on body weight. When possible, dose should be administered using a calibrated dosing syringe.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine, efavirenz or amprenavir		
7 to < 15 kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
> 10 to < 15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
> 20 to 25 kg		2.75 mL
> 25 to 30 kg		3.5 mL
> 30 to 35 kg		4.0 mL
> 35 to 40 kg		4.75 mL
> 40 kg	Adult dose	5 mL (or 2 tablets)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children > 12 years of age.

Concomitant Therapy: Efavirenz, nevirapine or amprenavir

A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to < 15 kg and 11/2.75 mg/kg for those 15 to 45 kg (approximately equivalent to 300/75 mg/m^2) twice-daily taken with food, up to a maximum dose of 533/133 mg in children > 45 kg twice-daily is recommended when used in combination with efavirenz, nevirapine or amprenavir in children 6 months to 12 years of age. The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz, nevirapine or amprenavir in children (see **CLINICAL**

PHARMACOLOGY– *Drug-drug Interactions* **Table 2** and/or **PRECAUTIONS** – **Table 10**).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
With nevirapine, efavirenz or amprenavir		
7 to < 15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
> 10 to < 15 kg		2.0 mL
15 to 45 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
> 20 to 25 kg		3.25 mL
> 25 to 30 kg		4.0 mL
> 30 to 35 kg		4.5 mL
> 35 to 40 kg		5.0 mL
> 40 to 45 kg	Adult dose	5.75 mL (or 2 tablets)
> 45 kg	Adult dose	6.5 mL (or 2 tablets)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children > 12 years of age.

HOW SUPPLIED

KALETRA (lopinavir/ritonavir) tablets are yellow film-coated ovaloid tablets debossed with the corporate logo and the Abbo-Code KA. KALETRA is available as 200 mg lopinavir/50 mg ritonavir tablets in the following package sizes:

Bottles of 120 tablets ..... (**NDC** 0074-6799-22)

Recommended storage: Store KALETRA film-coated tablets at 20°- 25°C (68°-77°F); excursions permitted to 15°-30°C (59° to 86°F)[see USP controlled room temperature] Dispense in original container. For patient use: exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.. KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid

supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:

160 mL bottle.....(**NDC** 0074-3956-46)

Recommended storage: Store KALETRA oral solution at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), oral solution should be used within 2 months.

DN1055V3

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
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----------(Perforation)----------

KALETRA®
(lopinavir/ritonavir) tablets
(lopinavir/ritonavir) oral solution

ALERT: Find out about medicines that should NOT be taken with KALETRA. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

PATIENT INFORMATION

KALETRA® (kuh-LEE-tra)

Generic Name: lopinavir/ritonavir (lop-IN-uh-veer/rit-ON-uh-veer)

Read this leaflet carefully before you start taking KALETRA. Also, read it each time you get your KALETRA prescription refilled, in case something has changed. This

information does not take the place of talking with your doctor when you start this medicine and at check ups. Ask your doctor if you have any questions about KALETRA.

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your bottle and the appearance of your medicine with the description provided below. Contact your pharmacist immediately if you believe a dispensing error has occurred.

What is KALETRA and how does it work?

KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV (human immunodeficiency virus) protease (PRO-tee-ase) inhibitor. KALETRA is always used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. KALETRA is for adults and for children age 6 months and older.

HIV infection destroys CD_4 (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

KALETRA blocks HIV protease, a chemical which is needed for HIV to multiply. KALETRA reduces the amount of HIV in your blood and increases the number of T cells. Reducing the amount of HIV in the blood reduces the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Does KALETRA cure HIV or AIDS?

KALETRA does not cure HIV infection or AIDS. The long-term effects of KALETRA are not known at this time. People taking KALETRA may still get opportunistic infections or other conditions that happen with HIV infection. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium complex* (MAC) infections.

Does KALETRA reduce the risk of passing HIV to others?

KALETRA does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

How should I take KALETRA?

- You should stay under a doctor's care when taking KALETRA. Do not change your treatment or stop treatment without first talking with your doctor.
- You must take KALETRA every day exactly as your doctor prescribed it. The dose of KALETRA may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the label.
- Dosing in adults (including children 12 years of age and older):
  The usual dose for adults is 2 tablets (400/100 mg) or 5.0 mL of the oral solution twice a day (morning and night), in combination with other anti-HIV medicines.

  The doctor may prescribe KALETRA as 4 tablets or 10.0 mL of oral solution (800/200 mg) once-daily in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past.
- KALETRA tablets should be swallowed whole and not chewed, broken, or crushed.
- KALETRA tablets can be taken with or without food.
- Dosing in children from 6 months to 12 years of age:
  Children from 6 months to 12 years of age can also take KALETRA. The child's doctor will decide the right dose based on the child's weight.
- Take KALETRA oral solution with food to help it work better.
- Do not change your dose or stop taking KALETRA without first talking with your doctor.
- When your KALETRA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood

may increase if the medicine is stopped for even a short time. The virus may develop resistance to KALETRA and become harder to treat.

- Be sure to set up a schedule and follow it carefully.
- Only take medicine that has been prescribed specifically for you. Do not give KALETRA to others or take medicine prescribed for someone else.

What should I do if I miss a dose of KALETRA?

It is important that you do not miss any doses. If you miss a dose of KALETRA, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much KALETRA?

If you suspect that you took more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately.

As with all prescription medicines, KALETRA should be kept out of the reach of young children. KALETRA liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of KALETRA, it could make him/her sick from too much alcohol. Contact your local poison control center or emergency room immediately if this happens.

Who should not take KALETRA?

Together with your doctor, you need to decide whether KALETRA is right for you.

- Do not take KALETRA if you are taking certain medicines. These could cause serious side effects that could cause death. Before you take KALETRA, you must tell your doctor about all the medicines you are taking or are planning to take. These include other prescription and non-prescription medicines and herbal supplements.

For more information about medicines you should not take with KALETRA, please read the section titled "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

- Do not take KALETRA if you have an allergy to KALETRA or any of its ingredients, including ritonavir or lopinavir.

Can I take KALETRA with other medications?*

KALETRA may interact with other medicines, including those you take without a prescription. You must tell your doctor about all the medicines you are taking or planning to take before you take KALETRA.

MEDICINES YOU SHOULD NOT TAKE WITH KALETRA:

- Do not take the following medicines with KALETRA because they can cause serious problems or death if taken with KALETRA.
  - Dihydroergotamine, ergonovine, ergotamine and methylergonovine such as Cafergot®, Migranal® D.H.E. 45®, Ergotrate Maleate, Methergine, and others
  - Halcion® (triazolam)
  - Hismanal® (astemizole)
  - Orap® (pimozide)
  - Propulsid® (cisapride)
  - Seldane® (terfenadine)
  - Versed® (midazolam)
- Do not take KALETRA with rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA in your blood and make it less effective.
- Do not take KALETRA with St. John's wort (hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's

wort. Taking St. John's wort may decrease KALETRA levels and lead to increased viral load and possible resistance to KALETRA or cross-resistance to other anti-HIV medicines.

- Do not take KALETRA with the cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between KALETRA and Lipitor® (atorvastatin); talk to your doctor before you take any of these cholesterol-reducing medicines with KALETRA.

Medicines that require dosage adjustments:

It is possible that your doctor may need to increase or decrease the dose of other medicines when you are also taking KALETRA. Remember to tell your doctor all medicines you are taking or plan to take.

Before you take Viagra® (sildenafil), Cialis® (tadalafil), or Levitra® (vardenafil) with KALETRA, talk to your doctor about problems these two medicines can cause when taken together. You may get increased side effects of VIAGRA, CIALIS, or LEVITRA such as low blood pressure, vision changes, and penis erection lasting more than 4 hours. If an erection lasts longer than 4 hours, get medical help right away to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you are taking oral contraceptives ("the pill") or the contraceptive patch to prevent pregnancy, you should use an additional or different type of contraception since KALETRA may reduce the effectiveness of oral or patch contraceptives.
- Efavirenz (Sustiva™), nevirapine (Viramune®), Agenerase (amprenavir) and Viracept (nelfinavir) may lower the amount of KALETRA in your blood. Your doctor may increase your dose of KALETRA if you are also taking efavirenz, nevirapine, amprenavir or nelfinavir. KALETRA should not be taken once-daily with these medicines.

- If you are taking Mycobutin® (rifabutin), your doctor will lower the dose of Mycobutin.
- **A change in therapy should be considered if you are taking KALETRA with:**
  - Phenobarbital
  - Phenytoin (Dilantin® and others)
  - Carbamazepine (Tegretol® and others)

These medicines may lower the amount of KALETRA in your blood and make it less effective. KALETRA should not be taken once-daily with these medicines.

- If you are taking or before you begin using inhaled Flonase® (fluticasone propionate) talk to your doctor about problems these two medicines may cause when taken together. Your doctor may choose not to keep you on inhaled Flonase®.
- **Other Special Considerations:**
  KALETRA oral solution contains alcohol. Talk with your doctor if you are taking or planning to take metronidazole or disulfiram. Severe nausea and vomiting can occur.
- **If you are taking both didanosine (Videx®) and KALETRA:**
  Didanosine (Videx®) can be taken at the same time as KALETRA tablets without food. Didanosine (Videx®) should be taken one hour before or two hours after KALETRA oral solution.

What are the possible side effects of KALETRA?

- This list of side effects is **not** complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

- The most commonly reported side effects of moderate severity that are thought to be drug related are: abdominal pain, abnormal stools (bowel movements), diarrhea, feeling weak/tired, headache, and nausea. Children taking KALETRA may sometimes get a skin rash.
- Blood tests in patients taking KALETRA may show possible liver problems. People with liver disease such as Hepatitis B and Hepatitis C who take KALETRA may have worsening liver disease. Liver problems including death have occurred in patients taking KALETRA. In studies, it is unclear if KALETRA caused these liver problems because some patients had other illnesses or were taking other medicines.
- Some patients taking KALETRA can develop serious problems with their pancreas (pancreatitis), which may cause death. You have a higher chance of having pancreatitis if you have had it before. Tell your doctor if you have nausea, vomiting, or abdominal pain. These may be signs of pancreatitis.
- Some patients have large increases in triglycerides and cholesterol. The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.
- Diabetes and high blood sugar (hyperglycemia) occur in patients taking protease inhibitors such as KALETRA. Some patients had diabetes before starting protease inhibitors, others did not. Some patients need changes in their diabetes medicine. Others needed new diabetes medicine.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- Some patients with hemophilia have increased bleeding with protease inhibitors.

- There have been other side effects in patients taking KALETRA. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.

What should I tell my doctor before taking KALETRA?

- *If you are pregnant or planning to become pregnant:* The effects of KALETRA on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking KALETRA. You should not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV, there is a chance that HIV can be transmitted through breast-feeding.
- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking KALETRA.
- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Tell your doctor if you have diabetes or an increase in thirst or frequent urination.
- *If you have hemophilia:* Patients taking KALETRA may have increased bleeding.

How do I store KALETRA?

- Keep KALETRA and all other medicines out of the reach of children.
- KALETRA tablets should be stored at room temperature. Exposure of Kaletra tablets to high humidity outside the original container for longer than 2 weeks is not recommended.
- Refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), KALETRA oral solution should be used within 2 months.
- Avoid exposure to excessive heat.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

General advice about prescription medicines:

Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have any concerns about this medicine, ask your doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

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02-9098-R1

Exp.

Lot

NDC 0074-6799-22

Kaletra®

(Lopinavir/Ritonavir) Tablets

200 mg / 50 mg

120 Tablets

ALERT: Find out about medicines that should NOT be taken with Kaletra®

Note to Pharmacist: Do not cover ALERT box with pharmacy label. Enclosure is provided with tear-off patient information.

Rx only

Abbott

Do not accept if seal over bottle opening is broken or missing.

Dispense in original container. For patient use: exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

Storage: Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

Each tablet contains: 200 mg Lopinavir and 50 mg Ritonavir.

Use by product expiration date.

See enclosure for prescribing information.

Abbott Laboratories
North Chicago, IL 60064, U.S.A.

Product of Germany.

Exhibit 8

PDD 7475

PHYSICAL AND ORAL DOG BIOAVAILABILITY EVALUATION OF ABT-538:PVP CO-PRECIPITATES.

L. Dias*, L. Al-Razzak, E. Eiden, R. Gao, D. Kaul, D. Lechuga-Ballesteros, K. Marsh and R. Poska. Pharmaceutical and Analytical R&D, Abbott Laboratories, North Chicago, IL 60064

Polyvinylpyrillodone (PVP) has been used to form co-precipitates of an insoluble antiviral compound, ABT-538, in an effort to increase bioavailability of this drug. PVP:drug co-precipitates were prepared using a solvent evaporation method. Two techniques were used to prepare the PVP:drug co-precipitates namely spray drying and layering onto suitable substrates. Several ratios of drug to PVP and various molecular weight grades of PVP were evaluated in this study using differential scanning calorimetry and X-ray powder diffraction. Preliminary studies indicate that the co-precipitates maintained the drug in an amorphous form which were stable at 80°C and at ambient room temperature/75% RH conditions for two weeks. Evaluation of the encapsulated spray dried material revealed a non-disintegrating mass during dissolution testing and this was reflected in the formulation having no bioavailability. In order to prevent the formation of this non-disintegrating mass and to increase the dissolution rate, the PVP:drug co-precipitate was layered onto substrates like microcrystalline cellulose (MCC) and silicon dioxide since they provided a large layering surface area. Dissolution of the layered substrate showed that all the drug was released in about one hour. However, the increase in dissolution rate was not consistently reflected in increased bioavailability indicating no *in vitro/in-vivo* correlation for this dosage form. The drug:PVP co-precipitates also showed further improvement in bioavailabilities when combined with surfactants and acidifying agents. Preliminary results indicate that a dramatic increase in the bioavailability of ABT-538 could be obtained using formulation modification techniques.

Exhibit 9

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34118 A2

(51) International Patent Classification[7]: A61K 9/14, 38/55

(21) International Application Number: PCT/US00/30910

(22) International Filing Date:
10 November 2000 (10.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/439,514 12 November 1999 (12.11.1999) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; Dept. 377, Bldg. AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: FORT, James, J.; 2700 Leafield Terrace, Midlothian, VA 23113 (US). KRILL, Steven, L.; 44 Meyersville Road, Chatham, NJ 07928 (US). LAW, Devalina; 835C Country Club Drive, Libertyville, IL 60048 (US). QIU, Yihong; 6118 Honeysuckle Lane, Gurnee, IL 60031 (US). PORTER, William, R.; 20 Manchester Lane, Vernon Hills, IL 60061 (US). SCHMITT, Eric, A.; 319 Evergreen Court, Libertyville, IL 60048 (US).

(74) Agents: CROWLEY, Steven, R. et al.; Dept. 377 Bldg. AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

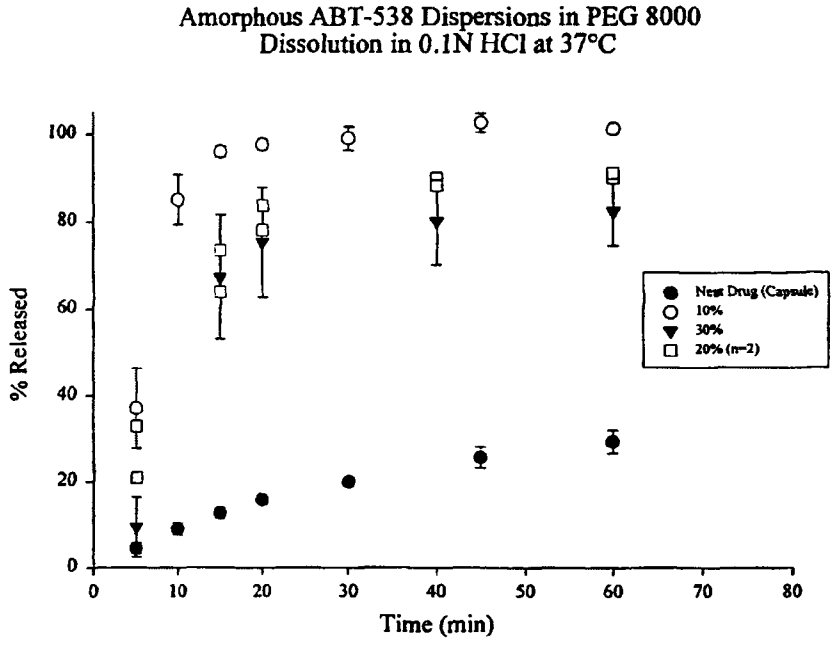
(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SOLID DISPERSION PHARMACEUTICAL FORMULATIONS



(57) Abstract: A pharmaceutical composition is disclosed which comprises a soliddispersion of an HIV protease inhibitor in a water soluble carrier, such as PEG, having enhanced bioavailability and improved dissolution properties. The solid dispersion may optionally be encapsulated in hard gelatin capsules, compressed into a tablet, or may be granulated with a pharmaceutically acceptable granulating agent. Also disclosed are methods of making said solid dispersion and methods of treating an HIV infection employing said solid dispersion.

WO 01/34118 A2

SOLID DISPERSION PHARMACEUTICAL FORMULATIONS

Technical Field of the Invention

The instant invention relates to the fields of pharmaceutical and organic chemistry, and provides novel solid dispersion pharmaceutical formulations with enhanced bioavailability.

Background of the Invention

One measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength, and first pass effect. Aqueous solubility is one of the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or

other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable solid dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

An alternative dosage form is a solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at

solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Sciences, 60*, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions.

Retroviral protease inhibiting compounds are useful for inhibiting HIV proteases *in vitro* and *in vivo*, and are useful for inhibiting HIV (human immunodeficiency virus) infections and for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability. Examples of HIV protease inhibiting compounds include

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methy l butanoyl]-amino-1,6-diphenylhexane (ABT-378);

N-(2(R)-hydroxy-1 (S)-indanyl)-2(R)-phenylmethyl

-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1-Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*])-N^1 [3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

VX-478; DMP-323; DMP-450; AG1343 (nelfinavir);

BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or combinations thereof.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily

follow that oral administration of such a solution would give good bioavailability for the drug.

Polyethylene glycol (PEG) solid dispersion formulations are generally known to improve the dissolution and bioavailability of many compounds. However, Aungst *et al.* has recently demonstrated that this was unable to improve the bioavailability of an HIV protease inhibitor with a cyclic urea structural backbone, called DMP 323 (Aungst *et al.*, *International Journal of Pharmaceutics, 156*, 79 (1997)).

Thus, it would be a significant contribution to the art to provide a solid dispersion pharmaceutical formulation of a retroviral protease inhibitor which is more stable and has enhanced bioavailability.

Summary of the Invention

The instant invention provides a stable solid dispersion comprising a retroviral protease inhibitor and PEG having improved bioavailability.

Also provided by the instant invention is a pharmaceutical composition comprising a stable solid dispersion as described above with a pharmaceutically acceptable carrier, diluent, or excipient.

Additionally provided by the instant invention is a method for preparing a stable solid dispersion as described above.

The instant invention still further provides a method of treating an HIV infection comprising administering an effective amount of a stable solid dispersion as described above to a mammal in need of such treatment.

Brief Description of the Figures

Figure 1 illustrates the dispersion of amorphous ABT-538 in PEG 8000.

Figure 2 illustrates the bioavailability of a dispersion of amorphous ABT-538 in PEG 8000.

Figure 3 illustrates the in vivo-in vitro correlation of ABT-538.

Figure 4 illustrates the dissolution of ABT-378.

Figure 5 illustrates the dissolution of nelfinavir.

Detailed Description of the Invention

This invention pertains to the preparation of solid dispersion systems for protease inhibitors with improved dissolution and oral bioavailability.

A solid (molecular) dispersion comprising an HIV protease inhibiting compound may be prepared by dissolving or dispersing the HIV protease inhibiting compound in a sufficient amount of an organic solvent followed by dispersion into a suitable water soluble carrier. Suitable organic solvents include pharmaceutically acceptable solvents such as methanol, ethanol, or other organic solvents in which the protease inhibitor is soluble. Suitable water soluble carriers include polymers such as polyethylene glycol (PEG), pluronics, pentaeythritol, pentaeythritol tetraacetate, polyoxyethylene stearates, poly-ε-caprolactone, and the like.

The organic solvent (preferably ethanol) may then be evaporated away, leaving the drug dispersed/dissolved in the molten matrix, which is then cooled. The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus

improving the bioavailability of a drug exhibiting dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the HIV protease inhibiting compound.

Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, and the like, that might be needed to prepare a capsule or tablet.

The resulting composition comprising the HIV protease inhibiting compound may be dosed directly for oral administration, diluted into an appropriate vehicle for

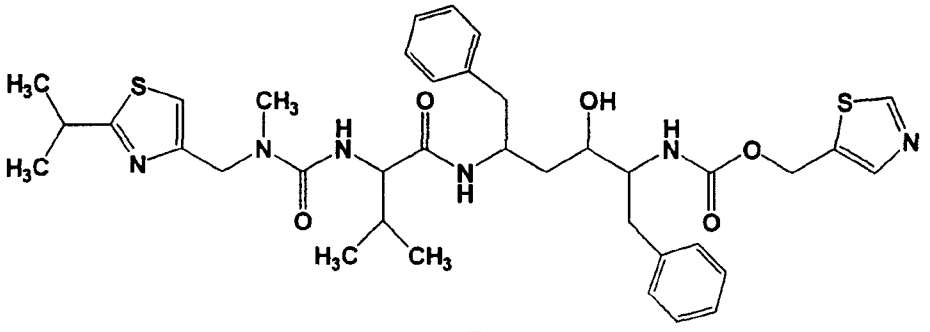
oral administration, filled into capsules, or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The composition can be used to improve the oral bioavailability and solubility of said HIV protease inhibiting compound.

Total daily dosing of HIV protease inhibitors may be administered to a human in single or divided doses in amounts, for example, from 0.001 to 1000 mg/kg body weight daily, but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

ABT-538 (ritonavir) was preferably used as the HIV protease inhibitor in the instant invention. Additionally, two other protease inhibitors, ABT-378 and nelfinavir mesylate, were tested in solid dispersions to demonstrate

the improved dissolution which can be achieved with this system.

One aspect of the instant invention provides a solid dispersion of a compound of formula I

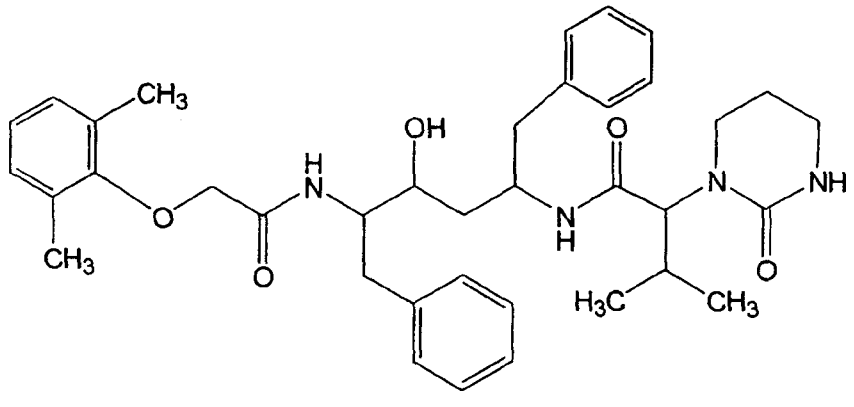


I

A compound of formula I is an HIV protease inhibitor marketed by Abbott Laboratories under the tradename Norvir®, with the common name ritonavir [(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane]. This and other compounds as well as methods for preparing same are disclosed in U.S. Patent

Nos. 5,648,497 and 5,541,206, the disclosures of which are herein incorporated by reference.

Additional HIV protease inhibitors which may be formulated into a solid dispersion include compounds of formula II

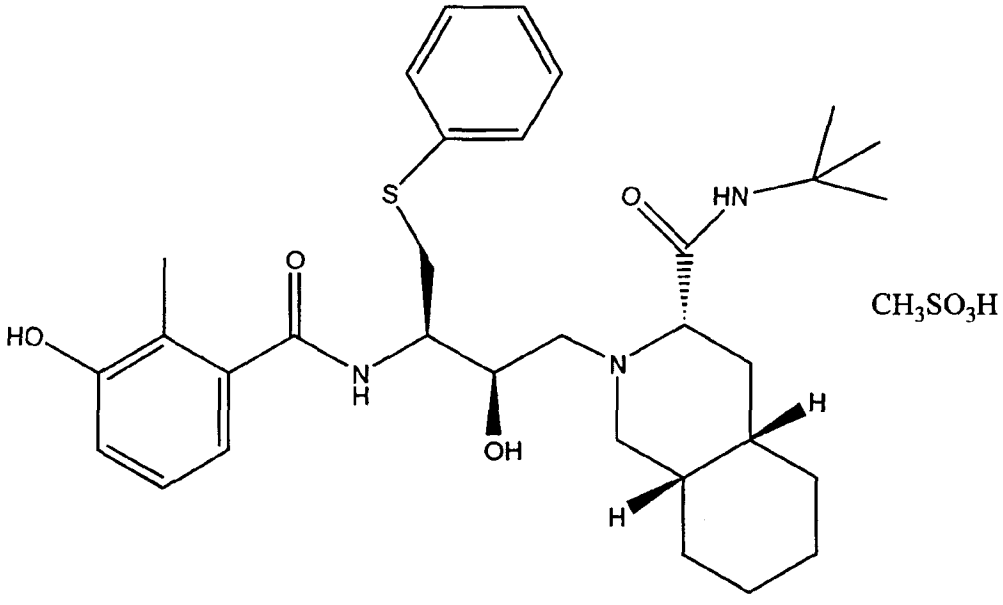


II

A compound of formula II is known as ABT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane). This and other compounds, as well as methods for preparing same, are

identified in U.S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference.

A compound of formula III provided hereinbelow is known as nelfinavir mesylate (marketed under the tradename Viracept® by Agouron Pharmaceuticals, Inc. in La Jolla, CA), and is another HIV protease inhibitor which may be formulated into a solid dispersion.



III

The following Examples are provided to further illustrate the present invention.

EXAMPLES

Example 1

Dispersion Preparations

A. Ritonavir (ABT-538) Dispersion Preparation:

The samples were prepared by dissolving ABT-538 in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 75 °C. The PEG 8000 was added to the hot alcohol solution with continual swirling until the PEG melted. The flask was then attached to a rotary evaporator, immersed in the water bath (75 °C) under vacuum for 15 minutes to remove the ethanol. After the majority of ethanol had evaporated, the flask was immersed in an ice bath for 15 minutes. The contents of the flask were then vacuum dried at room temperature for 6 hours. The solid was transferred to a crystallization dish and placed under vacuum overnight to remove residual ethanol. The material was then ground and sifted. Particles ranging in size from

149 to 420 μm were used for further studies. The drug loads used for these dispersions were 10, 20 and 30% w/w.

B. ABT-378 Dispersion Preparation:

A 10% dispersion was prepared using an alcoholic solution of ABT-378 (ca. 0.1 g/ml) by the same method as described in section A above.

C. Nelfinavir mesylate Dispersion Preparation:

Nelfinavir mesylate is available from Agouron Pharmaceuticals, Inc. under the tradename Viracept®.

A 10% dispersion was prepared using an alcoholic solution of nelfinavir (ca. 0.035 g/ml) by the same method as described in section A above.

The potency values of all the dispersions as well as the dissolution sample concentrations were determined via HPLC.

D. Results:

The *in vitro* dissolution data of the ABT-538 dispersions compared with ABT-538 in 0.1*N* HCl (shown in Figure 1, n=3 ± SD unless otherwise indicated) show that the dispersions markedly improved the dissolution rate of the drug. Drug loading decreases the rate of drug release in a rank order. A bioavailability study was conducted in

dogs with the above ABT-538 dispersions to elicit the drug load effects *in vivo*. Eight beagle dogs, obtained from Marshall Research Animals (North Rose, NY), were utilized in this study. The animals were fasted overnight prior to dosing in each period but water was allowed *ad libitum*. Approximately 30 minutes prior to dosing, each dog received a 100 μg/kg subcutaneous dose of histamine. Capsules containing 5 mg/kg of 10, 20 and 30% solid dispersion (formulations A, B and C, respectively) were tested against crystalline drug as a reference in a four-way crossover study.

Each dog received the dose followed by approximately 10 ml of water. A washout period of approximately 1 week was used to separate each dosing period. The plasma samples were analyzed by a method reported by Marsh *et al.* (Marsh, K.C., Eiden, E. and McDonald, E. Determination of Ritonavir, a new HIV Protease Inhibitor, in Biological Samples Using Reversed-Phase High-Performance Liquid Chromatography. *J. Chromatography B.* 704 (1997) 307-313.)

The results of the study are shown in Figure 2. The results show that the solid dispersions improve absorption compared to the reference. An *in vitro - in vivo*

correlation was established. A plot of the AUC versus the amount dissolved in 20 min, shown in Figure 3, is a straight line, indicating excellent correlation.

The dissolution properties of the two additional protease inhibitors (ABT-378 and nelfinavir mesylate) were also determined. The *in vitro* dissolution data (Figure 4) of the ABT-378 dispersion compared with reference clearly shows that the preparation of a dispersion markedly improves dissolution rate of the drug. The variability in the release rate from the dispersion is due to the fact that the preparation of these dispersions had not been optimized to completely overcome the wetting problem of the drug. Despite this, the improvements observed are significant [95% confidence intervals shown].

The nelfinavir mesylate solid dispersion also exhibits an improved *in vitro* dissolution rate compared to the neat drug (Figure 5).

E. Conclusions:

Solid dispersions of HIV protease inhibitors (for example, ABT-538 (ritonavir), ABT-378, and nelfinavir mesylate) markedly improve the dissolution rate of these

drugs. This improvement of dissolution rate is reflected in the improvement of bioavailability. An excellent *in vivo - in vitro* correlation established for the dispersions suggests that the *in vitro* dissolution reflects *in vivo* bioavailability for these systems.

Example 2

Stability of Dispersion in Molten PEG 8000

The stability of the dispersion of ABT-538 in PEG 8000 in the molten state at 70 °C was examined. Individual approximately 5 mg quantities of the dispersion (aged for 6 weeks at room temperature) were placed in 4 ml glass vials. These vials, with the exception of the initial time point, were placed in a

70 °C oven which was sampled at pre-determined intervals, chilled in ice water and placed in the freezer until HPLC analysis. After all samples were collected, they were analyzed for ABT-538 content by HPLC. The HPLC system consisted of a Hitachi AS 4000 autosampler, SP 8800 ternary pump, Applied Biosystems 783 detector, and PE Nelson Data

acquisition system. Other chromatographic details included a Regis Little Champ 5 cm C-18 column, a mobile phase consisting of an aqueous solution of 0.1% trifluoroacetic acid in 10 mM aqueous tetramethyl ammonium perchlorate (TMAP)/acetonitrile/methanol (55/40/5). The flow rate was 1 ml/minute, the wavelength of detection was 205 nm, and the injection volume was 100 µl. Standard curves of peak area of ABT-538 vs. concentration in the range of interest were compared with experimentally obtained area counts.

Example 3

Additional Protocol For Oral Bioavailability Studies

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) are fasted overnight prior to dosing, but are permitted water *ad libitum*. Each dog receives a 100 µg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog receives a single solid dosage form corresponding to a 5 mg/kg dose of the drug. The dose is followed by approximately 10 milliliters of water. Blood samples are obtained from each animal prior to dosing and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug

administration. The plasma is separated from the red cells by centrifugation and frozen (- 30 °C) until analysis. The concentrations of parent drug is determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve is calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition is calculated by comparing the area under the curve after oral dosing to that obtained from a single intravenous dose. Each capsule or capsule composition is evaluated in a group containing at least six dogs. The values reported are averages for each group of dogs.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a solid dispersion of an HIV protease inhibitor or combination of HIV protease inhibitors and a water soluble carrier.

2. The composition of Claim 1 wherein said water soluble carrier is polyethylene glycol (PEG).

3. The composition of Claim 1 wherein said HIV protease inhibitor is dissolved in an organic solvent.

4. The composition of Claim 3 wherein said organic solvent is ethanol.

5. The composition of Claim 2 wherein said HIV protease inhibitor is selected from the group consisting of:

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-

thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S, 3S, 5S)-2-(2,6Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methy 5 l butanoyl] amino-1,6-diphenylhexane (ABT-378);

N-(2(R)-hydroxy-1 (S)-indanyl)-2(R)-phenylmethyl -4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcar boxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2 10 -quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-iso quinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-15 3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*])-N^1-[3-[[[(1,1 - 20 dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

VX-478; DMP-323; DMP-450; AG1343 (nelfinavir); BMS 186,318; SC-55389a; BILA 1096 BS; U-140690, or combinations thereof.

6. The composition of Claim 2 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

7. The composition of Claim 2 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane (ABT-378).

8. The composition of Claim 2 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-

hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

9. The composition of Claim 2 wherein said solid dispersion is encapsulated in a hard gelatin capsule.

10. The composition of Claim 2 wherein said solid dispersion is compressed into a tablet.

11. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from the group consisting of pharmaceutically acceptable surfactants and antioxidants.

12. A method of preparing a composition of Claim 1 which comprises:

a) dissolving an HIV protease inhibitor into an organic solvent to form a solution;

b) adding a water soluble carrier to said solution to form a mixture;

c) optionally flash evaporating said solvent;

d) optionally drying the resulting residue remaining after evaporation;

e) optionally grinding and sieving the solid dispersion to obtain a resultant product.

13. The method of Claim 12 additionally comprising encapsulating the solid dispersion in a hard gelatin capsule.

14. The method of Claim 12 additionally comprising compressing said solid dispersion into a tablet.

15. The method of Claim 12 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

16. The method of Claim 12 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-

pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

17. The method of Claim 12 wherein said solvent is ethanol.

18. The method of Claim 12 wherein said water soluble carrier is polyethylene glycol (PEG).

19. A method of treating an HIV infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment.

20. The method of Claim 19 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

21. The method of Claim 19 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

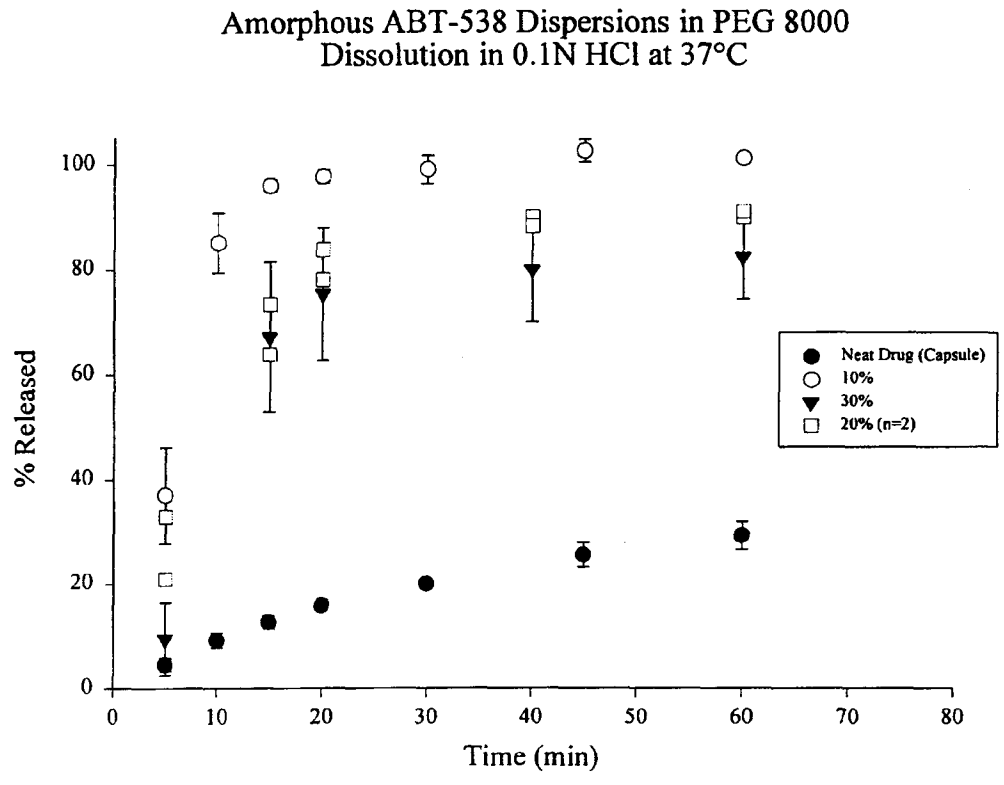

Amorphous ABT-538 Dispersions in PEG 8000
Dissolution in 0.1N HCl at 37°C
% Released
Time (min)
Neat Drug (Capsule)
10%
30%
20% (n=2)
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80

Figure 1

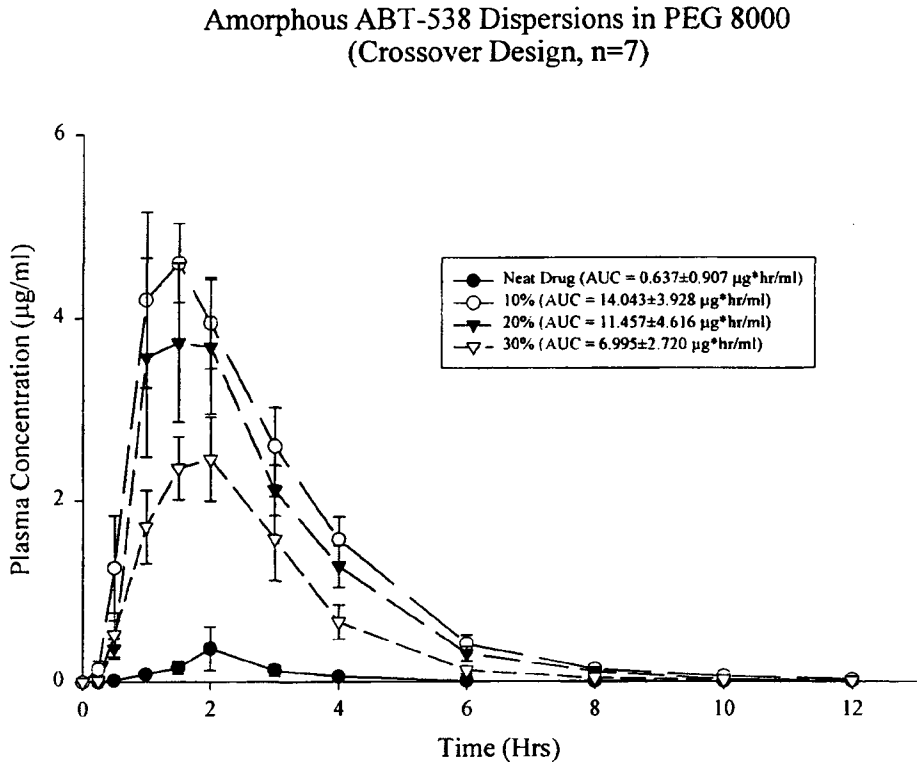

Amorphous ABT-538 Dispersions in PEG 8000
(Crossover Design, n=7)
Plasma Concentration (µg/ml)
Time (Hrs)
Neat Drug (AUC = 0.637±0.907 µg*hr/ml)
10% (AUC = 14.043±3.928 µg*hr/ml)
20% (AUC = 11.457±4.616 µg*hr/ml)
30% (AUC = 6.995±2.720 µg*hr/ml)
0
2
4
6
8
10
12

Figure 2

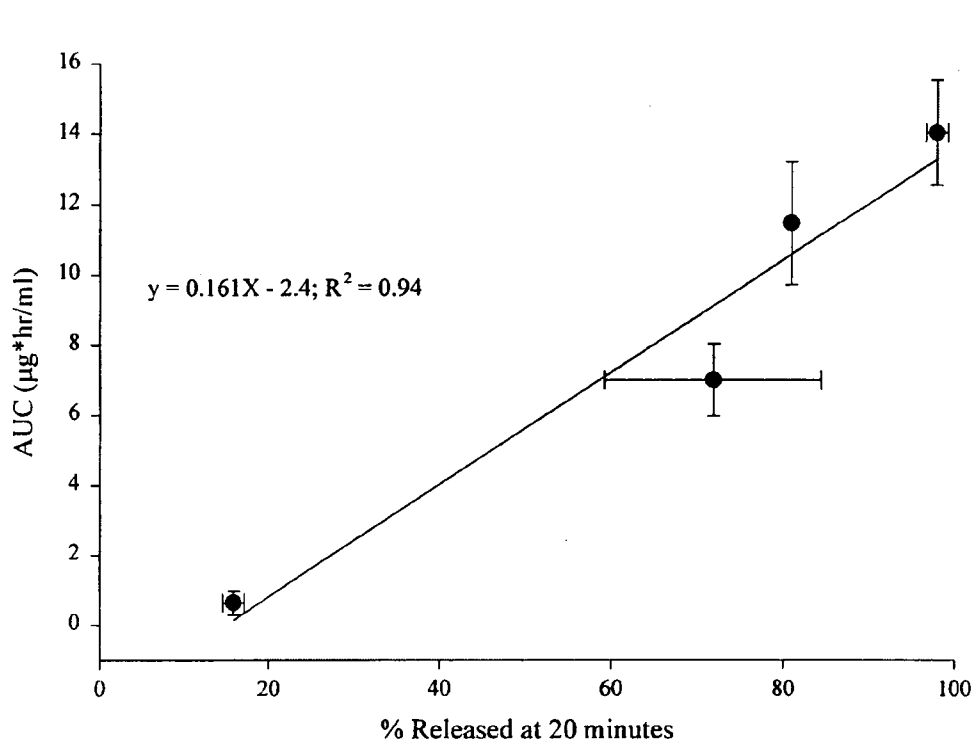

IVIV Correlation
Dog Studies 5 mg/Kg and Dissolution in 0.1N HCl at 37°C, 50 rpm
y = 0.161X - 2.4; R² = 0.94
AUC (µg*hr/ml)
% Released at 20 minutes
0
2
4
6
8
10
12
14
16
0
20
40
60
80
100

Figure 3

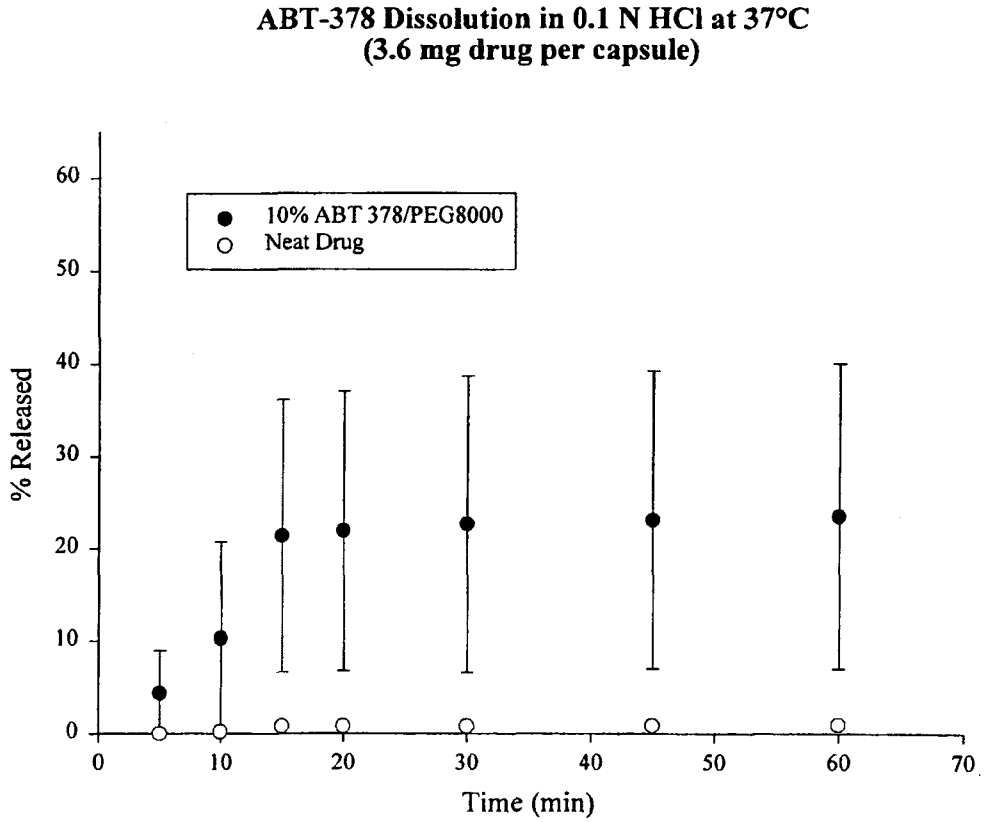

ABT-378 Dissolution in 0.1 N HCl at 37°C
(3.6 mg drug per capsule)
10% ABT 378/PEG8000
Neat Drug
% Released
Time (min)
0
10
20
30
40
50
60
70

Figure 4

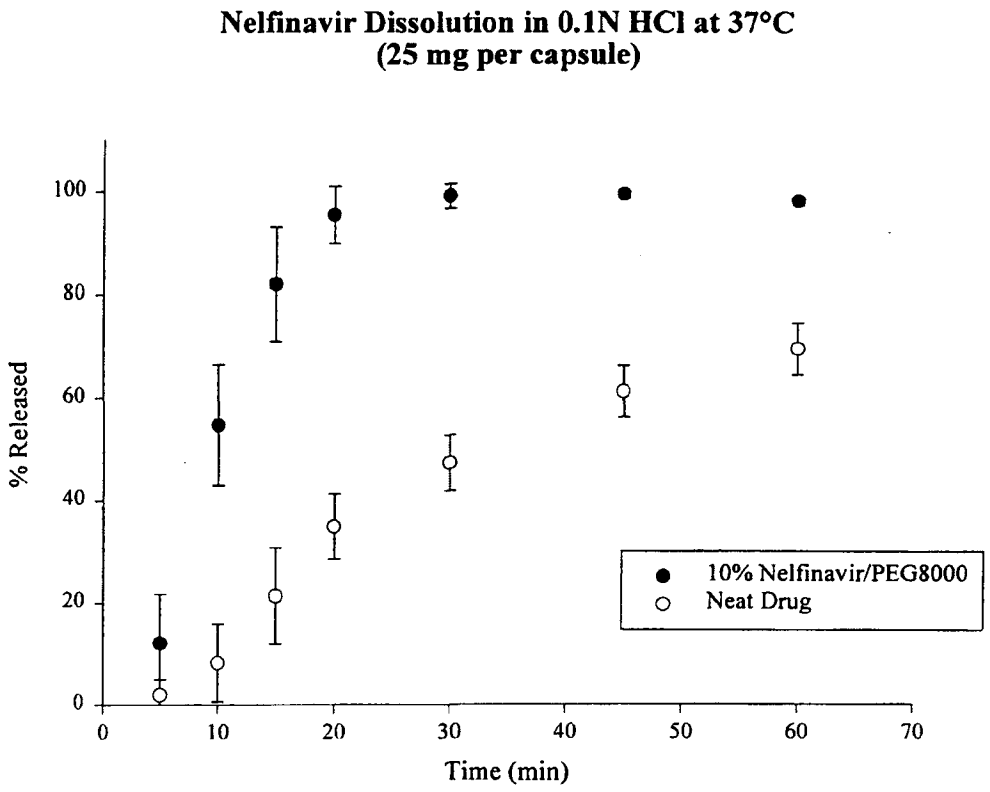

Nelfinavir Dissolution in 0.1N HCl at 37°C
(25 mg per capsule)
% Released
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Time (min)
10% Nelfinavir/PEG8000
Neat Drug

Figure 5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34118 A3

(51) International Patent Classification[7]: A61K 9/14, 31/427, 31/513, A61P 31/18

(21) International Application Number: PCT/US00/30910

(22) International Filing Date:
10 November 2000 (10.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/439,514 12 November 1999 (12.11.1999) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; Dept. 377, Bldg. AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: FORT, James, J.; 2700 Leafield Terrace, Midlothian, VA 23113 (US). KRILL, Steven, L.; 44 Meyersville Road, Chatham, NJ 07928 (US). LAW, Devalina; 835C Country Club Drive, Libertyville, IL 60048 (US). QIU, Yihong; 6118 Honeysuckle Lane, Gurnee, IL 60031 (US). PORTER, William, R.; 20 Manchester Lane, Vernon Hills, IL 60061 (US). SCHMITT, Eric, A.; 319 Evergreen Court, Libertyville, IL 60048 (US).

(74) Agents: CROWLEY, Steven, R. et al.; Dept. 377 Bldg. AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(81) Designated States *(national)*: CA, JP, MX.

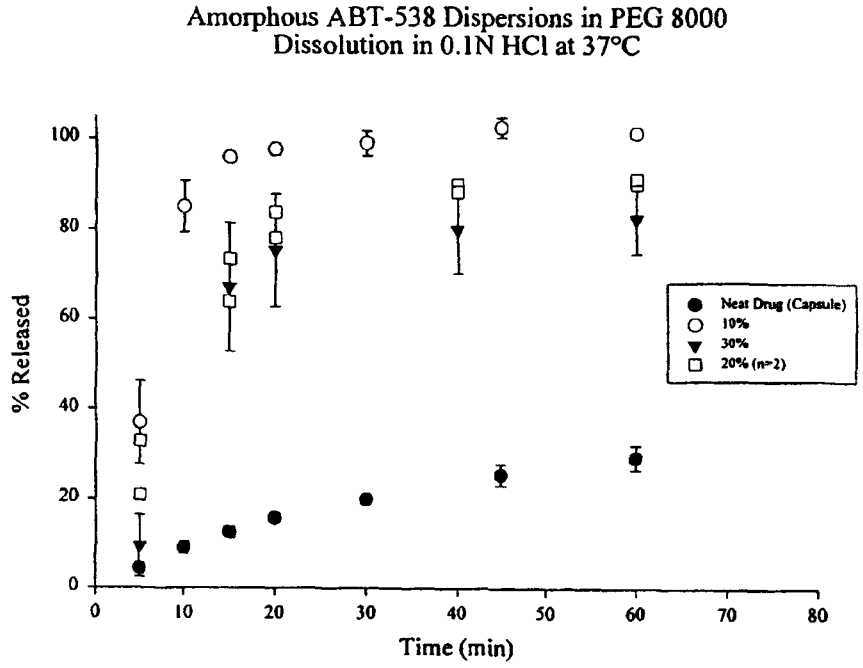
(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 January 2002

[Continued on next page]

(54) Title: SOLID DISPERSION PHARMACEUTICAL FORMULATIONS



(57) Abstract: A pharmaceutical composition is disclosed which comprises a soliddispersion of an HIV protease inhibitor in a water soluble carrier, such as PEG, having enhanced bioavailability and improved dissolution properties. The solid dispersion may optionally be encapsulated in hard gelatin capsules, compressed into a tablet, or may be granulated with a pharmaceutically acceptable granulating agent. Also disclosed are methods of making said solid dispersion and methods of treating an HIV infection employing said solid dispersion.

WO 01/34118 A3

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/L_ 00/30910

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K31/427 A61K31/513 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B.J. AUNGST ET AL.: "Amphiphilic vehicles improve the oral bioavailability of a poorly soluble HIV protease inhibitor at high doses" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 156, no. 1, 1997, pages 79-88, XP001009732 Amsterdam (NL) cited in the application page 81, paragraph 2.2	1-5,9,19
A	page 84; table 2	6-8, 10-18, 20,21
	--- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2001	04/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/ 00/30910

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 07696 A (ABBOTT LABORATORIES) 23 March 1995 (1995-03-23) page 1, paragraph 2 page 6, paragraph 4 page 17, paragraph 1 page 22; example 5 page 24; example 15	1-21

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/30910

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9507696 A	23-03-1995	AU 695516 B	13-08-1998
		AU 7717694 A	03-04-1995
		CA 2167412 A	23-03-1995
		EP 0719142 A	03-07-1996
		IL 110752 A	26-07-2000
		JP 9502715 T	18-03-1997
		US 5948436 A	07-09-1999
		US 5725878 A	10-03-1998
		US 5876749 A	02-03-1999

Exhibit 10

US 20040186066A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0186066 A1**

Petersen et al. (43) **Pub. Date: Sep. 23, 2004**

(54) **METHOD OF TREATMENT WITH NELFINAVIR**

(75) Inventors: **Carolyn Petersen**, San Diego, CA (US); **Edward F.C. Pun**, San Diego, CA (US)

Correspondence Address:
AGOURON PHARMACEUTICALS, INC.
10350 NORTH TORREY PINES ROAD
LA JOLLA, CA 92037 (US)

(73) Assignee: **AGOURON PHARMACEUTICALS, INC.**

(21) Appl. No.: **10/776,568**

(22) Filed: **Feb. 10, 2004**

Related U.S. Application Data

(60) Provisional application No. 60/446,444, filed on Feb. 10, 2003. Provisional application No. 60/524,259, filed on Nov. 21, 2003.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/7056**

(52) **U.S. Cl.** **514/43**

(57) **ABSTRACT**

The invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir in a pharmaceutical composition, wherein the nelfinavir is administered with food.

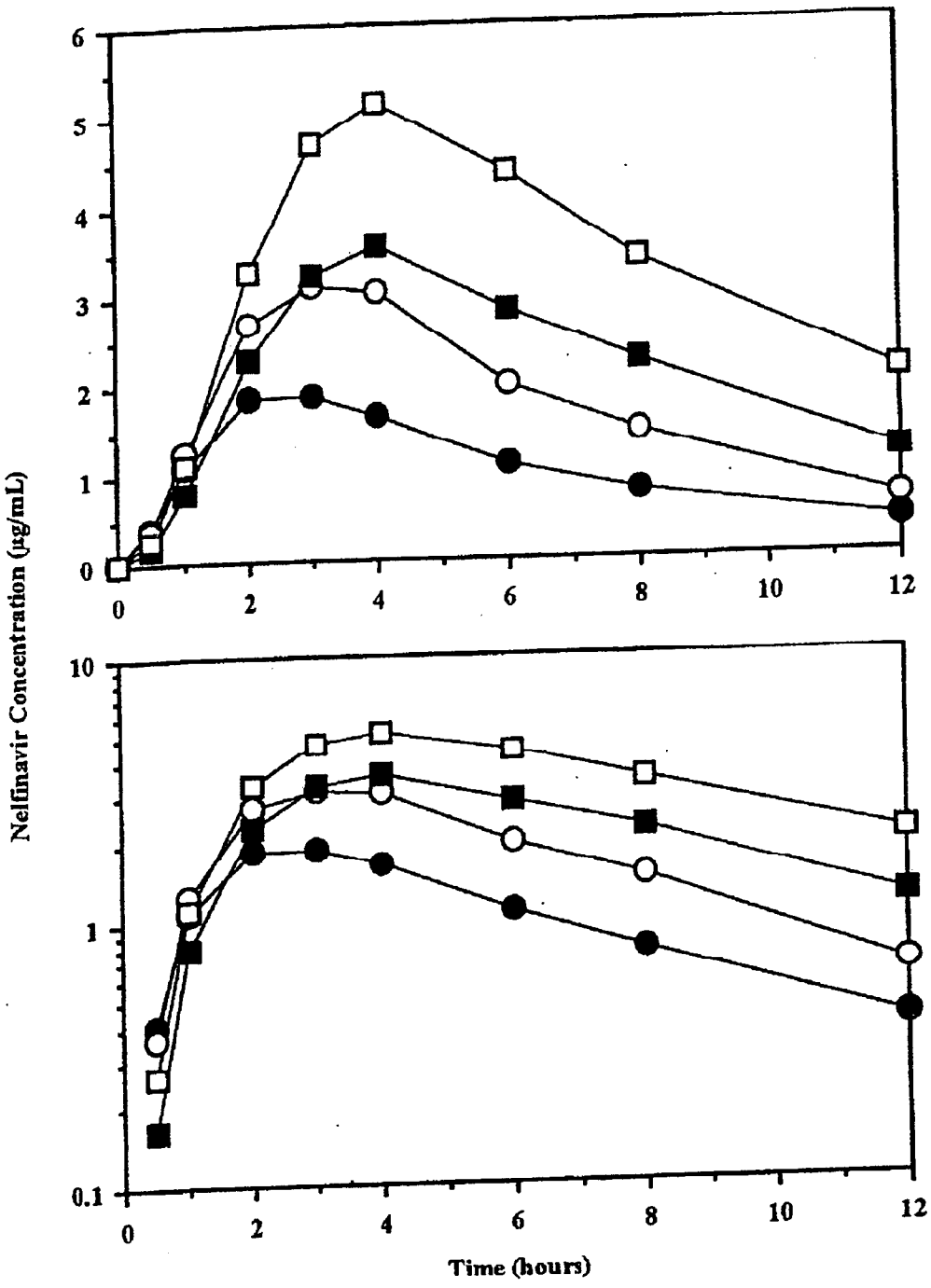

Nelfinavir Concentration (µg/mL)
6
5
4
3
2
1
0
0
2
4
6
8
10
12
10
1
0.1
0
2
4
6
8
10
12
Time (hours)

Figure 1

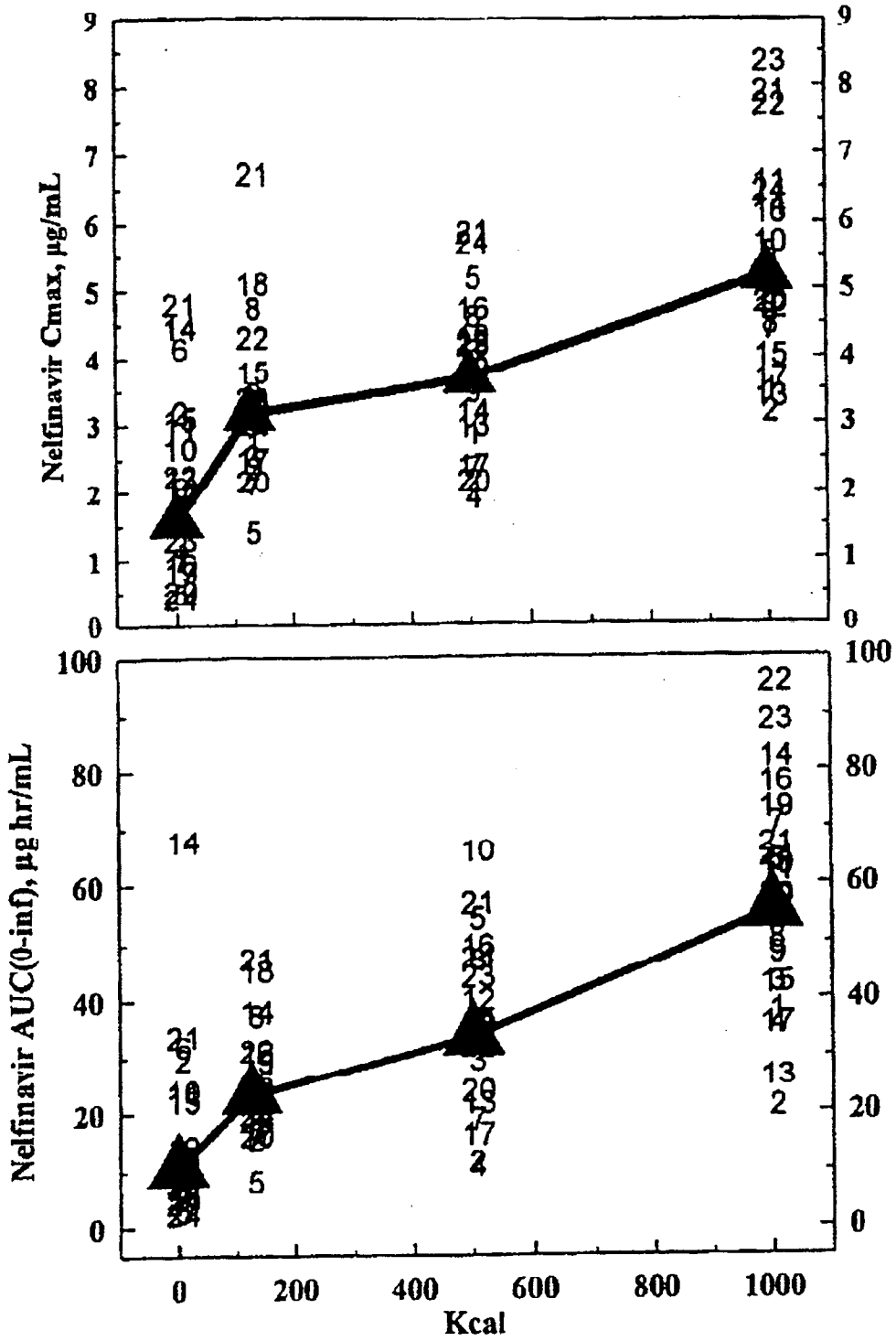

Nelfinavir Cmax, µg/mL
Nelfinavir AUC(0-inf), µg hr/mL
Kcal
0
200
400
600
800
1000

Figure 2

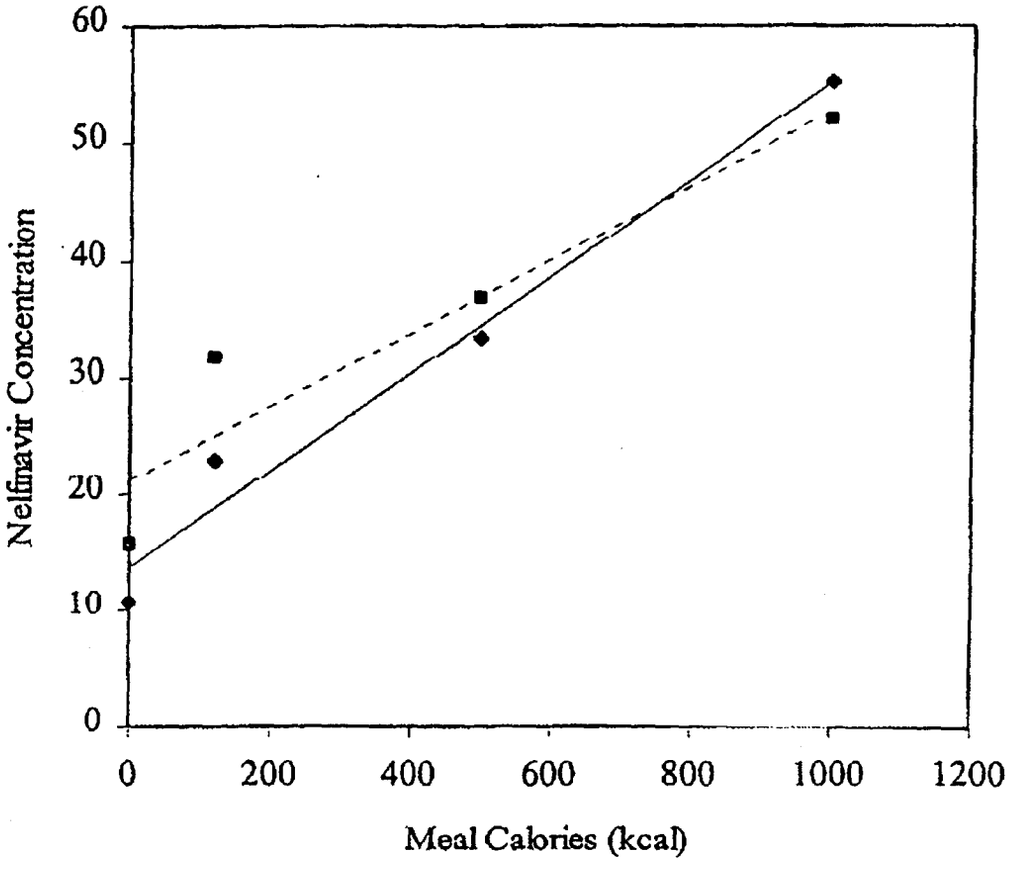

60
50
40
30
20
10
0
Nelfinavir Concentration
0
200
400
600
800
1000
1200
Meal Calories (kcal)

Figure 3

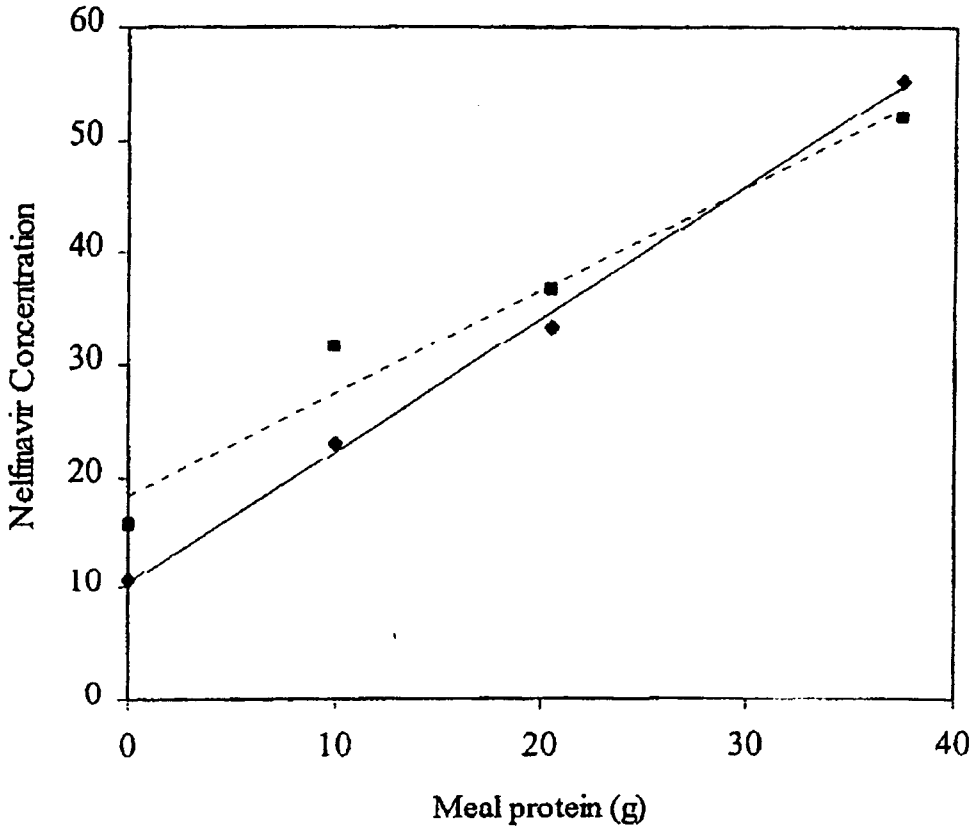

60
50
40
30
20
10
0
Nelfinavir Concentration
0
10
20
30
40
Meal protein (g)

Figure 4

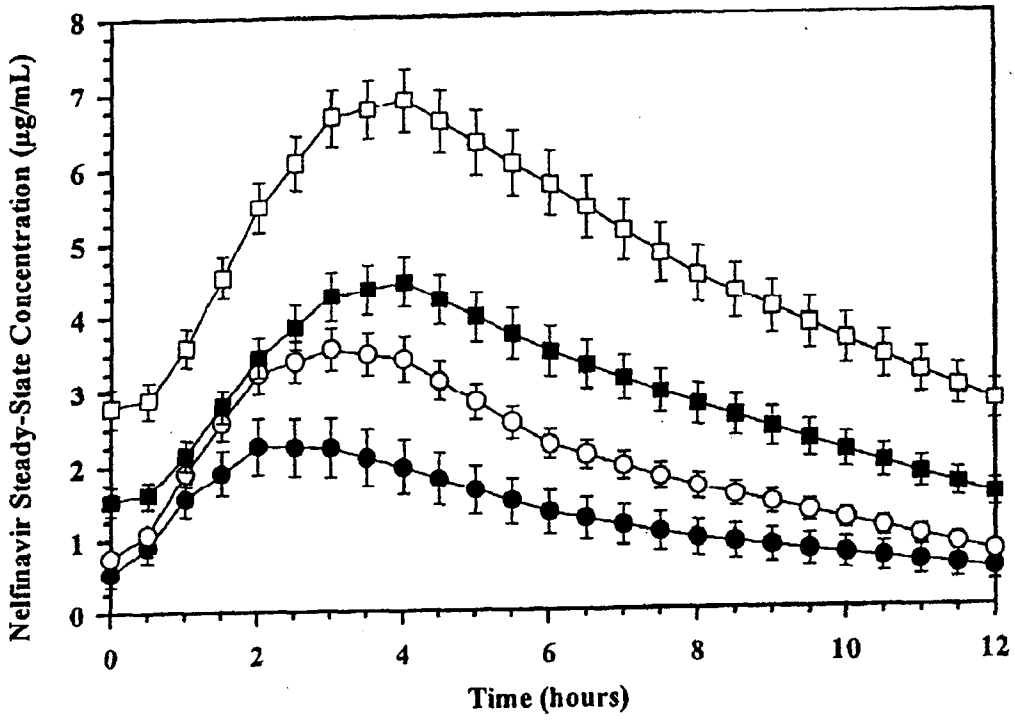

Nelfinavir Steady-State Concentration (µg/mL)
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
Time (hours)

Figure 5

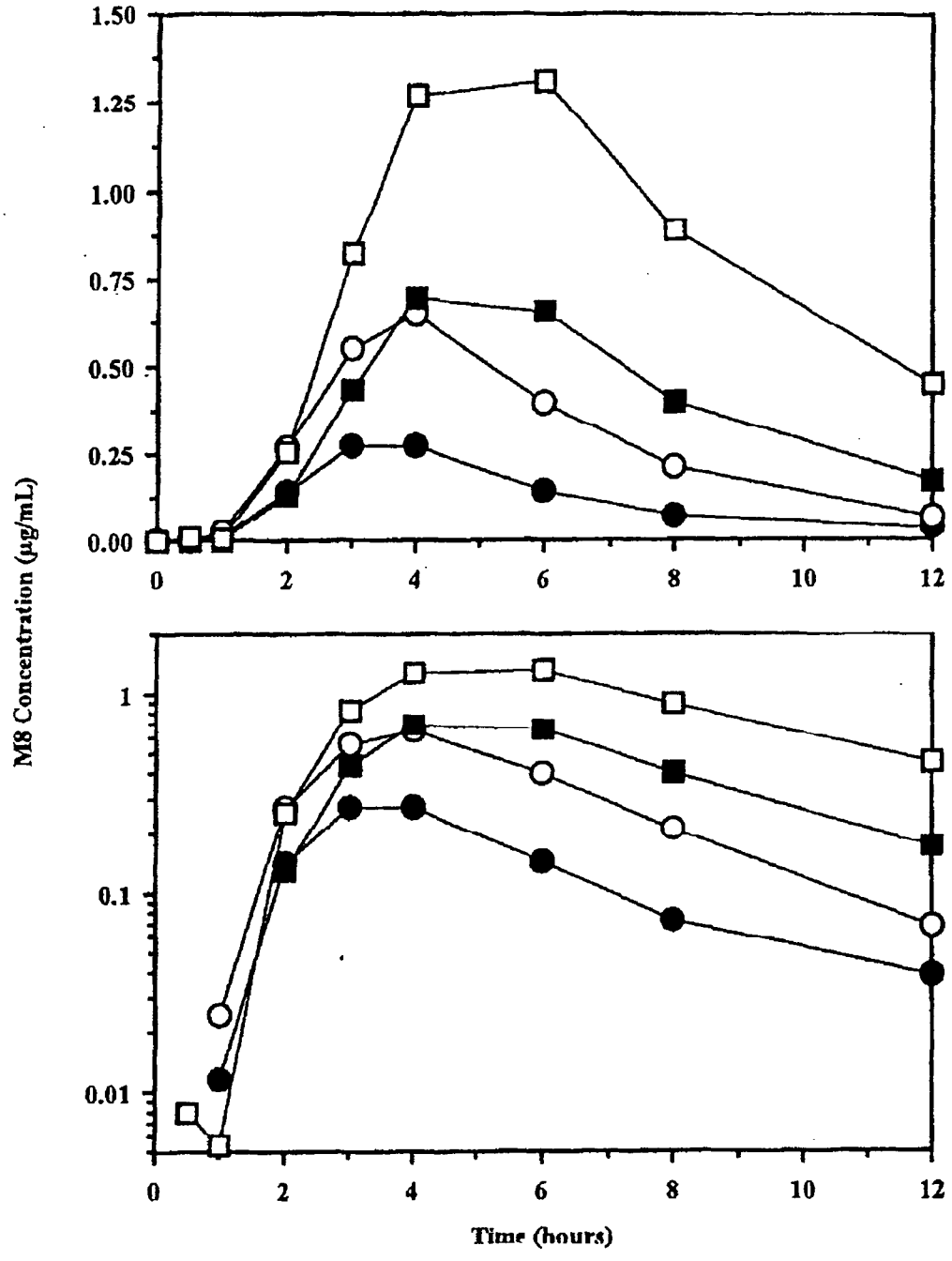

1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
12
M8 Concentration (µg/mL)
1
0.1
0.01
0
2
4
6
8
10
12
Time (hours)

Figure 6

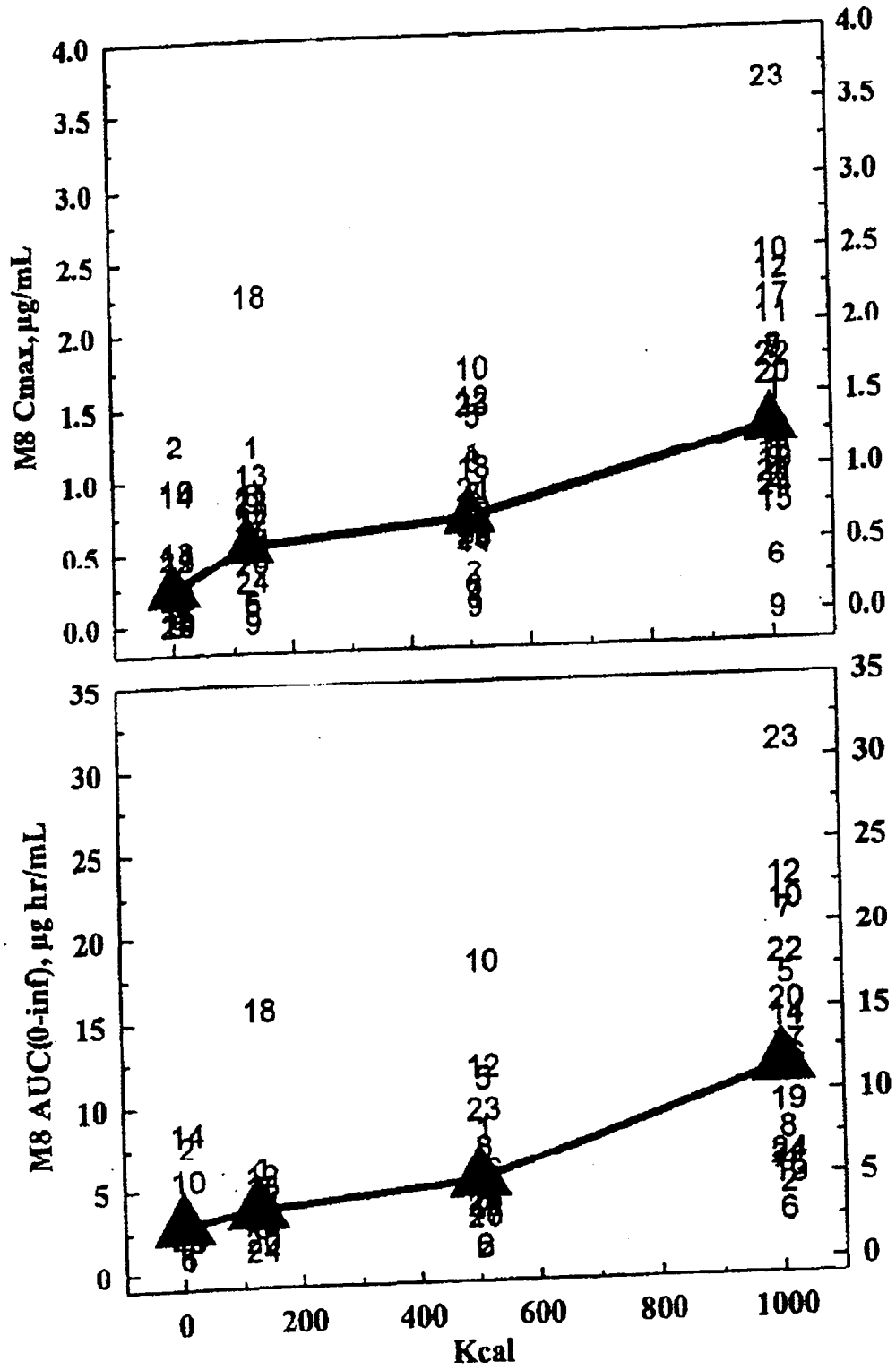


Figure 7

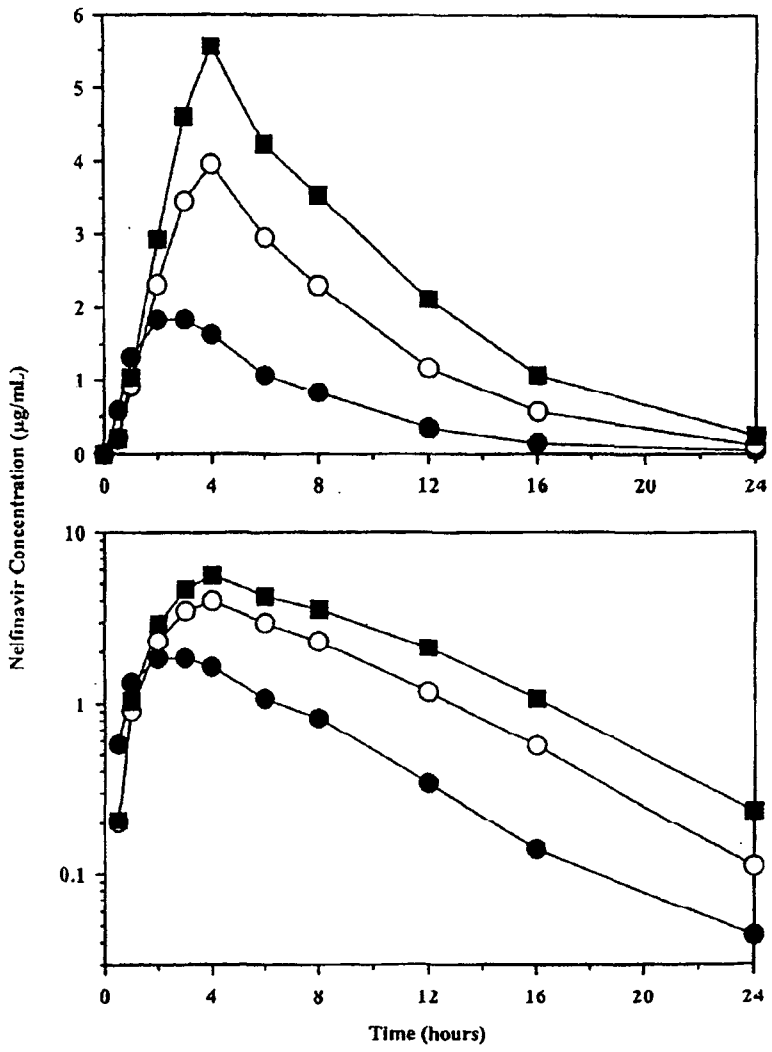


Figure 8. **Mean Nelfinavir Plasma Concentration-Time Profiles Following Administration of 5 x 250-mg Nelfinovir Tablets to Fasting Subjects (filled circles), During a Moderate Calorie/Low Fat Meal (open circles), and During a Moderate Calorie/High Fat Meal (filled squares) (Study A4301009). Upper and lower panels are linear and semi-logarithmic plots, respectively.**

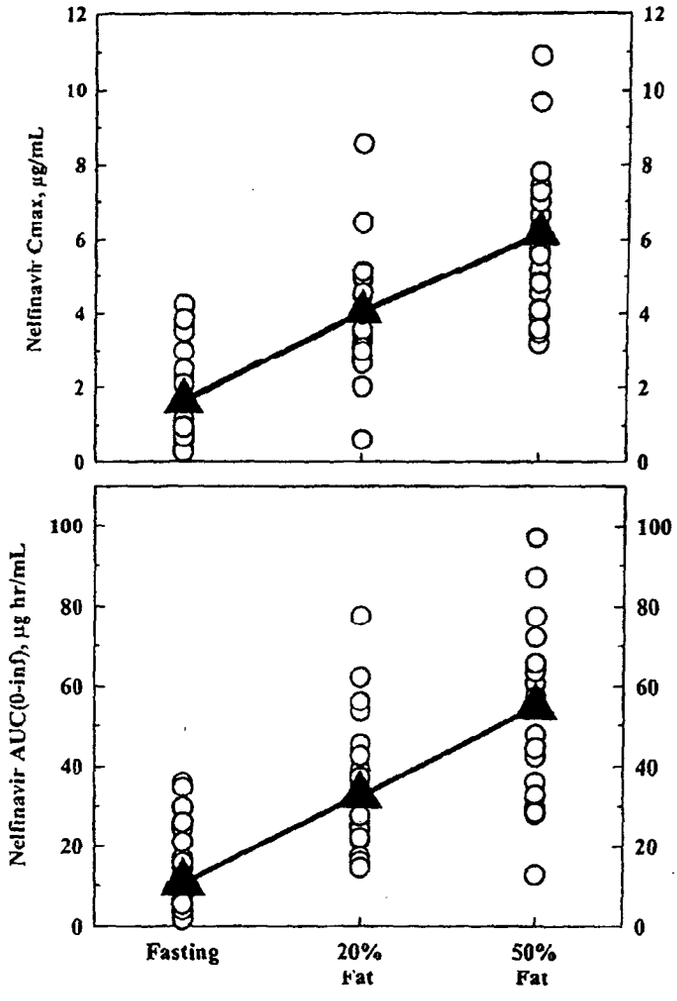


Figure 9. Individual Nelfinavir Cmax (upper panel) and AUC(0-∞) Values (lower panel) Following Administration of 5 x 250-mg Nelfinavir Tablets to Fasting Subjects, During a Moderate Calorie/Low Fat Meal, and During a Moderate Calorie/High Fat Meal (Study A4301009). Individual and mean values are represented by open circles and triangles, respectively.

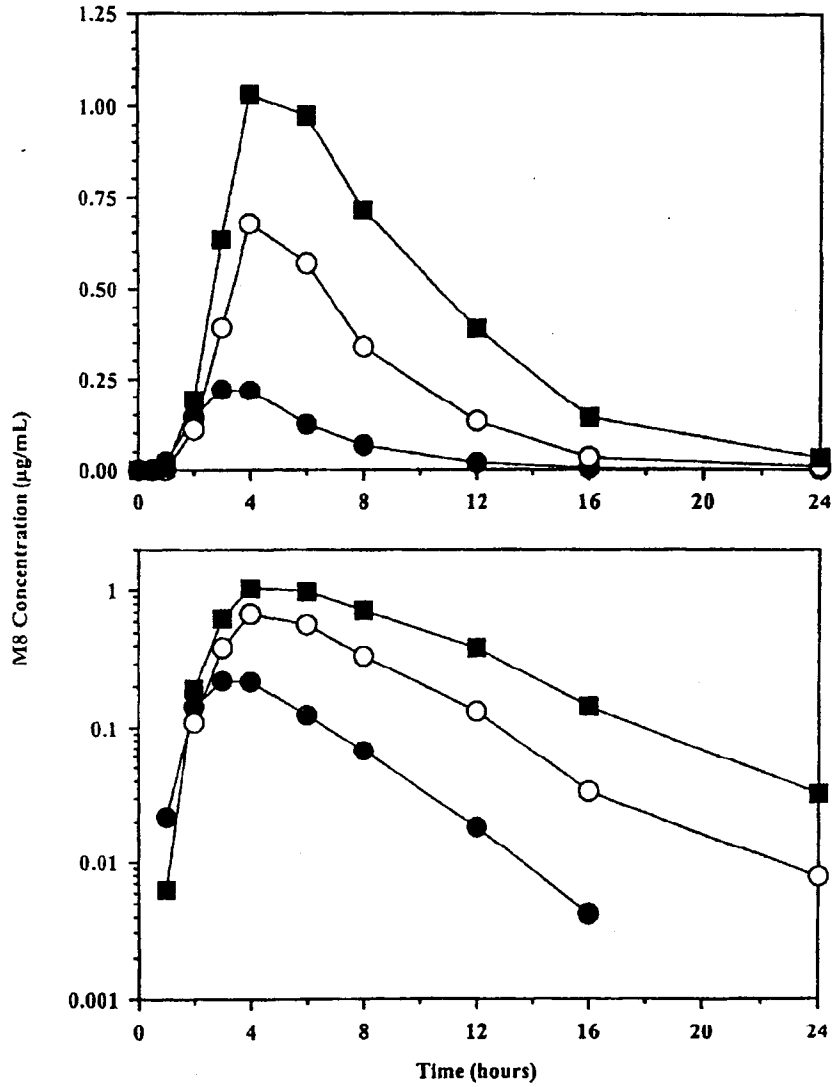


Figure 10. Mean M8 Plasma Concentration-Time Profiles Following Administration of 5 x 250-mg Nelfinavir Tablets to Fasting Subjects (filled circles), During a Moderate Calorie/Low Fat Meal (open circles), and During a Moderate Calorie/High Fat Meal (filled squares) (Study A4301009). Upper and lower panels are linear and semi-logarithmic plots, respectively.

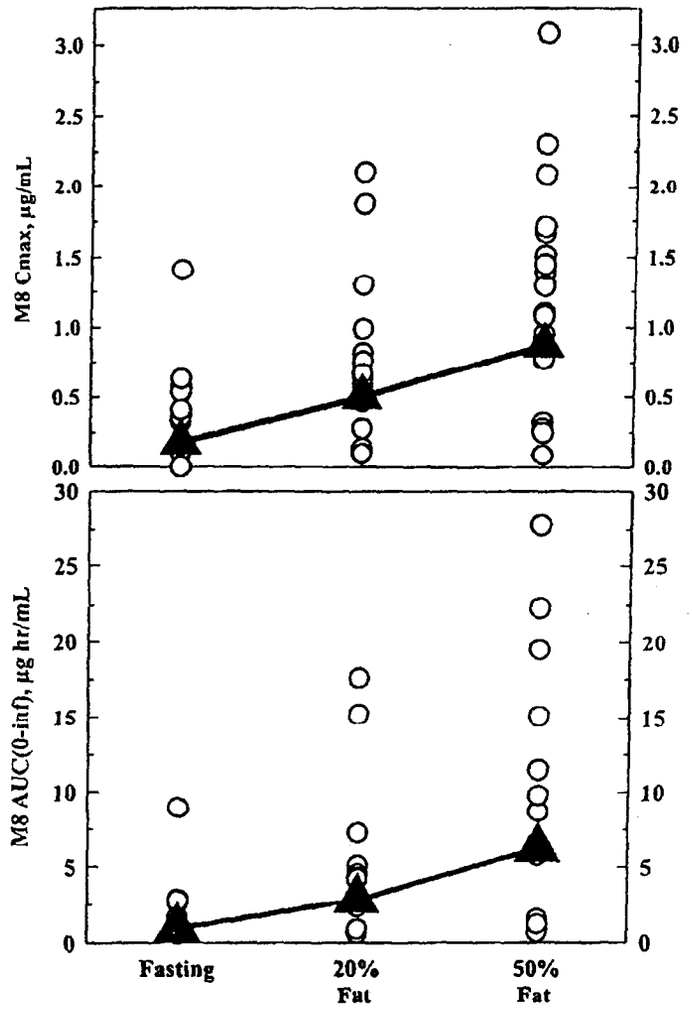


Figure 11. Individual M8 Cmax (upper panel) and AUC(0-∞) Values (lower panel) Following Administration of 5 x 250-mg Nelfinavir Tablets to Fasting Subjects, During a Moderate Calorie/Low Fat Meal, and During a Moderate Calorie/High Fat Meal (Study A4301009). Individual and mean values are represented by open circles and triangles, respectively.

METHOD OF TREATMENT WITH NELFINAVIR

[0001] This application claims priority from U.S. Provisional Application Serial No. 60/446,444 filed 10 Feb. 2003, and U.S. Provisional Application Serial No. 60/524,259, filed 21 Nov. 2003, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention is directed generally to methods of treating AIDS by administering nelfinavir in combination with food such that the bioavailability of nelfinavir is increased compared to its administration without food.

BACKGROUND OF THE INVENTION

[0003] Human immunodeficiency virus (HIV), the causative agent of AIDS, is a retrovirus that has an integral protease, Type 1 HIV Protease. The HIV protease is important in the maturation of the virus from a noninfectious to an infectious form. Inhibition of the HIV protease prevents post-translational processing such that immature and non-infectious viral particles are released. Several inhibitors of HIV protease are known.

[0004] One such inhibitor is [3S-(3R*, 4aR*, 8aR*, 2'S*, 3'S*)]-2-[2' hydroxy-3'-phenylthiomethyl-4'-aza-5'-oxo-5'-(2"-methyl-3"-hydroxy-phenyl)pentyl]-decahydroisoquinoline-3-N-t-butylcarboxamide methanesulfonic acid salt; also known as nelfinavir mesylate or nelfinavir and sold by Agouron Pharmaceuticals, Inc. (a Pfizer company) under the trademark Viracept®. Nelfinavir and methods of its manufacture and use are disclosed in the following patents, which are hereby incorporated herein in their entireties by reference: U.S. Pat. Nos. 5,484,926 (issued Jan. 16, 1996), 5,952,343 (issued Sep. 14, 1999), and 6,162,812 (issued Dec. 19, 2000).

[0005] Shetty et al (1996) observed that the oral bioavailability of nelfinavir mesylate was 43% in fed rats, dogs and monkeys, but was 29% in animals fasted overnight. Shetty et al, *Preclinical pharmacokinetics and distribution to tissue of AG* 1343, *an inhibitor of human immunodeficiency virus type* 1 *protease*, 40(1) Antimicrob. Agents Chemother. 110, 112 (1996). The fed state consisted of a meal 30 minutes before drug administration. Id. at 111.

[0006] Kurowski et al. (2002) reported that nelfinavir administration led to an $AUC_{0\text{-}12h}$ (plasma concentration integrated over twelve hours) that was 13% less when administered with a light breakfast comprising bread, jam, butter, milk and tea than when administered with a standard breakfast of bread, cheese, butter, milk, cornflakes, yogurt and tea. Kurowski, et al., *Limited effect of food consumption on the pharmacokinetics of nelfinavir administered twice daily*, 7 Eur. J. Med. Res. 453, 454 (2002). Although the authors consider d this difference statistically significant, they did not consider it clinically relevant. Id. No significant effects of the two different breakfasts were found for the remaining three parameters tested: $C_{1\text{-hour post dose}}$, C_{max}, and $C_{12\text{-hours}}$. The light breakfast had 350 kcal including 13 g of fat. The standard breakfast had 800 kcal including 35 g of fat. Id.

[0007] Aarnoutse et al. (2003) reported that meal consumption had a significant effect on the $AUC_{24h,\ corr}$ and C_{min} values for nelfinavir and nelfinavir plus M8, the active metabolite of nelfinavir. Aarnoutse, et al., *Pharmacokinetics, food intake requirements and tolerability of once-daily combinations of nelfinavir and low-dose ritonavir in healthy volunteers*, 55 Br. J. Clin. Pharmacol. 115, 120 (2003). In Aarnoutse et aL. (2003), the full breakfast had 610 kcal, 33% fat (about 22 g), 16% protein (about 24 g), and 51% carbohydrate. Id. at 116. The light breakfast had 271 kcal, 37% fat (about 11 g), 24% protein (about 16 g), and 39% carbohydrates. Id. at 117.

[0008] Quart et al. found that single dose administration of nelfinavir under fasting conditions resulted in AUC (area under the plasma concentration-time profile) values that were 27-50% of those observed when the drug was administered with food. Quart et al., *Phase I safety, tolerance, pharmacokinetics and food effect studies of AG* 1343—*a novel protease inhibitor*, Natl Conf. Hum. Retroviruses Relat. Infect. (2^{nd}) 167 (1995).

[0009] Petersen et al. found that food intake had a marked effect on nelfinavir pharmacokinetics with highest levels achieved after the greatest food intake, that M8 concentrations rose with increasing food intake, but remained at 15-20% of nelfinavir, and that the contribution of different quantities of fat on pharmacokinetics required further study. Petersen et al., *Pharmacokinetics of nelfinavir (Viracept®250 mg tablet): effect of food intake on single-dose PK parameters*, 10^{th} Conference on Retroviruses and Opportunistic Infections Abstract 544 (Feb. 10-14, 2003).

[0010] The Physician's Desk Reference (PDR) entry for Viracept® nelfinavir (rev. Nov. 2001), recommends that it be administered with food. The PDR reference discloses that the maximum plasma concentrations and AUC were two to three-fold higher under fed conditions compared to fasting. The meals evaluated contained 517 to 759 Kcal, with 153 to 313 Kcal derived from fat. Id. Thus, the advantage of moderate food intake with nelfinavir administration has been shown, but the effect of fat consumption and high caloric intake with nelfinavir has not been well studied.

[0011] Some HIV medications have shown strong food effects on bioavailability. Some anti-HIV reverse transcriptase inhibitors are recommended to be administered on an empty stomach, including efavirenz, AZT, ddC, and ddI. Other reverse transcriptase inhibitors can be taken without or with food. Inhibitors of HIV protease vary in their food effects. Indinavir is recommended for administration without food, but with copious amounts of water. In contrast, saquinavir, another HIV protease inhibitor, is recommended for administration with a high fat meal. Amprenavir and lopinavir may be taken without or with food. The differing effect of food on protease inhibitors suggests a lack of a common mechanism underlying the processing and uptake of the protease inhibitors from the gastrointestinal tract.

[0012] Optimizing dosaging of protease inhibitors such as nelfinavir is desirable both to minimize side effects and ensure efficacy against HIV. Protease inhibitor therapy is sometimes associated with side effects such as diarrhea, fat redistribution, insulin resistance, diabetes and hyperlipidemia. Lenhard et al., *Dietary fat alters HIV protease inhibitor-induced metabolic changes in mice*, Am. Soc. Nutr. Sci. 2361 (2000). Yet virological failure of nelfinavir-containing HIV regimens has been related to low plasma levels of nelfinavir. Burger et al., *Therapeutic drug monitoring* (TDM) *of nelfinavir* (NELFINAVIR) 1250*mg* BID *in*

treatment-naive patients improves therapeutic outcome after 1 year: results from ATHENA, 2d Int'l Workshop on Clinical Pharmacology of HIV Therapy, Noordwijk, the Netherlands (2001), Abstract 6.2b. Thus, there is a need for an improved nelfinavir therapy that provides for therapeutic effect while avoiding excessive nelfinavir plasma levels that could lead to undesired side effects.

SUMMARY OF THE INVENTION

[0013] In one aspect, the invention relates a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal.

[0014] In another aspect, the invention relates a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than about 900 kcal or about 1000 kcal.

[0015] In a further aspect, the invention relates to the administration of nelfinavir, according to the above-described methods, wherein administration of the nelfinavir occurs between 30 minutes prior to and two hours after consumption of food. The administration of nelfinavir, according to the above-described methods, may also occur between 30 minutes prior to and one hour after consumption of food, or the administration of nelfinavir may occur at about the same time as the consumption of food.

[0016] In yet another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal. In an alternative embodiment, the nelfinavir is administered at least twice daily for at least two weeks and at least twice daily nelfinavir is administered with food and the food comprises more than 800 kcal at each administration.

[0017] In still another aspect, the invention relates a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal and wherein the food comprises between about 40% fat and about 50% fat by energy content or between about 50% fat and about 60% fat by energy content or between about 60% fat and about 70% fat by energy content or between about 70% fat and about 80% fat by energy content or between about 80% fat and about 90% fat by energy content or between about 90% fat and about 100% fat by energy content. In an alternative embodiment of the above-described method, the food comprises more than 40%, 50%, 60%, 70%, 80% or 90% fat by energy content.

[0018] In still another aspect, the invention relates a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal and wherein the food comprises from 36 g to 55 g fat or from 40 g to 55 g fat or at least about 55 g fat.

[0019] In yet a further aspect, the invention relates a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal and wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state or at least about 5-fold greater than the AUC(0-∞) after administration in the fasted state.

[0020] In still a further aspect, the invention relates a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal and wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prodrug thereof.

[0021] In another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content.

[0022] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the administration of nelfinavir occurs between 30 minutes prior to and two hours after consumption of food or between 30 minutes prior to and one hour after consumption of food or at about the same time as the consumption of food.

[0023] In yet another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in

a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the food comprises between about 50% fat and about 60% fat by energy content or between about 60% fat and about 70% fat by energy content or between about 70% fat and about 80% fat by energy content or between about 80% fat and about 90% fat by energy content or between about 90% fat and about 100% fat by energy content.

[0024] In still another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the food comprises more than about 60%, 70%, 80% or 90% fat by energy content.

[0025] In still a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the food comprises from 36 g to 55 g fat or from 40 g to 55 g fat or at least about 55 g fat.

[0026] In still another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the food comprises at least about 600 kcal or at least about 700 kcal or at least about 800 kcal or at least about 900 kcal or at least about 1000 kcal.

[0027] In yet a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state.

[0028] In yet another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 5-fold greater than the AUC(0-∞) after administration in the fasted state.

[0029] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content and wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prodrug thereof.

[0030] In yet another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content.

[0031] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the administration of nelfinavir occurs between 30 minutes prior to and two hours after consumption of food or between 30 minutes prior to and one hour after consumption of food or the administration of nelfinavir occurs at about the same time as the consumption of food.

[0032] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein nelfinavir is administered at least twice daily for at least two weeks and at least twice daily nelfinavir is administered with food and the food comprises more than 500 kcal, 600 kcal, 700 or 900 kcal (and more than about 50% fat by energy content at each administration).

[0033] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the food comprises between about 50% fat and about 60%

fat by energy content, or between about 60% fat and about 70% fat by energy content, or between 70% fat and about 80% fat by energy content, or between about 80% fat and about 90% fat by energy content, or between about 90% fat and about 100% fat by energy content.

[0034] In still a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the food comprises more than about 60%, 70%, 80% or 90% fat by energy content.

[0035] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the food comprises from 36 g to 55 g fat or from 40 g to 55 g fat or the food comprises at least about 55 g fat.

[0036] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt or prodrug thereof.

[0037] In yet another aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state.

[0038] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 5-fold greater than the AUC(0-∞) after administration in the fasted state.

[0039] In a further aspect, the invention relates to a method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content and wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prodrug thereof.

[0040] In another aspect, the invention relates to a kit comprising a therapeutically effective oral dose of nelfinavir and a printed material comprising instructions for administering the dose with food comprising at least 800 kcal in a high-fat meal.

[0041] In a further aspect, the invention relates to a kit comprising a therapeutically effective oral dose of nelfinavir and a printed material comprising instructions for administering the dose with food comprising at least 800 kcal in a high-fat meal and wherein the label further comprises instructions for administering the dose with food comprising at least 50% fat by energy content

[0042] In yet another aspect, the invention relates to a kit comprising a therapeutically effective oral dose of nelfinavir and a printed material comprising instructions for administering the dose with food comprising at least 800 kcal in a high-fat meal and wherein the high-fat meal is recited to comprise more than about 36 g of fat.

[0043] In another aspect, the invention relates to a therapeutic composition for the treatment of human immunodeficiency virus (HIV) in a mammal comprising fat and a therapeutically effective amount of nelfinavir in a weight ratio of at least about 25 fat:1 nelfinavir.

[0044] In a further aspect, the invention relates to a therapeutic composition for the treatment of human immunodeficiency virus (HIV) in a mammal comprising fat and a therapeutically effective amount of nelfinavir in a weight ratio of at least about 25 fat:1 nelfinavir and wherein the weight ratio is greater than about 30 fat:1 nelfinavir

[0045] In yet another aspect, the invention relates to a therapeutic composition for the treatment of human immunodeficiency virus (HIV) in a mammal comprising fat and a therapeutically effective amount of nelfinavir in a weight ratio of at least about 25 fat:1 nelfinavir and wherein the amount of nelfinavir is between about 100 mg and about 1500 mg.

BRIEF DESCRIPTION OF THE FIGURES

[0046] **FIG. 1.** Mean nelfinavir plasma concentration-time profiles following administration of 1250-mg oral doses to fasting subjects (closed circles), with a low calorie/low fat meal (open circles), with a moderate calorie/low fat meal (closed squares), and with a high calorie/high fat meal (open squares). Upper panel and lower panel use linear and semi-logarithmic plots, respectively.

[0047] **FIG. 2.** Individual nelfinavir Cm, (upper panel) and AUC(0-∞) (lower panel) values following administra-

tion of 1250-mg nelfinavir oral doses to fasting subjects (0 Kcal), with a low calorie/low fat meal (125 Kcal), with a moderate calorie/low fat meal (500 Kcal), and with a high calorie/high fat meal (1000 Kcal). Individual subject and mean values are illustrated by numbers and triangles, respectively.

[0048] **FIG. 3**. Mean nelfinavir plasma concentration as a function of meal caloric content. The AUC(0-∞) (lozenge, solid line) values are in units of μg·hr/mL and have a correlation of r^2>0.97. The C_{max} (squares, dashed line) values are in units of μg/mL and have a correlation of r^2>0.89. Measurement followed administration of a 1250 mg oral dose of nelfinavir.

[0049] **FIG. 4**. Mean nelfinavir plasma concentrations as a function of meal protein content. The AUC(0-∞) (lozenge, solid line) values are in units of μg·hr/mL and have a correlation of r^2>0.99. The C_{max} (squares, dashed line) values are in units of μg/mL and have a correlation of r^2>0.96. Measurement followed administration of a 1250 mg oral dose of nelfinavir.

[0050] **FIG. 5**. Mean simulated nelfinavir steady-state plasma concentration-time profiles following BID administration of 1250-mg oral doses to fasting subjects (closed circles), with a low calorie/low fat meal (open circles), with a moderate calorie/low fat meal (closed squares), and with a high calorie/high fat meal (open squares). The bars represent standard errors.

[0051] **FIG. 6**. Mean M8 plasma concentration-time profiles following administration of 1250-mg nelfinavir oral doses to fasting subjects (closed circles), with a low calorie/low fat meal (open circles), with a moderate calorie/low fat meal (closed squares), and with a high calorie/high fat meal (open squares). Upper and lower panels represent linear and semi-logarithmic plots, respectively.

[0052] **FIG. 7**. Individual M8 C_{max} (upper panel) and AUC(0-∞) (lower panel) values following administration of 1250-mg nelfinavir oral doses to fasting subjects (0 Kcal), with a low calorie/low fat meal (125 Kcal), with a moderate calorie/low fat meal (500 Kcal), and with a high calorie/high fat meal (1000 Kcal). Individual subject and mean values are illustrated by numbers and triangles, respectively.

[0053] **FIG. 8**. Mean nelfinavir plasma concentration-time profiles following administration of 5×250-mg nelfinavir tablets to fasting subjects (filled circles), during a moderate calorie/low fat meal (open circles), and during a moderate calorie/high fat meal (filled squares), according to Example 2. Upper and lower panels are linear and semi-logarithmic plots, respectively.

[0054] **FIG. 9**. Individual nelfinavir C_{max} (upper panel) and AUC(0-∞) values (lower panel) following administration of 5×250-mg nelfinavir tablets to fasting subjects, during a moderate calorie/low fat meal, and during a moderate calorie/high fat meal, according to Example 2. Individual and mean values are represented by open circles and triangles, respectively.

[0055] **FIG. 10**. Mean M8 plasma concentration-time profiles following administration of 5×250-mg nelfinavir tablets to fasting subjects (filled circles), during a moderate calorie/low fat meal (open circles), and during a moderate calorie/high fat meal (filled squares) according to Example 2. Upper and lower panels are linear and semi-logarithmic plots, respectively.

[0056] **FIG. 11**. Individual M8 C_{max} (upper panel) and AUC(0-∞) values (lower panel) following administration of 5×250-mg nelfinavir tablets to fasting subjects, during a moderate calorie/low fat meal, and during a moderate calorie/high fat meal according to Example 2. Individual and mean values are represented by open circles and triangles, respectively.

DETAILED DESCRIPTION OF THE INVENTION

[0057] In one aspect the invention relates to a method of treating HIV in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir in a pharmaceutical composition with food and the food comprises more than 800 kcal. Alternatively, the food may comprise more than about 900 kcal or more than about 1000 kcal. The mammal preferably is a human.

[0058] Preferably, under the methods of the invention, HIV is treated by administering nelfinavir at least once daily for at least two weeks. More preferably, nelfinavir is administered at least twice daily. Other preferable conditions of treatment include nelfinavir administration three times daily. Preferably, nelfinavir therapy continues for at least two weeks. More preferably, nelfinavir is administered for at least four weeks. Other durations of treatment that are preferred are at least three months, at least six months, and at least one year.

[0059] Administration of nelfinavir should be with food. Preferably, nelfinavir is administered between 30 minutes prior to and two hours after consumption of food. More preferably, nelfinavir is administered between 30 minutes prior to and one hour after consumption of food. Still more preferably, the administration of nelfinavir occurs at about the same time as the consumption of food. Preferably, nelfinavir is administered at least once a day with one of the meals described herein. More preferably, nelfinavir is administered at least twice a day with each administration of nelfinavir being with one of the meals described herein. Also preferable is administration of nelfinavir three times a day with each administration of nelfinavir being with one of the meals described herein.

[0060] One of the preferred meals of the invention is at least 800 kcal. More preferably, nelfinavir is administered with food of at least 800 kcal and one of the following ranges of fat content as measured by percentage of energy content: between about 40% fat and about 50% fat, between about 50% fat and about 60% fat, between about 60% fat and about 70% fat, between about 70% fat and about 80% fat, between about 80% fat and about 90% fat and between about 90% fat

and about 100% fat. Also preferable is administration of nelfinavir with a meal of at least 800 kcal and at least one of the following levels of fat content as measured by percentage of energy content: more than 40% fat, more than 50% fat, more than 60% fat, more than 70% fat, more than 80% fat and more than about 90% fat. Also, nelfinavir may be administered with food comprising at least 800 kcal and an amount of fat from the following list: from 36 g to 55 g fat, from 40 g to 55 g fat and at least about 55 g fat.

[0061] Another method of the invention is treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content. Preferably, the food comprises at least about 500 kcal and has a fat content as measured by percentage of energy content from one of the following ranges: between about 50% fat and about 60% fat, between about 60% fat and about 70% fat, between about 70% fat and about 80% fat, between about 80% fat and about 90% fat, and between about 90% fat and about 100% fat. Also preferable is administration of nelfinavir with a meal of at least about 500 kcal and at least one of the following levels of fat content as measured by percentage of energy content: more than about 60% fat, more than about 70% fat, more than about 80% fat and more than about 90% fat. Also, nelfinavir may be administered with food comprising at least about 500 kcal and an amount of fat from the following list: from 36 g to 55 g fat, from 40 g to 55 g fat and at least about 55 g fat. Also preferable is administration of nelfinavir with food wherein the food comprises at least about 50% fat by energy content and at least 600 kcal, at least 700 kcal, at least 800 kcal, at least 900 kcal, or at least 1000 kcal.

[0062] In the methods of the invention, administration of a pharmaceutical composition of nelfinavir with food results in an increase in plasma concentration of nelfinavir. The plasma concentration can be measured as AUC. Preferably, the inventive methods result in an increase in the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food that is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state and, more preferably, is at least about 5-fold greater than the AUC(0-∞) after administration in the fasted state.

[0063] In one aspect, the plasma concentration can be measured as C_{max}. The method can further comprise increasing C_{max} values at least about 3-fold compared to a fasted subject.

[0064] In still yet another aspect of the method of the invention, administration of the nelfinavir composition with food as described herein increases plasma concentration of a metabolite of nelfinavir, hydroxyl-t-butylamide, also called M8. The method can further comprise increasing AUC values of M8 at least about 3-fold compared to a fasted subject and more preferably at least 5-fold.

[0065] The amount of the nelfinavir administered can be any therapeutically effective amount. For example, for an adult a dose of 1250 mg twice daily or 750 mg three times daily is recommended. In pediatric patients, an effective dose is 20-30 mg/kg three times daily. Nelfinavir can be administered in any pharmaceutically acceptable form, such as a salt, stereoisomer, solvate or prodrug of nelfinavir.

[0066] In another aspect of the invention, a composition comprising nelfinavir is administered to a subject to whom no other HIV medications are administered. In a particular aspect, a composition comprising nelfinavir is administered to a subject who is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prodrug thereof.

[0067] In yet another aspect, nelfinavir is administered to a subject suffering from an HIV infection who is receiving at least one other HIV medication including, but not limited to a protease inhibitor, a nucleoside analogue reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, a nucleotide analogue reverse transcriptase inhibitor, or a viral fusion inhibitor. The additional HIV medication can be, but is not limited to, one or more of the following drugs: Retrovir® (3'-azido-2',3'-dideoxythymidine or AZT), Epivir® (2',3'-dideoxy 3'-thiacytidine or 3TC), Combivir® (AZT in combination with 3TC), Videx® (2',3'-dideoxyinosine or didanosine or ddI), Hivid® (2',3'-dideoxycytidine or ddC), Zerit® (stavudine or 2',3'-didehydro-3'-deoxythymidine or 3'-deoxythymidin-2'-ene or d4T), Ziagen® (abacavir), Viramun® (nevirapine), Rescriptor® (delavirdine), Sustiva® (efavirenz), Preveon® (adefovir dipovoxil), Crixivan® (indinavir), Angenerase® (amprenavir) and Hydrea® (hydroxy urea).

[0068] The invention also relates to a kit comprising a therapeutically effective oral dose of nelfinavir and printed material comprising instructions for administering the dose with food according to one of the methods of the invention. For example, the printed material may comprise instructions that nelfinavir be administered with food comprising at least 800 kcal in a high-fat meal. The high-fat meal preferably is instructed to comprise at least 40% fat by energy content. Alternatively, the printed material may instruct that nelfinavir be administered with food comprising at least 500 kcal and 50% fat by energy content. In another embodiment, the printed material may instruct that the food comprise more than about 36 g of fat.

[0069] In still yet another aspect, the invention relates to a therapeutic composition for the treatment of HIV comprising fat and a therapeutically effective amount of nelfinavir in a weight ratio of at least about 25 fat: 1 nelfinavir. Also preferred is a composition in which the weight ratio is greater than about 30 fat: 1 nelfinavir. Preferably, the amount of nelfinavir is between about 100 mg and about 1500 mg, more preferably between 250 mg to 625 mg inclusive.

EXAMPLE 1

Evaluation of Total Kilocalories and Fat on Nelfinavir Bioavailability

[0070] A phase I, randomized, open-label crossover study to evaluate the impact of total kilocalories and fat content on single-dose pharmacokinetic parameters of the nelfinavir 250 mg tablet formulation in normal healthy volunteers was performed.

[0071] Methods

[0072] Healthy volunteers entered the study and received the following treatment in random order at least 1 week apart:

[0073] 1) 5×250 mg nelfinavir tablets, fasted

[0074] 2) 5×250 mg nelfinavir tablets (breakfast meal 1, 125 Kcal/20% fat=low cal/low fat)

[0075] 3) 5×250 mg nelfinavir tablets (breakfast meal 2, 500 Kcal/20% fat=medium cal/low fat)

[0076] 4) 5×250 mg nelfinavir tablets (breakfast meal 3, 1000 Kcal/50% fat=high cal/high fat).

[0077] Plasma concentrations of nelfinavir and its active hydroxy-t-butylamide metabolite (M8) were measured by validated high performance liquid chromatography (HPLC) methods. Pharmacokinetic parameters were determined from plasma concentration-time data using standard methods.

[0078] The following statistical methods were used:

[0079] 1) Log-transformed nelfinavir area under the concentration-time profile (AUC) was the primary parameter analyzed to determine the effect of caloric and fat content of meals on nelfinavir pharmacokinetics.

[0080] 2) Secondary parameters included were nelfinavir $T_{1/2}$, time to maximum observed plasma concentration (T_{max}), and log transformed C_{max}, as well as M8 pharmacokinetic parameters.

[0081] 3) Parameter values were evaluated by Analysis of Variance (ANOVA) using a model incorporating sequence, subject within sequence, period and treatment effects. Statistical tests were performed using the Type III sum of squares derived using WinNONlin Pro Version 2.1. Least squares treatment mean values were determined for each parameter.

[0082] 4) Results from ANOVA were used to calculate 90% confidence intervals for the ratio (test/reference) least-square treatment mean values, where administration of single nelfinavir doses in the fasting state was the reference treatment.

[0083] Menus for the standardized breakfast meals were as follows. Nutrient composition data is from the USDA Nutrient Database for Standard Reference, Release 14 and select manufacturer's data for specific brands.

Food	Amount	Energy, Kcal	Fat, gm	Protein, gm	Carbo., gm
Breakfast M al 1: 125 Kcal, 10 gm proteins, 3 gm fat (20%)					
Milk, 1%	10 fluid ounces	125	3.1	10.0	14.6
Breakfast Meal 2: 500 Kcal, 20 gm protein, 11 gm fat (20%)					
Orange Juice	8 fluid ounces	110	0.1	1.7	26.8
Yogurt, Dannon Light and Fit	4 ounces	60	0	5.0	26
Cereal, Cherrios	1 cup	110	1.8	3.1	22.9
Milk, 2%	8 fluid ounces	122	4.6	8.0	11.7
Toast, wheat	1 slice	65	1	2.7	11.8
Butter	1 teaspoon	34	3.8	0	0
Total		501	11.3	20.5	99.2
Breakfast Meal 3: 1000 Kcal, 36 gm protein, 56 gm fat (50%)					
Eggs fried in	2 extra large	172	11.6	14.5	1.4
Butter	2 teaspoons	68	7.6	0	0
Bacon	3 strips	108	9.3	5.9	0
Toast, wheat	2 slices	130	2	5.4	23.6
Butter	2.5 teaspoons	85	9.5	0	0
Hash Brown Potatoes, ORE IDA frozen, southern style OR shredded Cooked in Butter	4 ounces 1½ cups 2 teaspoons	105 68	0 7.6	2 0	23 0
Milk, whole 3.25%	8 fluid ounces	149	8.1	8.0	11.4
Orange juice	8 fluid ounces	112	0.1	1.7	26.8
Total		997	55.8	37.5	86.2

[0084] All subjects who were included in the study were willing to adhere to the specified restrictions, were between 18 and 60 years of age (inclusive), had a Body Mass Index (BMI) between 18 and 31 kg/M^2 (inclusive), and were HIV-1 and HIV-2 seronegative. All females were not pregnant, as determined by a serum pregnancy test prior to Day 1 and a urine pregnancy test prior to each dose.

[0085] All subjects received oral doses of nelfinavir according to the schedule in Table 1.

TABLE 1

Dosing Schedule for Nelfinavir

Treatment	Dose	Dosing Regimen	Duration of Treatment	Route of Administration
Nelfinavir tablet	1250-mg (5 × 250-mg)	Single dose	Days 1, 8, 15, and 22	Oral

[0086] Nelfinavir was administered as five 250-mg tablets with 240 mL of water. All subjects received a standardized snack the evening they were admitted to the in-patient facility. For the fasting evaluation, subjects were required to complete an overnight fast of at least 10 hours prior to dosing in the morning. For the fed pharmacokinetic evaluations, subjects were required to complete an overnight fast of at least 10 hours, prior to receiving the protocol-specific standardized breakfast meal (that is, Meal 1, Meal 2, or Meal 3). Subjects were given 30 minutes to complete their standardized breakfast meal. Dosing was performed in the morning, immediately following the subject's completion of the standardized breakfast meal and after the subject's pre-dose pharmacokinetic specimen had been collected. Subjects could not ingest water 1 hour prior to or 1 hour after dosing. A standardized lunch was given at least 4 hours after the morning dose and a standardized dinner was given at least 10 hours after the morning dose.

[0087] Subjects received nelfinavir according to a randomized schedule. Randomization codes, subject identifiers, and assigned treatments were provided to each investigator.

[0088] Subjects were to refrain from strenuous exercise within 48 hours prior to any clinical laboratory or pharmacokinetic evaluations.

[0089] In addition, subjects were to refrain from consuming alcohol, starting 48 hours before each dose and continuing 12 hours following each dose and abstain from grapefruit and products containing grapefruit for 7 days prior to study entry (Day 1) and continuing through study completion.

[0090] Twenty-four subjects entered the study and twenty subjects completed the study.

[0091] Pharmacokinetics

[0092] For pharmacokinetic sampling, blood samples, 5 mL each, were collected into heparinized vacuum tubes (green top tubes) via an indwelling catheter or direct venipuncture. The actual time of each collection was recorded on the source document. The timing of each sample collection was as follows: predose and at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose on Days 1, 8,15, and 22.

[0093] All blood samples were kept at 4° C. (using either ice or cryoblock) until centrifugation. Blood samples were centrifuged within 1 hour of collection, at approximately 1000xg for 15 minutes, to separate the plasma. The plasma samples were split evenly into 2 aliquots and stored in appropriately labeled polypropylene transport tubes. Plasma was stored frozen at −20° C. or lower until analysis.

[0094] Sample analysis conditions for nelfinavir and M8 in plasma are summarized in Table 2.

TABLE 2

Summary of Sample Analysis for Nelfinavir and M8 in Human Plasma (Example 1)

Method Description	
Matrix	Plasma (Sodium Heparin)
Type of Method	HPLC
Deviations From Validated Method	None
Sample Volume	250 μL
Internal Standard	ALD-126462

Study Assay Performance

	Analytical Range		Quality Control Samples	
Analyte	Lower Limit (LLOQ)	Upper Limit (ULOQ)	Precision (% CV)	Accuracy (% RE)
Nelfinavir	0.0500 μg/mL	10.0 μg/mL	≦7.31%	2.94 to +3.91%
M8	0.0500 μg/mL	10.0 μg/mL	≦4.23%	4.07 to 5.55%

Sample Handling

Storage Conditions	−20° C.
Stability Under Storage Conditions	656 days
Stability ≧ Longest Time From Collection to Analysis	Yes

[0095] Pharmacokinetic parameter values were calculated using WinNonlin Pro Version 2.1. Pharmacokinetic parameters determined in this study are given in Table 3.

TABLE 3

Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
Cmax	Maximum plasma concentration	Observed
Tmax	Time for Cmax	Observed
AUC(0–tlqc)	Area under plasma concentration-time profile from time zero to time for the last quantifiable concentration (lqc)	Linear trapezoidal method

TABLE 3-continued

Pharmacokinetic Parameters		
Parameter	Definition	Method of Determination
C_{12}	Concentration at 12 hours postdose	Observed
λz	Terminal rate constant	Absolute value of slope of linear regression of natural logarithm (ln) of concentration on time during the terminal phase of concentration-time profile
t½	Terminal half-life	ln(2)/λz
AUC(0–∞)	Area under plasma concentration-time profile from time zero extrapolated to infinite time	AUC(0–tlqc) + lqc/λz
AUCextrap	Percent AUC(0–∞) due to extrapolation	100% · lqc/[λz · AUC(0–∞)]

[0096] Descriptive statistics of nelfinavir Cmax and AUC, as well as C_{12} values were examined to determine the effect of meals of various Kcal content on the variability of these parameter values.

[0097] Individual nelfinavir plasma concentrations were used to predict steady-state plasma concentrations during BID administration with meals of various Kcal content. WinNonlin Pro Version 3.2 noncompartmental superposition was used for this simulation. Predicted steady-state Cmax and Cmin values were compared.

[0098] The food effect on nelfinavir was estimated by the log-difference between the AUC and Cmax observed at different Kcal levels and the AUC and Cmax observed under the fasted condition. The primary endpoint of this study is the log-difference in AUC between each of the caloric intake groups as compared to the fasted condition.

[0099] Based on the results of a 2×2 crossover study for 625 mg bioequivalence under the fasting condition, the Root Mean Square Error for log-AUC is 0.4 from the crossover ANOVA model. A 35% difference in mean AUC between two Kcal levels was equivalent to a 0.3 mean difference in log-AUC. With 5% Type I error and a two side test, 21 subjects in the study should have 90% power in detecting a 35% difference in mean AUC between any of the two caloric levels.

[0100] Pharmacokinetic Results

[0101] Pharmacokinetic parameter values in the comparison of nelfinavir administration with test meals relative to those to fasting subjects are summarized in Table 4 and reported in **FIGS. 1-7**.

TABLE 4

Summary of Nelfinavir Pharmacokinetic Parameter Values Following Administration of 1250 mg Nelfinavir Oral Doses to Fasting Subjects (Reference) or to Subjects taking Nelfinavir with a Meal.

	Least-Squares Mean Values			
Parameter	Fasting (Reference)	with Meal (Test)	Ratio	90% Confidence Interval
Low Calorie/Low Fat Meal				
N	22	21		
Cmax, μg/mL	1.57	3.16	201	163 to 249
tmax, hr	2.18	3.02	139	Not Applicable

TABLE 4-continued

Summary of Nelfinavir Pharmacokinetic Parameter Values Following Administration of 1250 mg Nelfinavir Oral Doses to Fasting Subjects (Reference) or to Subjects taking Nelfinavir with a Meal.

	Least-Squares Mean Values			
Parameter	Fasting (Reference)	with Meal (Test)	Ratio	90% Confidence Interval
AUC(0–tlqc), μg · hr/mL	9.04	20.0	221	173 to 283
AUC(0–∞), μg · hr/mL	10.6	23.1	218	166 to 285
t½, hr	4.10	3.59	87.5	69.4 to 106
Moderate Calorie/Low Fat Meal				
N	22	22		
Cmax, μg/mL	1.57	3.67	234	190 to 288
tmax, hr	2.18	3.87	178	Not Applicable
AUC(0–tlqc), μg · hr/mL	9.04	25.5	282	222 to 358
AUC(0–∞), μg · hr/mL	10.6	33.4	314	241 to 409
t½, hr	4.10	4.77	116	98.7 to 134
High Calorie/High Fat Meal				
N	22	23		
Cmax, μg/mL	1.57	5.20	331	270 to 406
tmax, hr	2.18	3.98	183	Not Applicable
AUC(0–tlqc), μg · hr/mL	9.04	38.9	430	340 to 543
AUC(0–∞), μg · hr/mL	10.6	55.3	520	402 to 674
t½, hr	4.10	5.63	139	121 to 156

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

[0102] Thus, based on area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC(0-∞)) values, the bioavailability of nelfinavir was 2.2-, 3.1-, and 5.2-fold higher following administration with meals 1, 2, and 3 respectively, relative to that in fasting subjects.

[0103] Administration of nelfinavir with meals of increasing caloric content resulted in longer nelfinavir time to maximum observed plasma concentration (tmax) values and higher Cmax values. Mean tmax values were approximately 1, 1.5, and nearly 2 hours longer when administered with a low, moderate, and high calorie meal, respectively, relative to that in fasting subjects; mean Cmax values were 2-, 2.3-,

and 3.3-fold higher, respectively. In general, caloric content did not have a profound effect on nelfinavir half-life (t½) values with mean values ranging from 3.6 to 5.6 hours.

[0104] As shown in FIG. 1, nelfinavir C_{12} values in subjects receiving the dose with the high calorie/high fat meal were higher than Cmax values in fasting subjects. Additionally, administration with meals decreases variability in nelfinavir plasma concentrations. The mean and coefficient of variation (% CV) nelfinavir C_{12} values were as follows:

Fasting	0.41 μg/mL (121%)
125 Kcal/20% fat	0.65 μg/mL (55%)
500 Kcal/20% fat	1.19 μg/mL (51%)
1000 Kcal/50% fat	2.07 μg/mL (42%).

[0105]

TABLE 5

Summary of Pharmacokenetic Results

		Food Intake (kcal/fat)		
PK Parameter	Fasting	125/20%	500/20%	1000/50%
AUC_{12}, μg · hr/mL (×fasting)	9.04	20.0 (2.2X)	25.5 (2.8X)	38.9 (4.3X)
90% CL, ×fasting		1.73–2.83X	2.22–3.58X	3.40–5.43X
AUCinf, μg · hr/mL (×fasting)	10.6	23.1 (2.2X)	33.4 (3.1X)	55.3 (5.2X)
90% CL, ×fasting		1.66–2.85X	2.14–4.09X	4.02–6.74X
Cmax, μg · hr/mL (×fasting)	1.57	3.16 (2.0X)	3.67 (2.3X)	5.20 (3.3X)
90% CL, ×fasting		1.63–2.49X	1.90–2.88X	2.70–4.06X
M8 AUCinf/ NFV AUCinf (%)	26.5	15.8	15.3	20.8

[0106] Mean plasma nelfinavir concentration-time profiles for each treatment are depicted in FIG. 1. Mean nelfinavir pharmacokinetic parameter values in the comparison of nelfinavir administration with test meals relative to those to fasting subjects are presented in the following tables:

[0107] FIG. 2 depicts individual Cmax and AUC(0-∞) values following administration of an 1250 mg oral dose of nelfinavir, as a function of the energy content of the accompanying meal, if any.

[0108] The average nelfinavir plasma concentration is depicted in FIG. 3 as a function of the caloric value of the accompanying meal. The solid line represents AUC(0-∞)(r^2>0.97) and the dashed line represents Cmax (r^2<0.95).

[0109] The average nelfinavir plasma concentration is depicted in FIG. 4 as a function of the protein content of the accompanying meal, if any. The solid line represents AUC(0-∞)(r^2>0.99) and the dashed line represents Cmax (r^2<0.95).

[0110] Mean plasma M8 concentration-time profiles for each treatment are depicted in FIG. 6. Mean M8 pharmacokinetic parameter values are presented in Table 6 along with ratios and confidence intervals. Individual Cmax and AUC(0-∞) values are illustrated in FIG. 7.

[0111] Effect of Caloric Content

[0112] This example shows that food intake has a marked effect on nelfinavir pharmacokinetics with the highest levels achieved after the greatest food intake. AUC values increased 3-5-fold over those in the fasting state by administering nelfinavir with meals containing 500-1000 kcal and 20-50% fat.

[0113] The metabolite, M8, plasma concentrations generally tracked those of nelfinavir. Based on the area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC (0-∞)) values, the bioavailability of M8 was 1.3-, 1.8 and 4.1-fold higher with increasing caloric intake relative to fasting. In the fed state the M8 AUC/nelfinavir AUC ranged from 15-21%.

[0114] The percentage of M8 relative to nelfinavir remained the same between the fed and fasted administration methods.

TABLE 6

Summary of M8 Pharmacokinetic Parameter Values Following Administration of 1250-mg Nelfinavir Oral Doses to Fasting Subjects (Reference), with a Low Calorie/Low Fat Meal, with a Moderate Calorie/Low Fat Meal, and with a High Calorie/High Fat Meal.

	Least-Squares Mean Values			
Parameter	Fasting (Reference)	with Meal (Test)	Ratio	90% Confidence Interval
Low Calorie/Low Fat/Low Protein Meal				
Cmax, μg/mL	0.228[a]	0.533[d]	234	165 to 333
tmax, hr	3.45[b]	3.88[e]	113	Not Applicable
AUC(0–tlqc), μg · hr/mL	0.655[a]	2.01[d]	343	207 to 568
AUC(0–∞), μg · hr/mL	2.81[c]	3.66[f]	130	88.3 to 192
t½, hr	2.68[h]	2.40[f]	89.4	65.2 to 114
Moderate Calorie/Low Fat/Moderate Protein Meal				
Cmax, μg/mL	0.228[a]	0.693[a]	304	216 to 428
tmax, hr	3.45[b]	4.49[a]	130	Not Applicable
AUC(0–tlqc), μg · hr/mL	0.655[a]	3.46[a]	529	323 to 865
AUC(0–∞), μg · hr/mL	2.81[c]	5.11[e]	182	126 to 263
t½, hr	2.68[c]	2.96[e]	110	87.3 to 133
High Calorie/High Fat/High Protein Meal				
Cmax, μg/mL	0.228[a]	1.28[g]	562	401 to 787
tmax, hr	3.45[b]	5.01[a]	145	Not Applicable
AUC(0–tlqc), μg · hr/mL	0.655[a]	7.58[g]	1157	712 to 1878
AUC(0–∞), μg · hr/mL	2.81[c]	11.5[a]	408	285 to 586
t½, hr	2.68[c]	3.90[a]	145	123 to 168

[a]N = 22;
[b]N = 17;
[c]N = 10;
[d]N = 21;
[e]N = 20;
[f]N = 18;
[g]N = 23

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

EXAMPLE 2

Evaluation of Fat on Nelfinavir Bioavailability

[0115] A study was conducted as a phase 1, randomized, open-label, crossover 3×3 study, designed to evaluate the impact of a fixed kilocalorie meal at 20% and 50% fat content on single-dose pharmacokinetic parameters of the nelfinavir 250 mg tablet formulation in normal, healthy volunteers.

[0116] Methods

[0117] Subjects were dosed with 1250 mg of nelfinavir 3 times at one-week intervals and 24-hour PK profiles were collected following each of the doses. Each subject was assigned three meals with different fat contents prior to dosing (fasting, 500kcal with 20% fat, 500 kcal with 50% fat) using a Latin square design.

[0118] Twenty-four subjects entered the study and twenty-two subjects completed it. Each subject received the following treatment in random order on Days 1, 8 and 15: 5×250 mg nelfinavir tablets with fasting; 5×250 mg nelfinavir tablets, with a meal comprising 500Kcal/20% fat; and 5×250 mg nelfinavir tablets with a meal having 500 Kcal/50% fat.

[0119] The moderate calorie/low fat meal consisted of 500 Kcal with 20% fat (11.3 grams of fat). The moderate calorie/high fat meal consisted of 500 Kcal with 50% fat (27.8 grams of fat).

[0120] Subjects were administered nelfinavir 1250-mg (five 250-mg tablets) on the morning of the pharmacokinetic evaluations. The nelfinavir terminal half-life (t½) in plasma is typically 3.5 to 5 hours. To ensure clearance of nelfinavir between evaluations, PK evaluations were performed on Days 1, 8 and 15 such that there would be a 7-day washout between doses. Subjects participated on an outpatient basis; however, subjects were admitted to the in-patient facility the evening prior to each PK evaluation and remained in the in-patient facility for approximately 16 hours post-dosing. The subjects returned the next morning (8 hours later) for their last 24 hr. pharmacokinetic blood draw. All pharmacokinetic evaluations were performed in the in-patient facility. Blood samples were collected and analyzed for plasma concentrations of nelfinavir and M8.

[0121] For the fasting evaluation, subjects were required to complete an overnight fast of at least 10 hours prior to dosing in the morning. For the fed PK evaluations, subjects were required to complete an overnight fast of at least 10 hours, prior to receiving the protocol-specific standardized breakfast meal. Subjects were given 30 minutes to complete their standardized breakfast meal. Dosing was performed in the morning, immediately following the subject's completion of the standardized breakfast meal and after the subject's predose PK specimen had been collected. Subjects could not ingest water 1 hour prior to or 1 hour after dosing. A standardized lunch was given at least 4 hours after the morning dose and a standardized dinner was given at least 10 hours after the morning dose.

[0122] Actual sampling times were used for all data evaluation. Mean Cmax and AUC values were calculated as the antilogs of least-squares mean log-transformed values (analogous to geometric means). Ratios and confidence intervals for Cmax and AUC values are also based on log-transformed values. Mean values for all other pharmacokinetic parameters are least-squares means. Ratios and confidence intervals for these parameters are based on untransformed values.

[0123] As in Example 1, healthy volunteers of any race and either gender, 18 to 60 years of age (inclusive), were used in the study. Volunteers were chosen who had a body mass index (BMI) between 18 to 31 kg/m^2 (inclusive), and who were seronegative for human immunodeficiency virus (HIV) -1/HIV -2. Females were required to be not pregnant and be using a reliable barrier method of birth control, have been surgically sterilized, or be postmenopausal.

[0124] Pharmacokinetics

[0125] Blood samples, 5 mL each, were collected as in Example 1. The timing of each sample collection was as follows: Predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose on Days 1, 8, and 15. All blood samples were kept at 40 C (using either wet ice or cryoblock) until centrifugation. Blood samples were centrifuged within 1 hour of collection, at 3000 rpm (approximately 2619×g) for 15 minutes, to separate the plasma. The plasma samples were split evenly into 2 aliquots and stored in appropriately labeled polypropylene transport tubes. Plasma was stored frozen at 20° C. or lower until analysis.

[0126] Sample analysis for nelfinavir and M8 in plasma is summarized in Table 7.

TABLE 7

Summary of Sample Analysis for Nelfinavir and M8 in Human Plasma (Example 2)

Method Description	Plasma (Sodium Heparin)
Matrix	HPLC
Type of Method	None
Deviations From Validated Method	250 μL
Sample Volume	ALD-126462
Internal Standard	

Study Assay Performance

	Analytical Range		Quality Control Samples	
Analyte	Lower Limit (LLOQ)	Upper Limit (ULOQ)	Precision (% CV)	Accuracy (% RE)
Nelfinavir	0.0500 μg/mL	10.0 μg/mL	≦9.59%	3.76 to 6.58%
MB (AG-1402)	0.0500 μg/mL	10.0 μg/mL	≦2.83%	4.29 to 6.64%

Sample Handling

Storage Conditions	-20° C.
Stability Under Storage Conditions	656 days
Stability ≧ Longest Time From Collection to Analysis	Yes

[0127] Pharmacokinetic parameter values were calculated from plasma nelfinavir and M8 concentration-time data using standard noncompartmental pharmacokinetic methods as in Example 1.

[0128] Log-transformed nelfinavir AUC was the primary parameter used in the evaluation of the potential effect of fat content of the meals on nelfinavir pharmacokinetics. Secondary parameters included in this analysis were nelfinavir

terminal half-life (t½), time to maximum plasma concentration (tmax), and log-transformed Cmax, as well as M8 pharmacokinetic parameters. Parameter values were evaluated by analysis of variance (ANOVA) using a model incorporating sequence, subject within sequence, period, and treatment effects. Statistical tests were performed using the Type III sum of squares derived using WinNonlin Pro Version 2.1. Least-squares treatment mean values were determined for each parameter.

[0129] Results from ANOVA were used to calculate 90% confidence intervals for the ratio (test/reference) least-squares treatment mean values, where administration of single nelfinavir doses fasting was the reference treatment. Confidence intervals were calculated using WinNonlin Pro Version 2.1. Confidence intervals were used as an aid in data interpretation. Descriptive statistics of nelfinavir Cmax and AUC were examined to determine the effect of meals of various fat content on the variability of these parameter values.

[0130] Plasma concentrations of nelfinavir and M8 were measured by validated high-performance liquid chromatography (HPLC) methods. Pharmacokinetic parameters were determined from plasma concentration-time data using standard noncompartmental methods.

[0131] Statistical Methods

[0132] Log-transformed nelfinavir area under the plasma concentration-time profile (AUC) values was the primary parameter analyzed to determine the effect of fat content of meals on nelfinavir pharmacokinetics. The 90% confidence intervals for the ratios of test (with test meal) to reference (fasting) least-squares mean AUC as well as maximum observed plasma concentration (Cmax) values were calculated using log-transformed data and expressed as a percentage of the reference mean. The relationship between nelfinavir exposure and fat content of the meals was examined.

[0133] Pharmacokinetic Results

[0134] Nelfinavir pharmacokinetic parameter values following administration of 5×250-mg nelfinavir tablets to fasting subjects (reference), during a moderate calorie/low fat meal, and during a moderate calorie/high fat meal are summarized in the following Table 8. 0

TABLE 8

Nelfinavir Pharmacokinetic Parameter Values, Example 2

Parameter	Least-squares Mean Values: Fasting (Reference)	With Meal (Test)	Ratio	90% Confidence Interval
	Test = Moderate Calorie/Low Fat			
N	22	22		
Cmax, μg/mL	1.63	4.04	248	199 to 308
tmax, hr	2.42	4.19	173	Not Applicable
AUC(0–tlqc), μg hr/mL	10.0	32.6	325	252 to 419
AUC(0–∞), μg hr/mL	10.7	32.7	305	239 to 389
t½, hr	4.10	3.08	75.0	46.5 to 104
	Test = Moderate Calorie/High Fat			
N	22	22		
Cmax, μg/mL	1.63	6.16	378	304 to 370
tmax, hr	2.42	4.48	186	Not Applicable

TABLE 8-continued

Nelfinavir Pharmacokinetic Parameter Values, Example 2

AUC(0–tlqc), μg hr/mL	10.0	52.6	524	407 to 676
AUC(0–∞), μg hr/mL	10.7	54.6	508	398 to 649
t½, hr	4.10	3.43	83.7	55.2 to 112

[0135] Definitions of terms used in the table include: "Ratio" is the ratio of treatment mean values, expressed as a percentage (100% x test/reference). "90% Confidence Interval" is the 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

[0136] Administration of nelfinavir with meals of similar caloric content and 20% and 50% fat content resulted in longer time to maximum plasma concentration (tmax) values and higher Cmax values. Mean tmax values were approximately 2 hours longer when administered with meals of 20% and 50% fat content, relative to that in fasting subjects. Mean Cmax values were approximately 2.5- and 3.8-fold higher in meals of 20% and 50% fat content, respectively. Based on area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC(0-∞)) values, the bioavailability of nelfinavir was approximately 3- and 5-fold higher following administration of meals containing 20% and 50% fat content, respectively, relative to that in fasting subjects. Fat content did not have a profound effect on nelfinavir terminal half-life (t½) values. Nelfinavir elimination t½ values following administration to fasting subjects and with test meals were similar, averaging approximately 4 hours.

[0137] Administration of nelfinavir with meals of 20% and 50% fat content resulted in lower variability in plasma concentrations, relative to that in fasting subjects. Values for % coefficient of variation (CV) for AUC(0-∞) were 75% in fasting subjects and 48% and 43% in subjects receiving the test meals containing 20% and 50% fat, respectively.

[0138] M8 plasma concentrations generally tracked those of nelfinavir. Mean M8 AUC(0-∞) were 3- and 6.8-fold higher following administration of test meals containing 20% and 50% fat, respectively, relative to that in fasting subjects.

[0139] Results

[0140] Mean plasma nelfinavir concentration-time profiles for each treatment are depicted in **FIG. 8**. Mean nelfinavir pharmacokinetic parameter values in the comparison of nelfinavir administration with test meals relative to those to fasting subjects are presented in Table 9, along with ratios and confidence intervals. Individual Cmax and AUC values are illustrated in **FIG. 9**. Corresponding data for M8 concentration—time profiles and also M8 Max and AUC are presented in **FIGS. 10 and 11**, respectively.

TABLE 9

Summary of Nelfinavir Pharmacokinetic Parameter Values Following Administration of 5 x 250-mg Nelfinavir Tablets to Fasting Subjects (Reference), During a Moderate Calorie/Low Fat Meal, and During a Moderate Calorie/High Fat Meal (Study 2)

Parameter	Least-squares Mean Values: Fasting (Reference)	With Meal (Test)	Ratio	90% Confidence Interval
	Test = Moderate Calorie/Low Fat			
N	22	22		
Cmax, μg/mL	1.63	4.04	248	199 to 308
tmax, hr	2.42	4.19	173	Not Applicable
AUC(0–tlqc), μg hr/mL	10.0	32.6	325	252 to 419
AUC(0–∞), μg hr/mL	10.7	32.7	305	239 to 389
t½, hr	4.10	3.08	75.0	46.5 to 104
	Test = Moderate Calorie/High Fat			
N	22	22		
Cmax, μg/mL	1.63	6.16	378	304 to 370
tmax, hr	2.42	4.48	186	Not Applicable
AUC(0–tlqc), μg hr/mL	10.0	52.6	524	407 to 676
AUC(0–∞), μg hr/mL	10.7	54.6	508	398 to 649
t½, hr	4.10	3.43	83.7	55.2 to 112

Parameters are described in Table 16

Ratio = Ratio of treatment mean values, expressed as a percentage (100% x test/reference)

90% Confidence = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean

[0141] This example indicates that fat intake has a marked effect on nelfinavir pharmacokinetic parameters after a single dose exposure. AUC values increased 3.2 fold with a 500 kcal, 20% fat breakfast and 5.2 fold with the same Kcal but 50% fat when compared to the fasting AUC. These values were similar to the values previously determined for a 500 Kcal, 20% fat breakfast and a 1000 Kcal, 50% fat breakfast. Thus fat content in meals affects nelfinavir PK in addition to its Kcal content suggesting a plateau effect for Kcal content.

[0142] The discovery that 500 kcal and 1000 kcal yield the same fold increase in plasma exposure if they are administered as 50% fat has important implications for optimal use of nelfinavir. A 500kcal/50% fat meal can be delivered as 3.5-4 ounces of roasted peanuts, less than one cup of canned coconut cream, or a variety of American breakfast fast foods. Also, the fat dependence allows the development of a formulation of nelfinavir with fat that would enhance compliance with optimal administration of the medication. This example also shows that M8 concentrations rose with increasing fat intake but that the percentage of M8 relative to nelfinavir remained the same, around 10%.

TABLE 10

Summary of Example 2: Pharmacokinetic Parameter Values

PK Parameter	Fasting	Kcal/Fat % 500/20%	Kcal/Fat % 500/50%
Nelfinavir AUC24, mg · hr/mL (xfasting)	10.0	32.6 (3.2X)	52.6 (5.2X)
90% CI, xfasting[1]		2.5–4.1X	4.1–6.8X
Nelfinavir AUC∞, mg · hr/mL (xfasting)	10.7	32.7 (3.0X)	54.6 (5.1X)
90% CI, xfasting		2.4–3.9X	4.0–6.5X
Nelfinavir Cmax, mg/mL, (xfasting)	1.63	4.0 (2.5X)	6.2 (3.8X)
90% CI, xfasting		2.0–3.1X	3.0–4.7X
M8 AUC∞/ Nelfinavir AUC∞(%)	8.6	8.7	11.4

[0143] The 90% confidence interval (90% CI) is calculated for the ratio above the CI. The ratio of plasma levels of nelfinavir metabolite to nelfinavir is expressed as "M8 AUC∞/nelfinavir AUC∞ (x100).

[0144] While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will recognize that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

We claim:

1. A method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily the nelfinavir is administered with food and the food comprises more than 800 kcal.

2. The method of claim 1, wherein the food comprises more than about 900 kcal.

3. The method of claim 1, wherein the food comprises more than about 1000 kcal.

4. The method of claim 1, wherein the administration of nelfinavir occurs between 30 minutes prior to and two hours after consumption of food.

5. The method of claim 1, wherein the administration of nelfinavir occurs between 30 minutes prior to and one hour after consumption of food.

6. The method of claim 1, wherein the administration of nelfinavir occurs at about the same time as the consumption of food.

7. The method of claim 1, wherein nelfinavir is administered at least twice daily for at least two weeks and at least twice daily nelfinavir is administered with food and the food comprises more than 800 kcal at each administration.

8. The method of claim 1, wherein the food comprises between about 40% fat and about 50% fat by energy content.

9. The method of claim 1, wherein the food comprises between about 50% fat and about 60% fat by energy content.

10. The method of claim 1, wherein the food comprises between about 60% fat and about 70% fat by energy content.

11. The method of claim 1, wherein the food comprises between about 70% fat and about 80% fat by energy content.

12. The method of claim 1, wherein the food comprises between about 80% fat and about 90% fat by energy content.

13. The method of claim 1, wherein the food comprises between about 90% fat and about 100% fat by energy content.

14. The method of claim 1, wherein the food comprises more than 40% fat by energy content.

15. The method of claim 1, wherein the food comprises more than about 50% fat by energy content.

16. The method of claim 1, wherein the food comprises more than about 60% fat by energy content.

17. The method of claim 1, wherein the food comprises more than about 70% fat by energy content.

18. The method of claim 1, wherein the food comprises more than about 80% fat by energy content.

19. The method of claim 1, wherein the food comprises more than about 90% fat by energy content.

20. The method of claim 1, wherein the food comprises from 36 9 to 55 g fat.

21. The method of claim 1, wherein the food comprises from 40 9 to 55 g fat.

22. The method of claim 1, wherein the food comprises at least about 55 g fat.

23. The method of claim 1, wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state.

24. The method of claim 23, wherein the AUC(0-∞) after nelfinavir administration with food is at least about 5-fold greater than the AUC(0-∞) after administration in the fasted state.

25. The method of claim 1, wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prod rug thereof.

26. A method of treating human immunodeficiency virus (HIV) in a mammal comprising administering orally to a mammal in need thereof a therapeutically effective amount of nelfinavir or pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition taken with food, wherein the food comprises at least about 500 kcal and at least about 50% fat by energy content.

27. The method of claim 26 wherein the administration of nelfinavir occurs between 30 minutes prior to and two hours after consumption of food.

28. The method of claim 26, wherein the administration of nelfinavir occurs between 30 minutes prior to and one hour after consumption of food.

29. The method of claim 26, wherein the administration of nelfinavir occurs at about the same time as the consumption of food.

30. The method of claim 26, wherein the food comprises between about 50% fat and about 60% fat by energy content.

31. The method of claim 26, wherein the food comprises between about 60% fat and about 70% fat by energy content.

32. The method of claim 26, wherein the food comprises between about 70% fat and about 80% fat by energy content.

33. The method of claim 26, wherein the food comprises between about 80% fat and about 90% fat by energy content.

34. The method of claim 26, wherein the food comprises between about 90% fat and about 100% fat by energy content.

35. The method of claim 26, wherein the food comprises more than about 60% fat by energy content.

36. The method of claim 26, wherein the food comprises more than about 70% fat by energy content.

37. The method of claim 26, wherein the food comprises more than about 80% fat by energy content.

38. The method of claim 26, wherein the food comprises more than about 90% fat by energy content.

39. The method of claim 26, wherein the food comprises from 36 g to 55 g fat.

40. The method of claim 26, wherein the food comprises from 40 g to 55 g fat.

41. The method of claim 26, wherein the food comprises at least about 55 g fat.

42. The method of claim 26, wherein the food comprises at least about 600 kcal.

43. The method of claim 26, wherein the food comprises at least about 700 kcal.

44. The method of claim 26, wherein the food comprises at least about 800 kcal.

45. The method of claim 26, wherein the food comprises at least about 900 kcal.

46. The method of claim 26, wherein the food comprises at least about 1000 kcal.

47. The method of claim 26, wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state.

48. The method of claim 47, wherein the AUC (0-∞) after nelfinavir administration with food is at least about 5-fold greater than the AUC (0-∞) after administration in the fasted state.

49. The method of claim 26, wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prod rug thereof.

50. A method of treating human immunodeficiency virus (HIV) in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of nelfinavir or a pharmaceutically acceptable salt or solvate thereof in a pharmaceutical composition at least once daily for at least two weeks, wherein at least once daily nelfinavir is taken with food and the food comprises more than about 500 kcal and more than about 50% fat by energy content.

51. The method of claim 50, wherein the administration of nelfinavir occurs between 30 minutes prior to and two hours after consumption of food.

52. The method of claim 50, wherein the administration of nelfinavir occurs between 30 minutes prior to and one hour after consumption of food.

53. The method of claim 50, wherein the administration of nelfinavir occurs at about the same time as the consumption of food.

54. The method of claim 50, wherein nelfinavir is administered at least twice daily for at least two weeks and at least twice daily nelfinavir is administered with food and the food comprises more than 500 kcal and more than about 50% fat by energy content at each administration.

55. The method of claim 50, wherein the food comprises more than about 600 kcal.

56. The method of claim 50, wherein the food comprises more than about 700 kcal.

57. The method of claim 50, wherein the food comprises more than about 900 kcal.

58. The method of claim 50, wherein the food comprises more than about 1000 kcal.

59. The method of claim 50, wherein the food comprises between about 50% fat and about 60% fat by energy content.

60. The method of claim 50, wherein the food comprises between about 60% fat and about 70% fat by energy content.

61. The method of claim 50, wherein the food comprises between about 70% fat and about 80% fat by energy content.

62. The method of claim 50, wherein the food comprises between about 80% fat and about 90% fat by energy content.

63. The method of claim 50, wherein the food comprises between about 90% fat and about 100% fat by energy content.

64. The method of claim 50, wherein the food comprises more than about 60% fat by energy content.

65. The method of claim 50, wherein the food comprises more than about 70% fat by energy content.

66. The method of claim 50, wherein the food comprises more than about 80% fat by energy content.

67. The method of claim 50, wherein the food comprises more than about 90% fat by energy content.

68. The method of claim 50, wherein the food comprises from 36 g to 55 g fat.

69. The method of claim 50, wherein the food comprises from 40 g to 55 g fat.

70. The method of claim 50, wherein the food comprises at least about 55 g fat.

71. The method of claim 50, wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt or prodrug thereof.

72. The method of claim 50, wherein the area under the curve from time zero extrapolated to infinite time (AUC(0-∞)) after nelfinavir administration with food is at least about 3-fold greater than the AUC(0-∞) after administration in the fasted state.

73. The method of claim 72, wherein the AUC (0-∞) after nelfinavir administration with food is at least about 5-fold greater than the AUC (0-∞) after administration in the fasted state.

74. The method of claim 50, wherein the mammal is not receiving ritonavir, saquinavir or lopinavir or a stereoisomer, solvate, salt, or prod rug thereof.

75. A kit comprising a therapeutically effective oral dose of nelfinavir and a printed material comprising instructions for administering the dose with food comprising at least 800 kcal in a high-fat meal.

76. The kit of claim 75, wherein the label further comprises instructions for administering the dose with food comprising at least 50% fat by energy content.

77. The kit of claim 75, wherein the high-fat meal is recited to comprise more than about 36 g of fat.

78. A therapeutic composition for the treatment of human immunodeficiency virus (HIV) in a mammal comprising fat and a therapeutically effective amount of nelfinavir in a weight ratio of at least about 25 fat: 1 nelfinavir.

79. The composition of claim 78, wherein the weight ratio is greater than about 30 fat:1 nelfinavir.

80. The composition of claim 78, wherein the amount of nelfinavir is between about 100 mg and about 1500 mg.

* * * * *

Exhibit 11

1. Nonproprietary Names

- BP: Copovidone
- PhEur: Copovidonum
- USPNF: Copovidone

2. Synonyms

Acetic acid vinyl ester, polymer with 1-vinyl-2-pyrrolidinone; copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 3 : 2 by mass; copolyvidone; *Kollidon VA 64*; *Luviskol VA*; *Plasdone S-630*; poly(1-vinylpyrrolidone–co-vinyl acetate); polyvinylpyrrolidone–vinyl acetate copolymer; PVP/VA; PVP/VA copolymer.

3. Chemical Name and CAS Registry Number

Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone [25086-89-9]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)_n \cdot (C_4H_6O_2)_m$ $(111.1)n + (86.1)m$

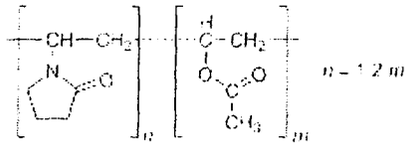
The ratio of n to m is approximately $n = 1.2m$. Molecular weights of 45 000–70 000 have been determined for *Kollidon VA 64*. The average molecular weight of copovidone is usually expressed as a *K*-value.

The *K*-value of *Kollidon VA 64* is nominally 28, with a range of 25.2–30.8. The *K*-value of *Plasdone S 630* is specified between 25.4 and 34.2. *K*-values are calculated from the kinematic viscosity of a 1% aqueous solution. Molecular weight can be calculated with the formula:

$$M = 22.22\,(K + 0.075K^2)^{1.65}$$

The PhEur 2005 and USPNF 23 (Suppl. 1) describe copovidone as a copolymer of 1-ethenylpyrrolidin-2-one and ethenyl acetate in the mass proportion of 3 : 2.

5. Structural Formula



6. Functional Category

Film-former; granulating agent; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Copovidone is used as a tablet binder, a film-former, and as part of the matrix material used in controlled-release formulations. In tableting, copovidone can be used as a binder for direct compression[1–3] and as a binder in wet granulation.[4,5] Copovidone is often added to coating solutions as a film-forming agent. It provides good adhesion, elasticity, and hardness, and can be used as a moisture barrier.

See Table I.

Table I

Table I: Uses of copovidone.

Use	Concentration (%)
Film-forming agent	0.5–5.0[a]
Tablet binder, direct compression	2.0–5.0
Tablet binder, wet granulation	2.0–5.0

[a] This corresponds to the % w/w copovidone in the film-forming solution formulation, before spraying.

8. Description

Copovidone is a white to yellowish-white amorphous powder. It is typically spray-dried with a relatively fine particle size. It has a slight odor and a faint taste.

See SEM: 1.

9. Pharmacopeial Specifications

See Table II.

Table II

Table II: Pharmacopeial specifications for copovidone.

Test	PhEur 2005	USPNF 23 (Suppl. 1)
Aldehydes	≤500 ppm	≤0.05%
Appearance of solution	+	+
Characters	+	—

Test	PhEur 2005	USPNF 23 (Suppl. 1)
Ethenyl acetate	35.3–42.0%	35.3–41.4%
Heavy metals	≤20 ppm	—
Hydrazine	≤1 ppm	≤1 ppm
Identification	+	+
K-value	90–110%	90.0–110.0%
Loss on drying	≤5.0%	≤5.0%
Monomers	≤0.1%	≤0.1%
Nitrogen content	7.0–8.0%	7.0–8.0%
Peroxides	≤400 ppm	≤0.04%
2-Pyrrolidone	≤0.5%	—
Sulfated ash	≤0.1%	≤0.1%
Viscosity, expressed as *K*-value	+	—

10. Typical Properties

Density (bulk):

0.24–0.28 g/cm^3

Density (tapped):

0.35–0.45 g/cm^3

Flash point:

215°C

Flowability:

relatively free-flowing powder.

Glass transition temperature:

106°C for *Plasdone S-630*.[6]

Hygroscopicity:

at 50% relative humidity, copovidone gains less than 10% weight.

K-value:

25.4–34.2 for *Plasdone S-630*.[6]

Melting point:

140°C

Solubility:

greater than 10% solubility in 1,4-butanediol, glycerol, butanol, chloroform, dichloromethane, ethanol (95%), glycerol, methanol, polyethylene glycol 400, propan-2-ol, propanol, propylene glycol, and water. Less than 1% solubility in cyclohexane, diethyl ether, liquid paraffin, and pentane.

Viscosity (dynamic):

the viscosity of aqueous solutions depends on the molecular weight and the concentration. At concentrations less than 10%, the viscosity is less than 10 mPa s (25°C).

11. Stability and Storage Conditions

Copovidone is stable and should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Copovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to high water levels, copovidone may form molecular adducts with some materials; see Crospovidone and Povidone.

13. Method of Manufacture

Copovidone is manufactured by free-radical polymerization of vinylpyrrolidone and vinyl acetate in a ratio of 6 : 4. The synthesis is conducted in an organic solvent owing to the insolubility of vinyl acetate in water.

14. Safety

Copovidone is used widely in pharmaceutical formulations and is generally regarded as nontoxic. However, it is moderately toxic by ingestion, producing gastric disturbances. It has no irritating or sensitizing effects on the skin.

LD_{50} (rat, oral): >0.63 g/kg[7]

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. When heated to decomposition, copovidone emits toxic vapors of NO_x. Eye protection, gloves, and a dust mask are recommended.

16. Regulatory Status

Copovidone is included in the FDA Inactive Ingredients Guide (oral tablets, oral film-coated tablets, sustained action).

17. Related Substances

Crospovidone; povidone.

18. Comments

Kollidon VA 64, has a spherical structure, with a high proportion of damaged spheres. The shell-like structure reduces flowability, but the damaged spheres cover a greater surface area of the filler particles, increasing the efficacy of its use as a dry binder.[8] Furthermore, when used in transdermal drug delivery systems, copovidone has been shown to significantly alter the melting behavior, by reducing the heat of fusion and the melting point of estradiol and various other sex steroids.[9]

Plasdone S-630 has been used in direct compression experiments with active substances that are difficult to compress, such as acetaminophen (paracetamol); and has been shown to produce harder tablets than those containing the same actives but made with microcrystalline cellulose.[10]

In general, copovidone has better plasticity than povidone as a tablet binder, and is less hygroscopic, more elastic, and less tacky in film-forming applications than povidone.

Up to about 1975, copovidone was marketed by BASF under the name *Luviskol VA 64*. *Luviskol* is currently used only for the technical/cosmetic grade of copovidone.

19. Specific References

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2. Selmeczi B. The influence of the compressional force on the physical properties of tablets made by different technological processes. *Arch Pharm (Weinheim)* 1974; **307**(10): 755–760.(PubMed)

3. Stamm A, Mathis C. The liberation of propyromazine from tablets prepared by direct compression. *J Pharm Belg* 1990; **29**(4): 375–389.

4. Vojnovic D, Rubessa F, Bogataj M, Mrhar A. Formulation and evaluation of vinylpyrrolidone/vinylacetate copolymer microspheres with griseofulvin. *J Microencapsul* 1993; **10**(1): 89–99.(PubMed)

5. Kristensen HG, Holm P, Jaegerskou A, Schaefer T. Granulation in high speed mixers. Part 4: Effect of liquid saturation on the agglomeration. *Pharm Ind* 1984; **46**(7): 763–767.

6. International Specialty Products. Technical Literature: *Plasdone S-630*, 2002.

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9. Lipp R. Selection and use of crystallization inhibitors for matrix-type transdermal drug-delivery systems containing sex steroids. *J Pharm Pharmacol* 1998; **50**: 1343–1349.(PubMed)

10. International Specialty Products. Technical literature: *Plasdone S0630: A binder for direct compression and wet/dry granulation*, 2002.

20. General References

1. BASF. Technical literature: *Kollidon VA 64*, March 2000.

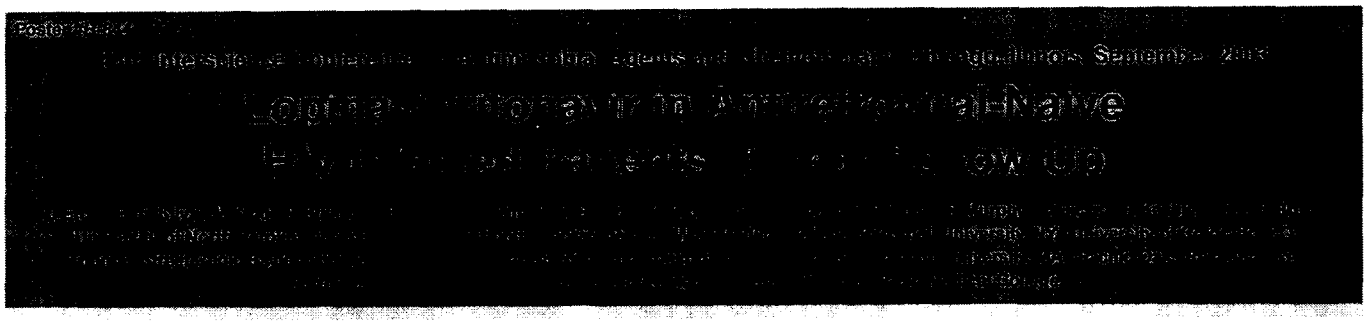
21. Authors

OA AbuBaker, D Pipkorn.

22. Date of Revision

1 August 2005.

Exhibit 12



BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir, which functions as an inhibitor of cytochrome P450 3A. Even at low ritonavir doses, there is a substantial increase in LPV exposure. At a dosage of 400 mg of LPV/100 mg ritonavir twice daily (3 co-formulated tablets BID), ritonavir concentrations are below those required for antiviral activity.[1] By contrast, the mean LPV C_{trough}/IC_{50} ratio (Inhibitory Quotient or IQ) for wild-type HIV is ≥70 when dosed at 400/100 mg twice a day, potentially providing a barrier to emergence of viral resistance and activity against resistant virus.

Lopinavir/ritonavir (LPV/r, marketed as Kaletra™) has been studied in both antiretroviral-naïve and experienced HIV-infected patients. However, few long-term data are available on continued safety and efficacy. The M97-720 study is an ongoing phase II trial of LPV/r in combination with d4T and 3TC in antiretroviral-naïve patients. This was the first trial of LPV/r in HIV-infected patients and hence provides the longest duration of follow-up for patients treated with LPV/r. This poster presents data on antiviral activity, immunologic parameters, and safety through 252 weeks (5 years).

METHODS

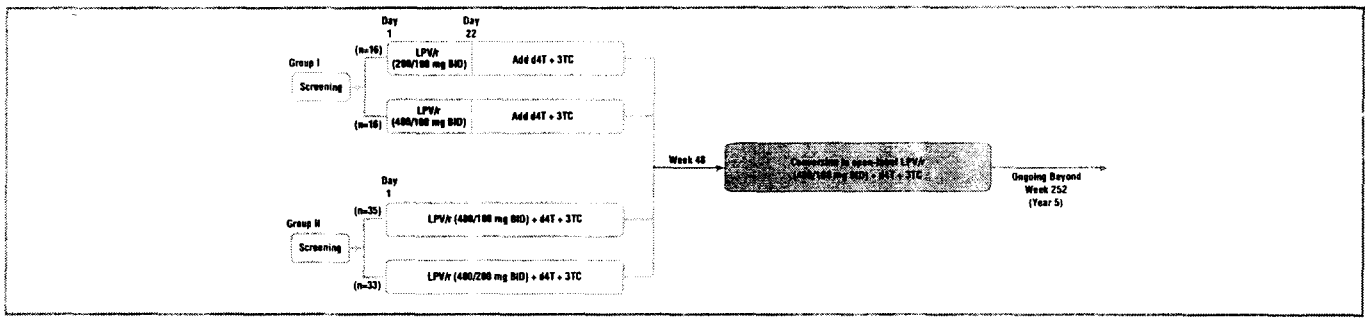
Entry Criteria

- Antiretroviral-naïve patients.
- Plasma HIV RNA ≥5,000 copies/mL with no CD4 cell count restriction.

Study Design and Analysis

- One hundred antiretroviral-naïve patients were randomized to receive one of three dosage levels of LPV/r (200/100 mg BID, 400/100 mg BID or 400/200 mg BID), together with d4T (40 mg BID) and 3TC (150 mg BID) given either after 3 weeks of monotherapy (Group I) or from study entry (Group II) (Figure 1).
- Enrollment into Group II began following an evaluation of preliminary efficacy and safety of LPV/r in Group I.
- After 48 weeks, all patients began conversion to open-label LPV/r 400/100 mg BID dosing.
- CD4+ cell counts were measured by flow cytometry.

Figure 1. M97-720 Study Schema



Efficacy

- Proportion of patients HIV RNA below the limit of quantitation (LOQ) was measured using an on-treatment method (missing values and values obtain edduring treatment interruptions excluded) and an intent-to-treat, noncompleter=failure method (ITT NC=F, missing values considered failure unless the immediately preceding and following values were below the LOQ).
- Time to loss of virologic response was analyzed using a Kaplan-Meier procedure. Loss of virologic response was defined by two consecutive HIV RNA measurements above 400 copies/mL following any value below 400 copies/mL or failure to achieve HIV RNA below 400 copies/mL. Patients were considered virologic failures if they met loss of response criteria even if they achieved viral resuppression without a change in study medication.
- Immunologic response was assessed by the mean change in CD4 count from baseline to each study visit.

Virologic Evaluation

- Samples from patients with sustained HIV RNA rebound to >400 copies/mL while receiving LPV/r during the study were submitted for genotypic and phenotypic analyses. Genotype (GeneSeq™) and phenotype (PhenoSense™) analyses were performed by ViroLogic, Inc.
- Genotypic resistance to LPV was defined as the development of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84, and 90) confirmed by phenotypic analyses (≥2.5 fold increase in IC_{50} to LPV relative to wild type HIV). Resistance to 3TC was defined as the presence of an M184V and/or M184I mutation in reverse transcriptase.

Safety

- Cumulative incidence through Week 252 for adverse events and grade 3/4 laboratory values was summarized, as was the prevalence at Week 252, defined as the presence of an ongoing adverse event or a grade 3/4 lab measurement obtained at the Week 252 visit.
- All laboratory measurements were obtained without regard to fasting.

RESULTS

Viral Load Suppression Below the LOQ

- Based on the ITT NC=F analysis through Week 252, 67% of patients had HIV RNA <400 copies/mL (on-treatment analysis: 99%) (Figure 2) and 64% of patients had HIV RNA <50 copies/mL (on-treatment analysis: 94%) (Figure 3). The only HIV RNA >400 copies/mL at year 5 occurred during a lengthy treatment interruption. Three patients with HIV RNA between 50 and 400 copies/mL (65, 100 and 274) maintained HIV RNA <400 copies/mL at the following visit (Week 264, ultrasensitive testing not conducted).

Figure 2. HIV RNA <400 copies/mL Through Week 252

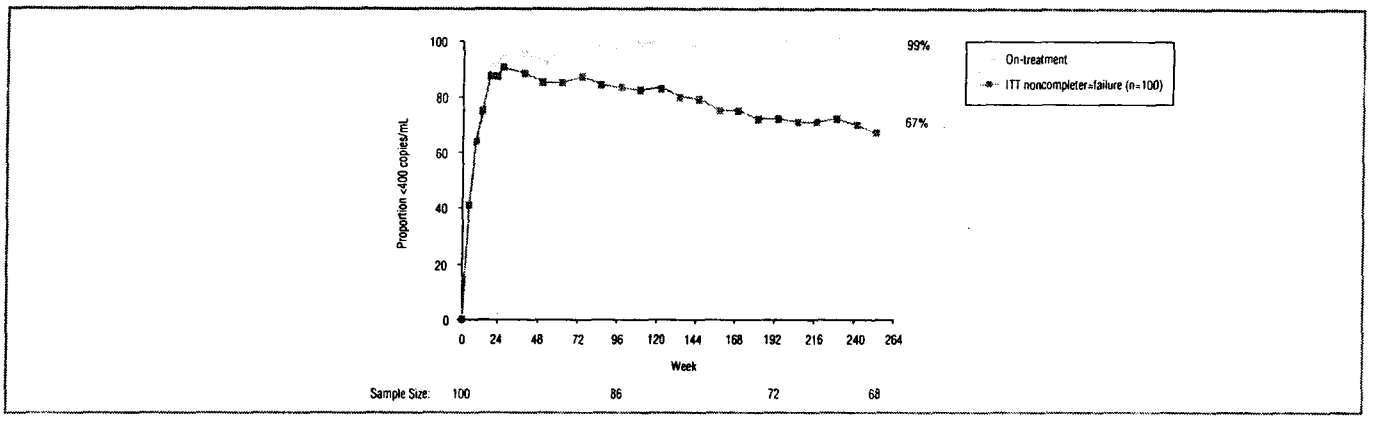
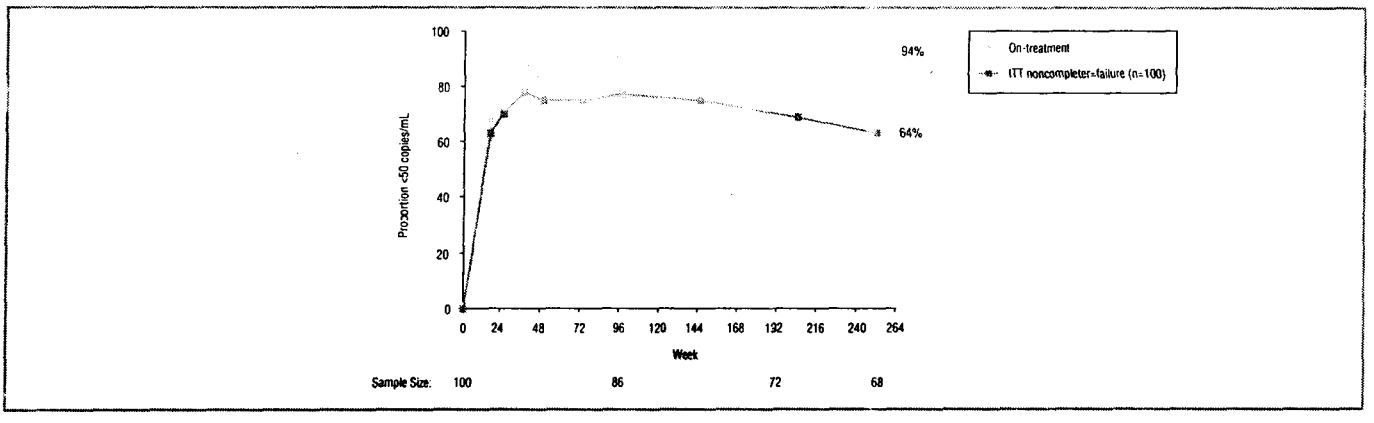


Figure 3. HIV RNA <50 copies/mL Through Week 252



Duration of Virologic Response Analysis

- Through Week 252, the proportion of patients maintaining virologic response was 81.4% by Kaplan-Meier analysis (Figure 4).
- Among the 17 patients with loss of virologic response, 9 remained on study through Week 252 without a change in regimen, and 8/9 patients had HIV RNA <50 copies/mL at Week 252 (Figure 5).

Figure 4. Kaplan-Meier Analysis of Time to Loss of Virologic Response

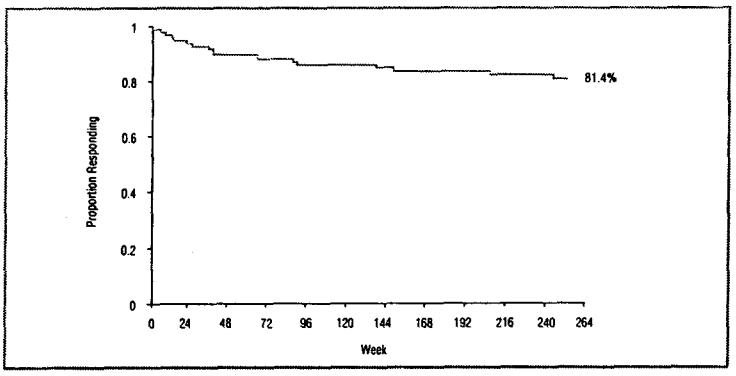
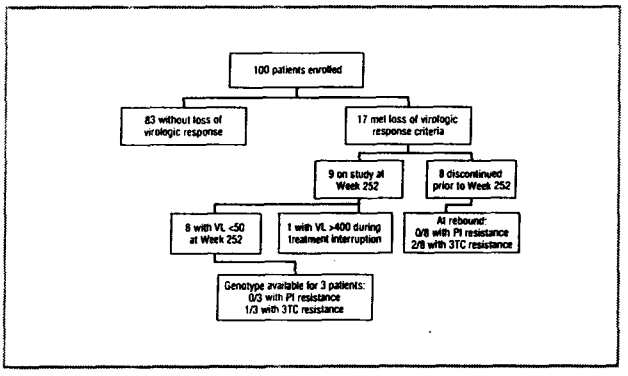


Figure 5. Virologic Disposition Through Week 252



RESULTS

- Through Week 252, genotype was available on 11 patients with confirmed HIV RNA rebound to >400 copies/mL while receiving LPV/r, including all 8 who prematurely discontinued the study. Consistent with results obtained in previous studies of LPV/r in ARV-naïve patients,[2,3] 0 of 11 patients demonstrated protease inhibitor resistance, and 3 of 11 demonstrated 3TC resistance.

CD4 Cell Count Response

- Among subjects with values at both baseline and Week 252, the mean CD4 cell count increased from 281 cells/mm³ at baseline to 791 cells/mm³ at Week 252, an increase of 510 cells/mm³ (Figure 6).
- CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count (Table 1). Among patients with baseline CD4 cell count <50 cells/mm³, mean CD4 cell count increased from 24 cells/mm³ at baseline to 543 cells/mm³ at Week 204, an increase of 519 cells/mm³.
- Other studies have observed an association between higher age and lower CD4 count increases,[4,5] but no correlation was observed between age and CD4 count increase in this study through Week 252 (r=0.013, p=0.92).

Figure 6. CD4 Cell Count (mean change from baseline)

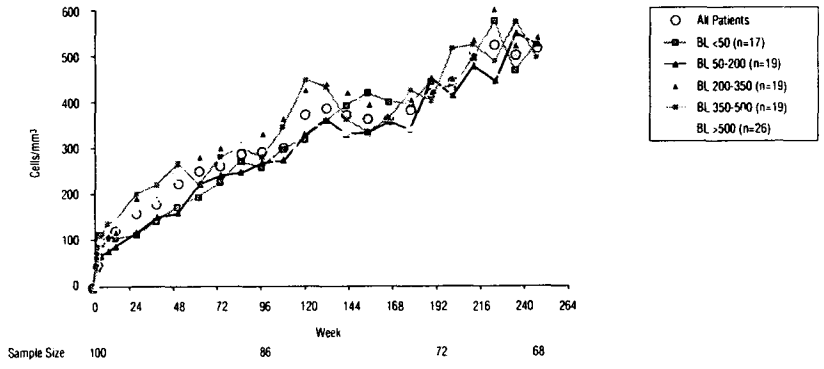


Table 1. CD4 Cell Count Increase at Week 252 by Baseline CD4 Cell Count

Baseline CD4 Cell Count (cells/mm³)	Mean CD4 Cell Count Increase from Baseline to Week 252 (cells/mm³)
<50 (n=16)	519
50-199 (n=12)	523
200-349 (n=15)	533
350-499 (n=12)	488
≥500 (n=13)	480

Safety

Table 2. Patient Disposition Through Week 252

Patients enrolled	100
Discontinuations prior to Week 252	32
Discontinuations probably or possibly related to study drugs	
AST/ALT increases	2
Diarrhea	1
Liver pain, enlargement, fatty deposits	1
Arthralgia	1
Elevated cholesterol	1
Fat redistribution	3
Death[1]	1
Other reasons for discontinuation	
Adverse Event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification[2])	3
Lost to follow-up	9
Noncompliance	5
Personal/other reasons (moved (3), drug addiction, "virologic success"[3])	5
Patients on study at Week 252	68

[1] Death of unknown cause occurred in a patient 10 days following thoracic spinal surgery with perioperative myocardial infarction.
[2] One patient was discontinued due to both noncompliance and alcohol detoxification.
[3] One patient discontinued based on the primary physician's recommendation to temporarily suspend ARV treatment because the patient was "doing so well on present regimen."

RESULTS

Table 3. Most Common Adverse Events (occurring in ≥10% of patients) Through Week 252

Moderate/Severe Drug-related AEs	Incidence Through Week 252 (n=100)	Prevalence at Week 252 (n=68)
Diarrhea	28%	0%
Nausea	16%	0%
Lipodystrophy	12%	15%
Abdominal pain	10%	0%

Table 4. Most Common Grade 3/4 Laboratory Abnormalities (occurring in ≥10% of patients) Through Week 252

Grade 3/4 Lab Abnormalities	Incidence Through Week 252 (n=100)	Prevalence at Week 252 (n=68)
Cholesterol (>300 mg/dL)	23%	0%
Triglycerides (>750 mg/dL)	26%	6%
AST/ALT (>5X ULN)	11%	0%

Table 5. Distribution of Lipid Values at Week 252

Category	Prevalence at Week 204 (n=68)
Total Cholesterol (mg/dL)	
<200	29 (43%)
200-240	28 (41%)
>240-300	11 (16%)
300-400	0
>400	0
Triglycerides (mg/dL)	
<250	33 (49%)
250-400	19 (28%)
400-750	12 (18%)
>750-1200	4 (6%)
>1200	0

23 patients with grade 2 or higher lipid values initiated lipid-lowering agents, and all but 2 subsequently demonstrated grade 0-1 lipid values.

CONCLUSIONS

- Through 5 years of follow-up, antiretroviral-naïve patients receiving LPV/r-based therapy exhibited sustained virologic response, with 67% of patients demonstrating HIV RNA <400 copies/mL and 64% demonstrating HIV RNA <50 copies/mL by intent-to-treat (NC=F) analysis. Corresponding on-treatment response rates were 99% and 94%, respectively.
- Through 252 weeks of follow-up, no protease inhibitor resistance mutations have been observed in subjects with sustained viral load rebound.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (10/100, 10%).

ACKNOWLEDGMENTS

M97-720 Study Subjects	
Covance Central Laboratory Services	
AIDS Research Consortium of Atlanta	*Sanders J*
Beth Israel Deaconess Medical Center–Harvard	*Fitch H*
Cornell Clinical Trials Unit	*Stroberg T*
Duke University Medical Center	*Harmon L*
Northwestern University	*Bruce J*
Pacific Oaks Research	*Sandoval B*
Rush Presbyterian St. Luke's Medical Center	*Fritsche J*
Thomas Street Clinic	*Sepcie B*
University of Colorado	*Canmann S, Putnam B*
University of North Carolina at Chapel Hill	*Marcus C*
PPD Development	*Wheat R, McCarley S, Bullard M*
Abbott Laboratories	*Sheehan K, Yang G, Tokimoto D, King KR*

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Exhibit 13

(Nos. 3956 and 3959)
NEW

KALETRA™

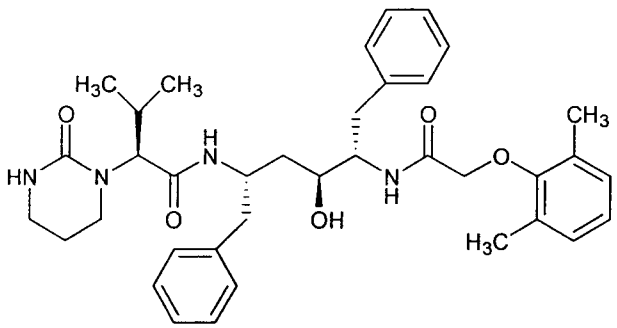
(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution

R_x only

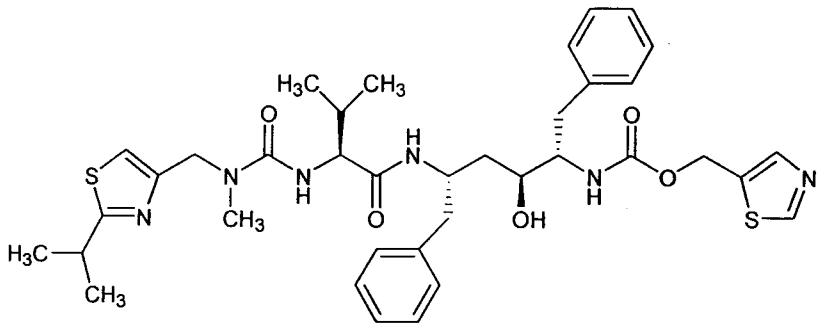
DESCRIPTION

KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

KALETRA capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA oral solution contains 42.4% alcohol (v/v).

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of action: Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006 – 0.017 μg/mL, 1 μg/mL = 1.6 μM) and ranged from 4-11 nM (0.003 – 0.007 μg/mL) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 – 289 nM (0.04 – 0.18 μg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance: HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to KALETRA in antiretroviral treatment naive patients has not yet been characterized. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. The assessment of these mutational patterns is under study.

Cross-resistance - Preclinical Studies: Varying degrees of cross-resistance have been observed among protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed >4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed <4-fold reduced susceptibility to lopinavir. Isolates with >4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor therapy. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA >1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC_{50} against wild type HIV. Fifty-five percent of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir with a mean reduction in lopinavir susceptibility of 27.9-fold.

After 24 weeks of treatment with KALETRA, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤400 copies/mL was observed in 93% (27/29) and 65% (15/23) of patients with <10-fold and ≥10-fold reduced susceptibility to lopinavir at baseline, respectively.

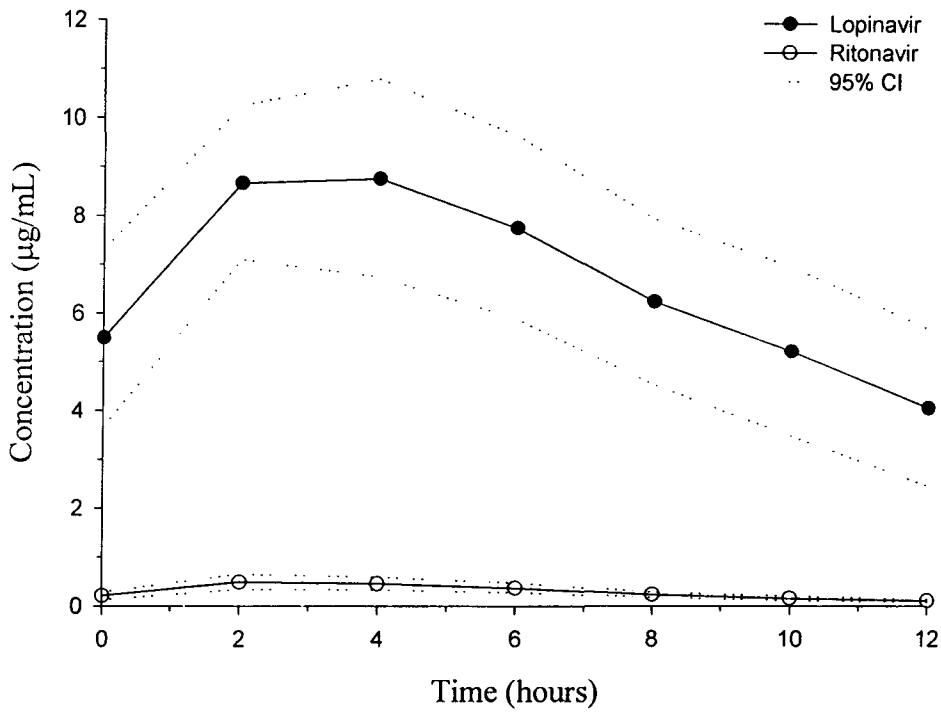
In addition, virologic response was observed in 96% (24/25) of patients whose baseline viral isolates contained up to 5 mutations recognized to be associated with protease inhibitor resistance. Fourteen of those 25 isolates contained mutations at positions 82, 84 and/or 90. Virologic response was observed in 67% (18/27) of patients whose baseline viral isolates contained 6 or more mutations, including those at positions 82, 84 and/or 90 plus multiple other mutations. There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA 400/100 mg BID yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg BID. The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

Figure 1displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg BID for 3-4 weeks from a pharmacokinetic study in HIV-infected adult subjects (n=21).

Figure 1
Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 21)



Absorption: In a pharmacokinetic study in HIV-positive subjects (n=21) without meal restrictions, multiple dosing with 400/100 mg KALETRA BID for 3 to 4 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

Effects of Food on Oral Absorption: Administration of a single 400/100 mg dose of KALETRA capsules with a moderate fat meal (500-682 Kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max}, respectively, relative to fasting. For KALETRA oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of KALETRA with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability KALETRA should be taken with food.

Distribution: At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg KALETRA BID, and is similar between healthy volunteers and HIV-positive patients.

Metabolism: *In vitro* experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination: Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The half-life of lopinavir over a 12 hour dosing interval averaged 5-6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 L/h.

Special Populations:

Gender, Race and Age: Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Pediatric Patients: The pharmacokinetics of KALETRA 300/75 mg/m^2 BID and 230/57.5 mg/m^2 BID have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 ± 31.1 μg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 μg/mL, respectively after KALETRA 230/57.5 mg/m^2 BID without nevirapine (n=12), and were 85.8 ± 36.9 μg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5

μg/mL, respectively after 300/75 mg/m^2 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (3 months to 8 years) or 4 mg/kg BID (>8 years).
Renal Insufficiency: Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.
Hepatic Impairment: Lopinavir is principally metabolized and eliminated by the liver. Although KALETRA has not been studied in patients with hepatic impairment, lopinavir concentrations may be increased in these patients (see **PRECAUTIONS**).
Drug-Drug Interactions: See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS: Drug Interactions.**

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS**).

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 1 (effect of other drugs on lopinavir) and Table 2 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 6 in **PRECAUTIONS**.

Table 1: Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	0.89 (0.83, 0.95)	0.85 (0.81, 0.90)	0.81 (0.74, 0.89)
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz[2]	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nevirapine	200 QD, 14 days; BID, 6 days	400/100 BID, 20 d	5, 9*	0.95 (0.73, 1.25)	0.99 (0.74, 1.32)	1.02 (0.68, 1.53)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk[3]	300/75 mg/m^2 BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 QD, 10 d	400/100 BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
Ritonavir[4]	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

[1] Composite effect of amprenavir 450 and 750 mg Q12h regimens on lopinavir pharmacokinetics.

[2] The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

[3] Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.

[4] Study conducted in HIV-positive adult subjects.

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA
(See Precautions, Table 6 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	See text below for discussion of interaction.		
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Efavirenz	600 QHS, 9 d	400/100 BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir	600 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		
Ketoconazole	200 single dose	400/100 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin 25-0-desacetyl rifabutin Rifabutin + 25-O-desacetyl rifabutin[1]	300 QD, 10 d; 150 QD, 10 d	400/100 BID, 10 d	12	2.12 (1.89, 2.38) 23.6 (13.7, 25.3) 3.46 (3.07, 3.91)	3.03 (2.79, 3.30) 47.5 (29.3, 51.8) 5.73 (5.08, 6.46)	4.90 (3.18, 5.76) 94.9 (74.0, 122) 9.53 (7.56, 12.01)
Saquinavir	800 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.
N/A =not available.

Effect of KALETRA on other Protease Inhibitors (PIs): The pharmacokinetics of single-dose indinavir and saquinavir, and multiple-dose amprenavir obtained in healthy subjects after at least 10 days of KALETRA 400/100 mg BID were compared to historical data in HIV-infected subjects (refer to Table 2 for information on study design and doses). Because of the limitations in the study design and the use of comparisons between healthy and HIV infected subjects, it is not possible to recommend definitive dosing recommendations. However, based on these comparisons, amprenavir 750 mg BID and indinavir 600 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC, lower C_{max}, and higher C_{min} compared to their respective established clinical dosing regimens. Saquinavir 800 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC and higher C_{min} to its respective established clinical dosing regimen (no comparative information regarding C_{max}). The clinical significance of the lower C_{max} and higher C_{min} is unknown. Appropriate doses of amprenavir, indinavir and saquinavir in combination with KALETRA with respect to safety and efficacy have not been established (see **PRECAUTIONS** – Table 6).

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in a controlled study of KALETRA of 24 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration. At present, there are no results from controlled trials evaluating the effect of KALETRA on clinical progression of HIV.

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA BID + stavudine + lamivudine compared to nelfinavir TID + stavudine + lamivudine

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg BID) plus stavudine and lamivudine versus nelfinavir (750 mg TID) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

The percent of patients with HIV RNA <400 copies/mL and outcomes of patients through 24 weeks are summarized in Figure 2 and Table 3, respectively.

Figure 2: Virologic Response Through 24 Weeks (Study 863)

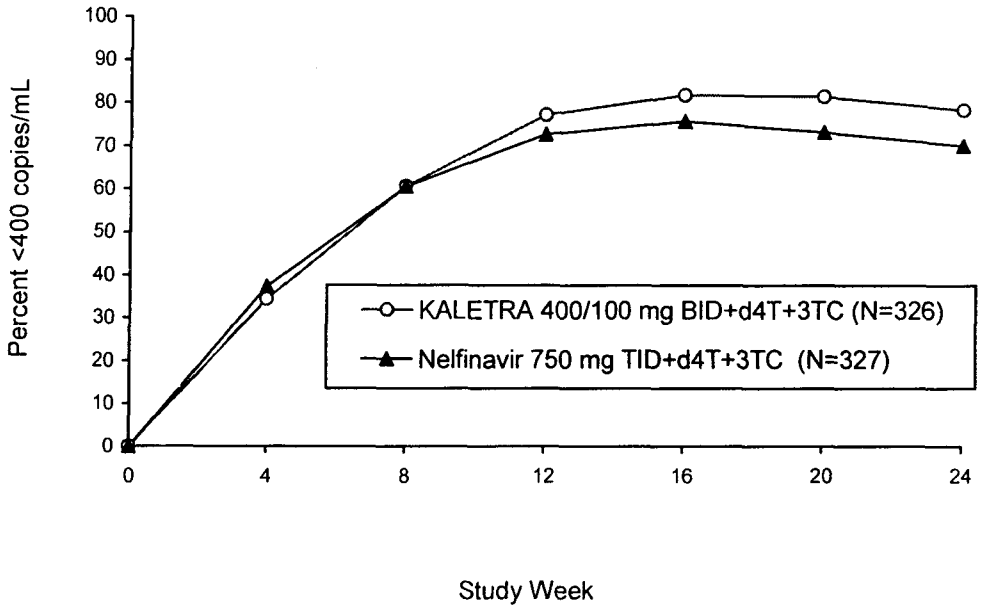


Table 3: Outcomes of Randomized Treatment Through Week 24 - (Study 863)

Outcome	KALETRA (400/100mg BID) + d4T + 3TC N=326	NELFINAVIR (750mg TID) + d4T + 3TC N=327
HIV RNA <400 copies/mL	79%	70%
HIV RNA >400 copies/mL	8%	16%
Discontinued due to KALETRA or nelfinavir adverse event*	2%	2%
Discontinued due to other adverse event*	2%	1%
Other**	8%	7%
Missing HIV RNA Level	2%	2%

*Includes laboratory abnormalities leading to discontinuation
**Lost to follow up, noncompliance, or consent withdrawn

In the KALETRA arm, the proportion <400 copies/mL for patients with baseline HIV RNA >100,000 copies/mL (78%) was similar to that for patients with baseline HIV RNA <100,000 copies/mL (81%).

Through 24 weeks of therapy, the proportion of patients with HIV RNA <50 copies/mL was 65% in the KALETRA arm and 60% in the nelfinavir arm.

Through 24 weeks of therapy, the mean increase from baseline in CD4 cell count was 154 cells/mm^3 for the KALETRA arm and 150 cells/mm^3 for the nelfinavir arm.

Four patients in the KALETRA arm and 6 patients in the nelfinavir arm experienced a new CDC Class C event following at least one week of treatment, including 3 patients in each arm who achieved HIV RNA <400 copies/mL at 24 weeks.

Study 720: KALETRA BID + stavudine + lamivudine

Study 720 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at three dose levels (Group I: 200/100 mg BID and 400/100 mg BID; Group II: 400/100 mg BID and 400/200 mg BID) plus lamivudine (150 mg BID) and stavudine (40 mg BID) in 100 patients. All patients were converted to open-label KALETRA at the 400/100 mg BID dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm^3 (range: 3 to 918 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 3.3 to 6.3 log_{10} copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 80% (78%) and the mean increase from baseline in CD4 cell count was 256 cells/mm^3 for the 51 patients originally randomized to the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (13%) had discontinued the study for any reason. Four discontinuations (4%) were secondary to adverse events or laboratory abnormalities, and one of these discontinuations (1%) was attributed to a KALETRA adverse event.

Patients with Prior Antiretroviral Therapy

Study 765: KALETRA BID + nevirapine + NRTIs

Study 765 is an ongoing, randomized, blinded, multicenter trial evaluating treatment with KALETRA at two dose levels (400/100 mg BID and 400/200 mg BID) plus nevirapine (200 mg BID) and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40 years (range 22-66), were 73% Caucasian, and were 90% male. Mean baseline CD4 cell count was 372 cells/mm^3 (range 72 to 807 cells/μL) and mean baseline plasma HIV-1 RNA was 4.0 log_{10} copies/mL (range 2.9 to 5.8 log_{10} copies/mL).

Through 72 weeks of treatment, the proportion of patients with HIV RNA < 400 (<50) copies/mL was 75% (58%) and the mean increase from baseline in CD4 cell count was 174 cells/mm^3 for the 36 patients receiving the 400/100 mg dose of KALETRA. At 72 weeks, 13 patients (19%) had discontinued the study for any reason. Six discontinuations (9%) were secondary to adverse events or laboratory abnormalities, and three of these discontinuations (4%) were attributed to KALETRA adverse events.

CONTRAINDICATIONS

KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 4.

Table 4: Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antiarrhythmics	Flecainide, Propafenone
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about drugs that should not be taken with KALETRA. This statement is included on the product's bottle label.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics: Drug-Drug Interactions, CONTRAINDICATIONS – Table 4: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 5: Drugs That Should Not Be Co-administered With KALETRA** and **Table 6: Established and Other Potentially Significant Drug Interactions**).

Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for sildenafil.)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

Concomitant use of KALETRA and St. John's wort (hypericum perforatum), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS – Lipid Elevations**). Patients with advanced HIV disease may be at

increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see **MICROBIOLOGY**).

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS** – Table 8). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at

periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS Table 6: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: "**ALERT: Find out about drugs that should NOT be taken with KALETRA.**" A Patient Package Insert (PPI) for KALETRA is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients taking didanosine should take didanosine one hour before or two hours after KALETRA.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy including protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the

most susceptible to large increases in AUC (>3-fold) when co-administered with KALETRA.

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 6: Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with KALETRA are included in **Table 5: Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 5: Drugs That Should Not Be Co-administered With KALETRA

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: flecainide, propafenone	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 6: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
(See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 1 and 2)

Concomitant Drug Class: Drug Name	Effect on Concentration of lopinavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ Lopinavir	A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **DOSAGE AND ADMINISTRATION**). NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (given with food).
HIV-Protease Inhibitors: amprenavir*, indinavir*, saquinavir*	↑ Amprenavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Indinavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Saquinavir (Similar AUC, ↑ C_{min})	Appropriate doses of the combination with respect to safety and efficacy have not been established (see **CLINICAL PHARMACOLOGY**: Table 2 and Effect of KALETRA on other Protease Inhibitors (PIs)).
HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Anti-infective: clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered:

		• For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole	↑ Ketoconazole ↑ Itraconazole	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Disulfiram/metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*, cerivastatin	↑ Atorvastatin ↑ Cerivastatin	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppresants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.

* See **CLINICAL PHARMACOLGY** for Magnitude of Interaction, Tables 1 and 2

Other Drugs:
Drug interaction studies reveal no clinically significant interaction between KALETRA and pravastatin, stavudine or lamivudine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

Pregnancy
Pregnancy Category C: No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naive patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 24 weeks of therapy, the proportion of patients with HIV RNA < 400 copies/mL was 82% for antiretroviral naive patients and 66% for antiretroviral experienced patients. The mean increase from baseline in CD4 cell count was 328

cells/mm^3 for antiretroviral naive and 335 cells/mm^3 for antiretroviral experienced patients treated through 24 weeks. At 24 weeks, one patient (1%) had prematurely discontinued the study. This discontinuation was secondary to an HIV-related event in an antiretroviral experienced patient that was not attributed to a KALETRA adverse event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

ADVERSE REACTIONS

Adults:

Treatment-Emergent Adverse Events: KALETRA has been studied in 612 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 2.8% in KALETRA and 3.1% in nelfinavir treated patients in Study 863.

Drug related clinical adverse events of moderate or severe intensity in ≥ 2% of patients treated with combination therapy including KALETRA for up to 24 weeks (Phase III) and for up to 72 weeks (Phase I/II) are presented in Table 7. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS**.

Table 7: Percentage of Patients with Treatment-Emergent[1] Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Patients

	Antiretroviral Naive Patients			Protease Inhibitor Experienced Patients
	Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
	KALETRA 400/100 mg TID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID[2] + d4T + 3TC (N= 84)	KALETRA BID[3] + nevirapine + NRTIs (N= 186)
Body as a Whole				
Abdominal Pain	3.1%	2.4%	4.8%	1.1%
Asthenia	3.4%	2.8%	7.1%	5.4%
Headache	2.5%	1.8%	7.1%	1.6%
Pain	0.3%	0.0%	2.4%	1.6%
Digestive System				
Abnormal Stools	0.0%	0.3%	6.0%	1.6%
Diarrhea	13.8%	14.4%	23.8%	15.1%
Nausea	6.4%	4.0%	15.5%	2.2%
Vomiting	2.1%	2.4%	4.8%	1.6%
Nervous System				
Insomnia	1.5%	1.2%	2.4%	1.1%
Skin and Appendages				
Rash	0.6%	1.2%	3.6%	2.0%

1 Includes adverse events of possible, probable or unknown relationship to study drug.

2 Includes adverse event data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35]) and 400/200 mg BID [N=36]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

3 Includes adverse event data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving KALETRA in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with KALETRA and of at least moderate intensity are listed below by body system.

Body as a Whole: Back pain, chest pain, chest pain substernal, chills, drug interaction, drug level increased, face edema, fever, flu syndrome, malaise, and viral infection.

Cardiovascular System: Deep vein thrombosis, hypertension, palpitation, thrombophlebitis, and vasculitis.

Digestive System: Anorexia, cholecystitis, constipation, dry mouth, dyspepsia, dysphagia, enterocolitis, eructation, esophagitis, fecal incontinence, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, hemorrhagic colitis, increased appetite, pancreatitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System: Cushing's syndrome and hypothyroidism.

Hemic and Lymphatic System: Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight loss.

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, depression, dizziness, dyskinesia, emotional lability, encephalopathy, hypertonia, libido decreased, nervousness, neuropathy, paresthesia, peripheral neuritis, somnolence, thinking abnormal, and tremor.

Respiratory System: Bronchitis, dyspnea, lung edema, and sinusitis.

Skin and Appendages: Acne, alopecia, dry skin, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, skin benign neoplasm, skin discoloration, and sweating.

Special Senses: Abnormal vision, eye disorder, otitis media, taste perversion, and tinnitus.

Urogenital System: Abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, and urine abnormality.

Laboratory Abnormalities: The percentages of adult patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 8.

Table 8: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

Variable	Limit[1]	Antiretroviral Naive Patients			Antiretroviral Experienced Patients
		Study 863 (24 Weeks)		Study 720 (72 Weeks)	Phase I/II and Phase III
		KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA BID[2] + d4T + 3TC (N=84)	KALETRA BID[3] + NNRTI + NRTIs (N=186)
Chemistry	High				
Glucose	>250 mg/dL	1.6%	0.6%	2.4%	4.4%
Uric Acid	>12 mg/dL	1.3%	0.3%	3.6%	0.5%
SGOT/AST	>180 U/L	0.3%	2.2%	9.5%	4.4%
SGPT/ALT	>215 U/L	1.0%	2.2%	8.3%	6.6%
GGT	>300 U/L	N/A	N/A	3.6%	24.6%[4]
Total Cholesterol	>300 mg/dL	6.7%	2.8%	14.3%	25.7%
Triglycerides	>750 mg/dL	5.1%	0.9%	10.7%	26.2%
Amylase	>2 x ULN	1.9%	1.9%	4.8%	3.3%

Chemistry	Low				
Inorganic Phosphorus	<1.5 mg/dL	0.0%	0.0%	0.0%	2.2%
Hematology	Low				
Neutrophils	0.75 x 10^9/L	0.6%	1.6%	2.4%	2.7%

[1] ULN = upper limit of the normal range; N/A = Not Applicable.
[2] Includes clinical laboratory data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=36]).
[3] Includes clinical laboratory data from patients receiving 400/100 mg BID, 400/200 mg BID, and 533/133 mg BID for 16-72 weeks. All 186 patients received KALETRA in combination with NRTIs and either nevirapine or efavirenz.
[4] GGT was only measured in 69 patients receiving 400/100 mg BID or 400/200 mg BID in combination with nevirapine.

Pediatrics:

Treatment-Emergent Adverse Events: KALETRA has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Rash (2%) was the only drug-related clinical adverse event of moderate or severe intensity in ≥ 2% of pediatric patients treated with combination therapy including KALETRA (300/75 mg/m^2) for up to 24 weeks (Study 940). This includes adverse events of at least possible, probable or unknown relationship to study drug.

Laboratory Abnormalities: The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 9.

Table 9: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients

Variable	Limit[1]	KALETRA BID[2]+ RTIs (N=100)
Chemistry	High	
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	7.0%
SGPT/ALT	>215 U/L	4.0%
Total cholesterol	> 300 mg/dL	2.0%
Amylase	> 2.5 x ULN	4.0%
Chemistry	Low	
Sodium	< 130 mEq/L	3.0%
Hematology	Low	
Platelet Count	< 50 x 10^9/L	4.0%
Neutrophils	< 0.40 x 10^9/L	2.0%

[1] ULN = upper limit of the normal range.
[2] Includes clinical laboratory data from the 230/57.5 mg per m^2 (N=49) and 300/75 mg per m^2 (N=51) dose arms.

OVERDOSAGE

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with KALETRA is limited. Treatment of overdose with KALETRA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with KALETRA. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of KALETRA is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz or nevirapine in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Pediatric Patients

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to <15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children >40 kg (5.0 mL or 3 capsules) twice daily. The following table contains dosing guidelines for KALETRA oral solution based on body weight.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		2.5 mL
>25 to 30 kg		3.0 mL
>30 to 40 kg		3.5 mL
>40 kg	Adult dose	5 mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15 to 50 kg (approximately equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children >50 kg twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)

With nevirapine or efavirenz		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
>10 to <15 kg		2.0 mL
15 to 50 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
>20 to 25 kg		3.25 mL
>25 to 30 kg		4.0 mL
>30 to 40 kg		4.5 mL
>40 to 50 kg		5.0 mL (or 3 capsules)
>50 kg	Adult dose	6.5 mL (or 4 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

HOW SUPPLIED

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the corporate logo and the Abbo-Code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules in the following package sizes:
Bottles of 180 capsules each..... (**NDC** 0074-3959-77)
Packages of 120 unit dose blisters.....(**NDC** 0074-3959-11)

Recommended storage: Store KALETRA soft gelatin capsules at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:
160 mL bottle.....(**NDC** 0074-3956-46)

Recommended storage: Store KALETRA oral solution at 36°F - 46°F (2°C - 8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), oral solution should be used within 2 months.

Revised: NEW

ABBOTT
LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

----------(Perforation)----------

KALETRA™
(lopinavir/ritonavir) capsules

Exhibit 14

Conference Reports for NATAP

ICAAC
Interscience Conference on Antimicrobal
Agents and Chemotherapy
December 16-19, 2005 Washington DC

Back

Kaletra Tablet: PK/adverse events in healthy volunteers

New Tablet Formulation of Lopinavir/Ritonavir Is Bioequivalent to the Capsule at a Dose of 800/200 mg

T. Zhu, Y. Chiu, T. Doan, C. Klein, M. Chang, S. Brun, G. Hanna, W. Awni Abbott Laboratories, Abbott Park, IL

Reported by Jules Levin
ICAAC Dec 17 2005, Wash DC
Poster H-1894

AUTHOR CONCLUSIONS
A single dose of 800/200 mg LPV/r administered as the tablet was bioequivalent, with respect to LPV, to 800/200 mg LPV/r as the SGC.

The 90% confidence interval for LPV AUC and Cmax of the tablet compared to the SGC was within 0.80–1.25.

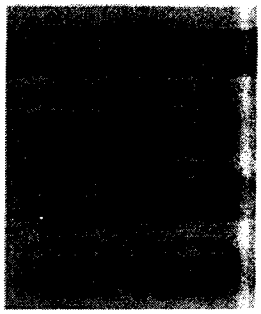
The new LPV/r tablet formulation exhibited slightly higher bioavailability, approximately 17%, for both LPV and RTV following a single dose of 800/200 mg compared to the SGC.

The tablet formulation was well tolerated and tended to result in a lower incidence of gastrointestinal side effects compared to the SGC in healthy adults receiving single 800/200 mg doses.

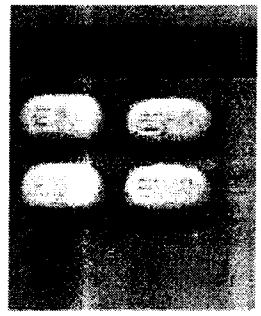
Introduction
Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with low-dose ritonavir (RTV), which enhances LPV pharmacokinetics (PK), and is marketed as Kaletra.
- A dose of lopinavir/ritonavir (LPV/r) 800/200 mg once daily (QD) was recently approved in the United States for use in combination therapy for therapy-naïve HIV-infected adults.
- LPV/r is currently available as 133.3/33.3 mg soft gelatin capsule (SGC) or 80/20 mg/mL liquid formulations, requires refrigerated storage prior to dispensing and is recommended to be taken with food in order to maximize lopinavir exposure.
- A novel melt-extrusion technology was used to reduce pill count from 6 SGC per day to 4 tablets per day. In addition, this 200/50 mg tablet formulation of LPV/r does not require refrigeration.
- Bioavailability and safety data of a single dose of LPV/r 400/100 mg administered as the tablet to healthy adults was previously reported.1 – At a dose of 400/100 mg, the tablet provided LPV and RTV exposures similar to the SGC under fed (moderate fat meal) conditions.
-- The tablet also provided more consistent LPV and RTV exposures across meal conditions (fasting, moderate fat meal, high fat meal), with reduced pharmacokinetic variability compared to the SGC.

Healthy subjects (N=15) with Body Mass Index of 18 to 27 kg/m2 were enrolled into this Phase 1, open-label, randomized, cross-over study (Table 1). - Single doses of LPV/r 800/200 mg as tablet or SGC formulation were separated by at least 5 days.
- LPV/r was administered after a moderate-fat breakfast (492 kCal, 23% from fat), as the SGC is recommended to be taken with food.

SGC



Tablet



Safety Profile

15 healthy adults received the tablet formulation at a dose of 800/200 mg. All adverse events (AE) were mild in severity.

Table 4. Adverse Events with 800/200 mg Dose

	Tablet	SGC
Any AE	27%	40%
Loose Stool or Diarrhea	13%	27%
Headache	13%	7%
Abdominal Pain	7%	7%
Taste Perversion	0%	7%

Table 2. Pharmacokinetic Parameters of Lopinavir and Ritonavir Following a Single 800/200 mg Dose

Formulation	Tablet	SGC
Pharmacokinetic Parameters (units)	N=15	N=15
	Lopinavir	
Tmax (h)	5.5 ± 2.3	6.1 ± 2.1
Cmax (µg/mL)	13.74 ± 4.92*	11.72 ± 2.43
C24 (µg/mL)	3.98 ± 2.01	4.00 ± 2.54
AUC* (µg•h/mL)	214.2 ± 69.6*	181.4 ± 51.5
t1/2 (h)	2.49 ± 0.68	2.36 ± 0.49
	Ritonavir	
Tmax (h)	4.8 ± 1.0*	5.5 ± 0.9
Cmax (µg/mL)	1.96 ± 0.86*	1.72 ± 0.74
C24 (µg/mL)	0.09 ± 0.06	0.11 ± 0.12
AUC* (µg•h/mL)	16.1 ± 7.6*	13.3 ± 5.6
t1/2 (h)	3.63 ± 0.55	3.79 ± 0.60

Mean ± Standard Deviation
800/200 mg administered after a moderate-fat meal.
Statistically significantly different from SGC (ANOVA, $p<0.05$).

Following a single dose of LPV/r 800/200 mg, the tablet is bioequivalent to the SGC with respect to LPV Cmax and AUC under moderate-fat
meal conditions (Table 3).

Table 3. Tablet Provides Similar Exposure to SGC Under Moderate-Fat Meal Conditions

	Central Values*	
Parameter	**Tablet**	**SGC**
		Lopinavir
C_{max}	13.1 µg/mL	11.5 µg/mL
AUC_t	202.2 µg•h/mL	173.1 µg•h/mL
AUC_∞	203.7 µg•h/mL	173.9 µg•h/mL
		Ritonavir
C_{max}	1.8 µg/mL	1.6 µg/mL
AUC_t	14.0 µg•h/mL	11.9 µg•h/mL
AUC_∞	14.1 µg•h/mL	12.0 µg•h/mL

* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
Note: Tablets and SGCs administered as a single 800/200 mg dose.

The concentration-time profiles for LPV and RTV were similar following single dose administration of 800/200 mg as the tablet or SGC (Figures 1 and 2).

Table 1. Demographics of Subjects Receiving 800/200 mg Dose

	N=15
Subjects	Healthy Adults
Sex	12 Males (80%) 3 Females (20%)
Race/Ethnicity	12 White (80%) 1 Black (7%) 2 Hispanic (13%)
Age (years)*	36 ± 12 (19–53)
Weight (kg)*	77 ± 10 (58–96)
Height (cm)*	175 ± 6.2 (158–183)

* Mean ± SD (range)

Melt Extrusion Technology (Meltrex)

LPV/r is a low solubility/low permeability drug (Biopharmaceutics Classification System Class 4). Historically, solid formulations of LPV/r showed poor bioavailability.

- Unformulated solid fails to provide bioavailability (<5%).
- Incorporation of surfactants, acids or other wetting agents with traditional technologies failed to provide adequate bioavailability for solid formulations.
- In vitro dissolution did not necessarily correlate with in vivo bioavailability.

Melt extrusion technology (Meltrex) has overcome these challenges. - Meltrex significantly improves the bioavailability of poorly soluble compounds like LPV/r by dissolving drug in polymer in a solvent-free environment. The drug remains in a state of molecular dispersion as the polymer hardens to form extruded material.

- This extruded material can be further processed into conventional tablets. - Excipients used for the tablet are different than those in the SGC. Specifically, the tablet does not contain certain excipients (such as oleic acid, propylene glycol, sorbitol and castor oil) found in the SGC, which may contribute to gastrointestinal side effects.

STUDY METHODS

- Healthy subjects (N=15) with Body Mass Index of 18 to 27 kg/m2 were enrolled into this Phase 1, open-label, randomized, cross-over study.
- Single doses of LPV/r 800/200 mg as tablet or SGC formulation were separated by at least 5 days.
- LPV/r was administered after a moderate-fat breakfast (492 kCal, 23% from fat), as the SGC is recommended to be taken with food.

Pharmacokinetic Analysis

Blood samples were collected for LPV and RTV assay as follows:

- Pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours following a single dose

Drug concentrations were measured by validated LC/MS/MS methods:

- LPV limit of quantitation (LOQ) = 20 ng/mL
- RTV LOQ = 11 ng/mL

LPV and RTV PK parameters were calculated with standard non-compartmental analysis using WINNONLIN v. 4.1 software (Pharsight Corp., Mountain View, CA) to estimate the maximum observed concentration (Cmax), concentration 24 hours post-dosing (C24), area under the plasma concentration time curve (AUC)

to the last measured concentration (AUCt) and to infinity (AUC°), and terminal phase half-life (t1/2).

Statistical Analysis

The bioavailability of the tablet relative to the SGC was assessed by a two one-sided tests procedure via 90% confidence intervals obtained from the analysis of the natural logarithms of Cmax, AUCt and AUC° within the framework of the ANOVA model using the SAS system v. 6.12 software (SAS Institute, Cary, NC).

Safety Analysis

Safety and tolerability were assessed throughout the study based on reported adverse events, vital signs, electrocardiograms and clinical laboratory measurements.

Figure 1. LPV Concentration-Time Profile

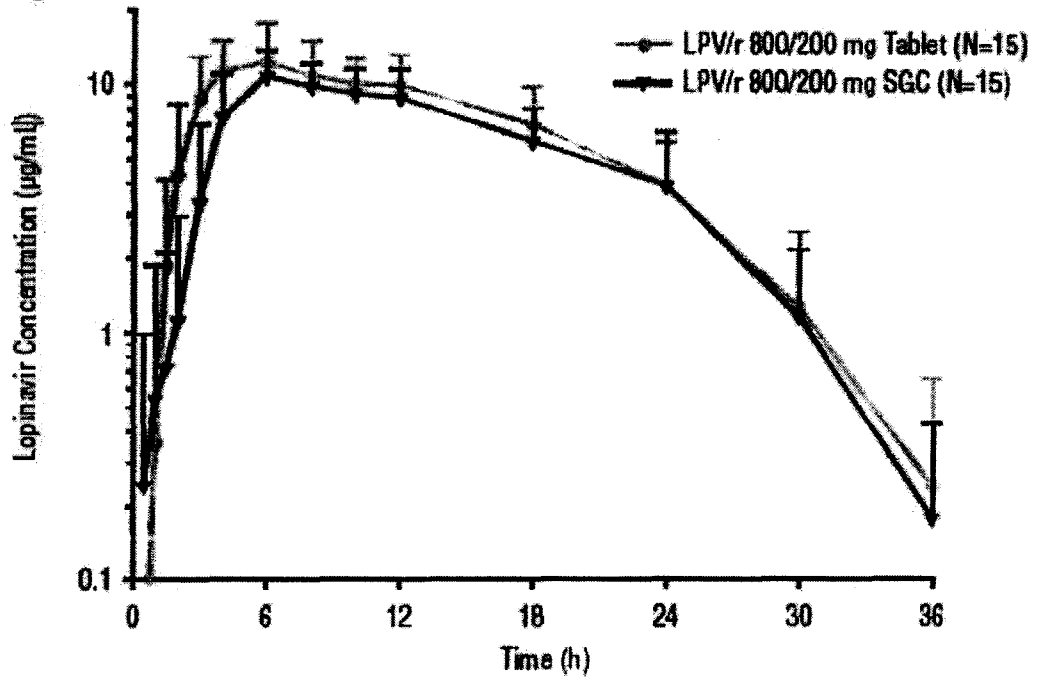


Figure 2. RTV Concentration-Time Profile

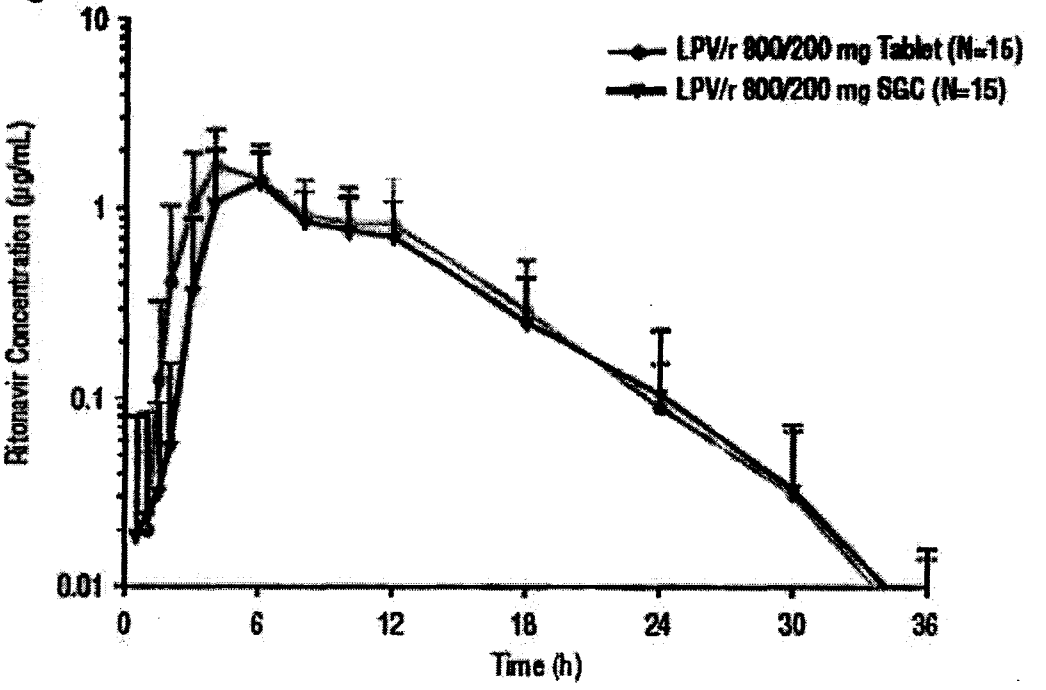


Exhibit 15

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-906

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(s)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-906	Submission Date(s): April 28, 2005
Brand Name	Kaletra
Generic Name	Lopinavir/Ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVP
Sponsor	Abbott
Relevant NDA(s)	21-226 and 21-251
Relevant IND(s)	51,715
Submission Type; Code	505 (b) (1), 1P
Formulation; Strength(s)	Film-Coated Tablet; 200 mg/50 mg
Dosing regimen	Antiretroviral-naïve: 400/100 mg twice daily or 800/200 once daily Antiretroviral-experienced: 400/100 mg twice daily
Indication	Treatment of HIV-1 infection

Table of Contents

1 Executive Summary

The sponsor submitted a New Drug Application for Kaletra (lopinavir 200 mg/ritonavir 50 mg) film-coated tablets for the treatment of HIV-1 infection. The proposed to-be-marketed tablet formulation has several advantages over the currently marketed soft gel capsule (SGC) formulation, such as reduced pill burden, diminished food effect, and less restrictive storage requirements.

1.1 Recommendation

The clinical pharmacology and biopharmaceutics information provided by the sponsor is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to the approval of this application.

1.2 Post Marking Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Single dose BE studies indicate that the to-be-marketed tablet formulation is about 20% more bioavailable than the currently marketed capsules under non-fasting conditions. However, the results from a cross-study comparison indicate that the steady-state pharmacokinetics of lopinavir and ritonavir after administration of lopinavir/ritonavir 400/100 mg BID as the to-be-marketed tablet formulation were similar to that seen in previous multiple-dose studies in healthy subjects using SGC formulations.

No new exposure-response information regarding lopinavir/ritonavir are presented in this NDA. The proposed dose regimens for Kaletra tablets are identical to those for capsule formulation approved in September 2000 and April 2005. The currently approved dose regimens for Kaletra SGC formulation are 400/100 mg lopinavir/ritonavir twice daily or 800/200 mg lopinavir/ritonavir once daily in treatment-naïve patients and 400/100 mg lopinavir/ritonavir twice daily in treatment-experienced patients. The original approval was based on the clinical trials M97-720 and M97-765 where Kaletra dose regimens 200/100 mg BID, 400/100 mg BID and 400/200 mg BID were studied. 400/100 mg dose regimen provides efficacious drug exposure for patients with wild-type virus and some resistant virus, but 400/100 mg dose regimen may not be adequate for patients with more resistant virus. Although the 400/200 mg BID regimen provided higher lopinavir trough concentrations, it was not tolerated as well as the 400/100 mg regimen. The main tolerability issues were GI-related. Triglycerides were also increased to a greater degree at the 400/200 mg dose.

The new tablet formulation with slightly higher exposures compared to the capsule formulation is expected to have an efficacy profile similar to the capsule formulation. No new or unexpected safety signals were identified in the application. The slightly higher increases in LPV and RTV produced by the new tablet formulation will not likely

Exhibit 16

MAIN REQUEST (claims 1-13 filed on 16.03.2009):

The main request does not meet the requirements of Article 52(1) EPC because the subject-matter of independent claim 1 is not new over D3 within the meaning of Article 54(3) EPC.

D3 discloses solid dosage forms for use in the treatment of a HIV patient comprising solid solutions or solid dispersions of a HIV protease inhibitor in a water-soluble polymer (with a Tg of at least 50 °C) and a surfactant, wherein said dosage forms are administered to patients in a fed state.
As the expression "without regard to whether the patient is in a fed or fasted state" used in claim 1 encompasses two alternatives, i.e. that the patient can be in a fasted or in a fed state, the disclosure of D3 is regarded as falling within the scope of claim 1.

Exhibit 17

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel. +49 (0)89 2399 - 0
Fax +49 (0)89 2399 - 4465

Thalhammer, Wolfgang
Reitstötter, Kinzebach & Partner (GbR)
Patentanwälte
Postfach 21 11 60
67011 Ludwigshafen
ALLEMAGNE

Formalities Officer
Name: Christensen
Tel.: 8052
or call:
+31 (0)70 340 45 00

Date: 26-05-2010

Reference	Application No./Patent No.
M/48379	06735552.9 - 2112 / 1855683

Applicant/Proprietor: ABBOTT LABORATORIES

Noting of loss of rights pursuant to Rule 112(1) EPC

The European Patent application is deemed to be withdrawn under Rule 71(7) EPC.

The communication under Rule 71(3) EPC dated 02.12.09 invited the applicant to pay / file:

☒ the fees for grant and printing (paid on _____)

☒ printing fee for additional pages (paid on _____)

☐ claim fee(s) (paid on _____)

☒ translations of the claims in the two other EPO official languages (received on _____).

These items were not paid / not paid in due time, not filed / not filed in due time.

☐ The present case is not one of the exceptions of Guidelines C-VI, 14.4.1.

Means of redress

Request for a decision (R. 112(2) EPC)
If the applicant considers that the finding of the European Patent Office is inaccurate, he may, within a (non-extendable) period of **two months** after notification of this communication, apply in writing for a decision on the matter. The application can only lead to the finding being reversed if this does not actually correspond to the factual or legal situation.

Further processing (Art. 121 EPC)
The legal consequence of the failure to observe the time limit shall be deemed not to have ensued if, within a (non-extendable) period of **two months** after notification of this communication, further processing is requested by payment of the fee prescribed under Article 2(12) of the Rules relating to Fees and the omitted act is completed (R. 135(1) EPC).

In case of non-payment of additional claims fees under Rule 71(6) EPC in addition to the non-fulfilment of (one of) the requirements under Rule 71(3) EPC, both 50% of the additional claims fees and a flat-rate fee for the requirements under Rule 71(3) EPC have to be paid as the fees for further processing (see Article 2 item 12 of the Rules relating to Fees).

Registered letter

Request under Article 7(3) and (4) Rules relating to Fees
The fee is considered to have been paid in due time if, within a period of **two months** from notification of this communication and in accordance with the requirements under Article 7(3) and (4) Rules relating to Fees, evidence is provided to the EPO that the payment was effected in an EPC Contracting State within the period in which the payment should have been made and, if applicable, the surcharge of 10% of the relevant fee(s) is paid.

Important note to users of the automatic debiting procedure
The fee for further processing will be debited automatically on the day on which the above-mentioned omitted act is completed (see Arrangements for the automatic debiting procedure, Supplement to OJ EPO 3/2009).

For the Examining Division

Exhibit 18

Europäisches Patentamt
European Patent Office
Office européen des brevets

attach to EP 10 159 672.4

Closure of the procedure in respect of application No. 06735552.9 - 2112 04.09.10

1. The procedure in respect of the above application is closed for the following reason:

   ADWI 10/26.05.10 The time limit under Rule 112(2) EPC has expired.
   No request for a decision under Rule 112(2), or for further processing under Article 121 EPC or for re-establishment of rights under Article 122 EPC has been filed.

2. The EPASYS situation has been verified in respect of item 1:

   DFIL: 21.02.06
   NOAP: ////
   RDEC: ////
   RFPR: //
   REES: ///

   ~~REX~~3/ADWI 3 **and DEAD 1 coded. Date of legal effect** 13.04.2010

3. Position regarding **fees**:

DEST03	005	00607982	14.09.07	EUR	560,00
EXAM02	006	00607982	14.09.07	EUR	1 490,00
CLMS(2)	015	00607982	14.09.07	EUR	180,00
FFEE01	020	00607982	14.09.07	EUR	95,00
RFEE 03	033	00168832	08.02.08	EUR	400,00
RFEE 04	034	00142543	09.02.09	EUR	500,00
RFEE 05	035	00058851	08.02.10	EUR	700,00
EXPT02	404	00607982	14.09.07	EUR	102,00
EXPT02	404	00019490	19.10.07	EUR	76,69
EXPT02	406	00607982	14.09.07	EUR	102,00
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EXPT02	408	00607982	14.09.07	EUR	102,00
EXPT02	408	00019490	19.10.07	EUR	76,50
EXPT02	409	00607982	14.09.07	EUR	102,00
EXPT02	409	00019490	19.10.07	EUR	76,50

☐ 3.1 Form **2058A** submitted to 1st examiner (if applicable)

☐ 3.2 Refund(s) ordered:

☐ 75% Exam fee ☐ Other fees: _____

4. Mark "DEAD" on the paper file and:

☒ Check whether a divisional application is pending and if so attach the DEAD file to it.

☐ Any **models** still in the Office's possession were returned on _____
(for dealing with models, please refer to Fil d'Ariane).

☐ Submit it to 1st examiner if a request for feedback is present.

☐ Keep paper file in file store (separate place) until next action for file destruction.

06-09-2010 Stark, Saskia

Date Formalities Officer

To 1st examiner/Director for information : Giró A room 2280

Exhibit 19

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Reitstötter - Kinzebach
Patentanwälte
Sternwartstrasse 4
81679 München
ALLEMAGNE

Formalities Officer
Name: Hohmann, Birgit
Tel: +49 89 2399 - 8798
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Giró, Annalisa
Tel: +49 89 2399 - 2763

Application No.	Ref.	Date
10 159 672.4 - 2112	M/48379-EP-DIV	02.12.2011
Applicant: Abbott Laboratories		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Giró, Annalisa
Primary Examiner
For the Examining Division

Enclosure(s): 4 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**

Description, Pages

1-36 as originally filed

Claims, Numbers

1-9 received on 13-01-2011 with letter of 13-01-2011

Drawings, Sheets

1/2, 2/2 as originaliy filed

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

D1 WO 2005/039551 A (ABBOTT LABORATORIES; ROSENBERG, JOEERG; REINHOLD, ULRICH; LIEPOLD, BER) 6 May 2005

D2 WO 2004/032903 A2 (ABBOTT GMBH & CO KG [DE]; ROSENBERG JOERG [DE]; BERNDL GUNTHER [DE]; M) 22 April 2004

D3 WO 01/34119 A (ABBOTT LABORATORIES) 17 May 2001

D4 US 2001/051721 A1 (DICKMAN DANIEL A ET AL) 13 December 2001

Documents D1-D4 are cited in the European Search Report.

Document D1 constitutes prior art in accordance with Article 54(3) EPC.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the search report.

1. Amendments (Article 123 EPC).

Amended claims 2-9 filed with letter of 13.01.2011 do not meet the requirements of Article 123(2) EPC in that they do not appear to be based on the original application.

No basis can be found in the application as filed for the combinations of the embodiments claimed in dependent claims 2-9 with the features of new claim 1.

Indeed, new claim 1 is directed to the combination of original claims 1 and 2, which is allowable. New dependent claims 2-9 refer back to new claim 1, while, however, their corresponding original dependent claims were dependent only on original claim 1. In this way new embodiments (combinations of original claims 1 and 2 with features of the corresponding original dependent claims) are isolated, for which no basis can be found in the application as filed.

Further, the passages of the description referring to the features of the original dependent claims describe them as particular / preferred embodiments, so that a combination of at least three of them (subject-matter of original claim 1 + original claim 2 + one embodiment described in the description), as addressed now in new dependent claims 2-9, cannot be allowed under Article 123(2) EPC.

2. Novelty (Articles 52(1) and 54(3) EPC).

2.1 The novelty objection raised in the European Search Opinion is maintained. The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of independent claim 1 is regarded as not new within the meaning of Article 54(3) EPC over D1.

The PCT application No. WO 2005/039551 (D1) published on 06.05.2005 claims the priority date of 28.08.2003. It has been supplied to the European Patent Office in one of its official languages according to Article 153(3) and (4) EPC and the filing fee provided for in Rule 159(1)(c) EPC or Article 39(1) PCT has been paid. The requirements of Rule 165 EPC are thus fulfilled. Its content as filed is therefore considered to be comprised in the state of the art relevant to the question of novelty, pursuant to Article 54(3) EPC.

This earlier application discloses solid dosage forms for use in the treatment of a HIV patient comprising solid solutions or solid dispersions of lopinavir in a water-soluble polymer (with a Tg of at least 50 °C) and a surfactant, wherein the water-soluble polymer is present in amounts falling within the claimed range of 50-85% by weight (see Examples 1-7). Said dosage forms are administered to the patient without food, as they are not administered together (mixed or combined) with food (see protocol on page 15, lines 11-25).

The Applicant argues in his letter dated 13.01.2011 that the expression "without food" is a synonymous of "on empty stomach", or that "the patient has not eaten a substantial amount of food before, during to after taking the dosage form". It is however noted the wording of claim 1 does not exclude also a more literal interpretation of said expression from the scope of the claim (e.g. by specifically defining the non-eating conditions).

Therefore, D1 is still regarded as prejudicial to the novelty of the subject-matter of independent claim 1 of the present application.

3. Inventive Step (Article 56 EPC).

The attention of the Applicant is again drawn to the fact that, even if the novelty of present claim 1 could be restored over D1, said claim might not involve an inventive step in the sense of Article 56 EPC.

D2 could be considered to be the prior art closest to the subject-matter of claim 1. Contrary to what the Applicant states in his letter, this document discloses in Example 3 a solid dosage forms for use in the treatment of a HIV patient comprising solid solutions or solid dispersions of lopinavir in a 50-85% by weight water-soluble polymer (with a Tg of at least 50°C) and a surfactant.

Hence, the only difference between D2 and claim 1 is that D2 does not specify how said dosage forms are administered, i.e. it does not disclose that they are administered to the patient without food.

According to the application, the use of the claimed formulations in a patient under fasting conditions results in a good lopinavir pharmacokinetic profile (acceptable Cmax and AUC values with low variations, see from page 32, line 21 to page 33, line 2 and figures 1 and 2), which does not significantly differ from the profile obtained under fed conditions. This result offers patients the alternative of taking lopinavir also under fasting conditions, making their life easier.

On the one hand, anyway, the attention of the Applicant is drawn to the fact that the wording of claim 1 does not necessarily relate to the use of the claimed dosage forms for the treatment of a patient which is under fasting conditions. In fact, the expression "administering to said patient said solid pharmaceutical dosage form without food" does not exclude the possibility that the patient is in a fed state, but rather implies that the dosage forms are not administered together (mixed or combined) with food. For example, the administration of said dosage forms immediately before or after a meal can be regarded as falling within the scope of claim 1.

On the other hand, according to the present application, no particular technical effect appears to be related to the the feature "administered without food".

The problem to be solved by the present invention could therefore be regarded as how to provide a way of administration for the dosage forms of D2.

Anyway, the administration without food is one of the most used routes for solid dosage forms. The majority of tablets, e.g., are swallowed with a drink (water), without mixing them with food.

The solution proposed in present claim 1 would be therefore regarded as obvious and not meeting the inventive step requirements of Article 56 EPC.

4. Final remarks.

4.1 The applicant is invited to file new claims which take account of the above comments.

4.2 Should the new claims also not fulfil the requirements of the EPC, summons to oral proceeding is to be expected.

4.3 It is noted that the present application and the application number EP10184860 filed by the same Applicant have the same effective date and appear to relate to overlapping subject-matter.

In this context, the Applicant is reminded that the EPO adheres to the principle, accepted in most of the patent systems, that two patents cannot be granted to the same applicant for one invention.