S. MAJUMDAR & CO.

PATENT & TRADEMARK ATTORNEYS

Undertakings : Intellectual Property Laws,
Patents, Trademarks, Designs, Copyrights,
Licencing, Investigations, Litigations
DOMESTIC AND INTERNATIONAL

202, Elecon Chambers, Behind Saki Naka Tel. Ex., Off Kurla-Andheri Road, Saki Naka, Mumbai- 400 072, India
Tel. : 91-22-2852 2901/ 2902, Fax : 91-22-2852 2903, e-mail : bom@patentindia.com

PI
Pre-grant opposition

The Controller of Patents
The Patent Office
Mumbai

April 24, 2009

Dear Sir,

Re: Opposition under Section 25(1) against
Patent Application No: 676/MUMNP/2007 dated May 8, 2007
Applicant: Abbott Laboratories.
Opponent: Matrix Laboratories Limited
Our Ref: **PII 332**

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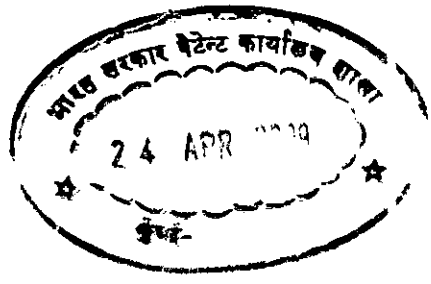
1. Sending herewith representation under Section 25(1) in duplicate. Please take the documents on record and take necessary action.
2. Please grant a hearing in due course.

To follow: Power of Authority in our favour



Yours faithfully,

Mythili Venkatesh
Of S. Majumdar & Co.
Opponent's Attorney

Encl: a/a.

BEFORE THE CONTROLLER OF PATENTS
PATENT OFFICE BRANCH,
MUMBAI

In the matter of section 25(1) of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act 2005,

And

In the matter of The Patents Rules, 2006

And

IN THE MATTER of Patents Application 676/MUMNP/2007 dated May 8, 2007 made by Abbott Laboratories.

.....Applicant

And

IN THE MATTER of opposition of the grant of a patent thereto by Matrix Laboratories Limited, 1-1-151/1, 4th Floor, SaiRam Towers, Alexander Road Secunderabad – 500 003.

.....Opponent

24 APR 2009

REPRESENTATION UNDER SECTION 25(1)

We, Matrix Laboratories Limited, 1-1-151/1, 4th Floor SaiRam Towers, Alexander Road, Secunderabad – 500 003 (hereinafter called 'opponent') makes the following representation under Section 25(1) of the Act in opposing the grant of patent on the application indicated in the cause title.

OPPONENT'S BUSINESS AND ACTIVITIES

Matrix Laboratories Limited ("Matrix") is a key player and has significant commercial interests on a global level in the business of anti-retro viral drugs [field to which the present Application pertains]. 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 and hence is directly impacted by the Application.

LIMITATION

The Opponent believes that a patent has not yet been granted on the Application under opposition. Thus the Opponent is within time to file the present opposition and the opposition ought to be taken on record.

APPROPRIATE OFFICE

The Application was filed at the Patent Office in Mumbai. Therefore the Mumbai Patent Office is the appropriate office and thus is the sole forum that has the jurisdiction to entertain, hear and adjudicate the present opposition.

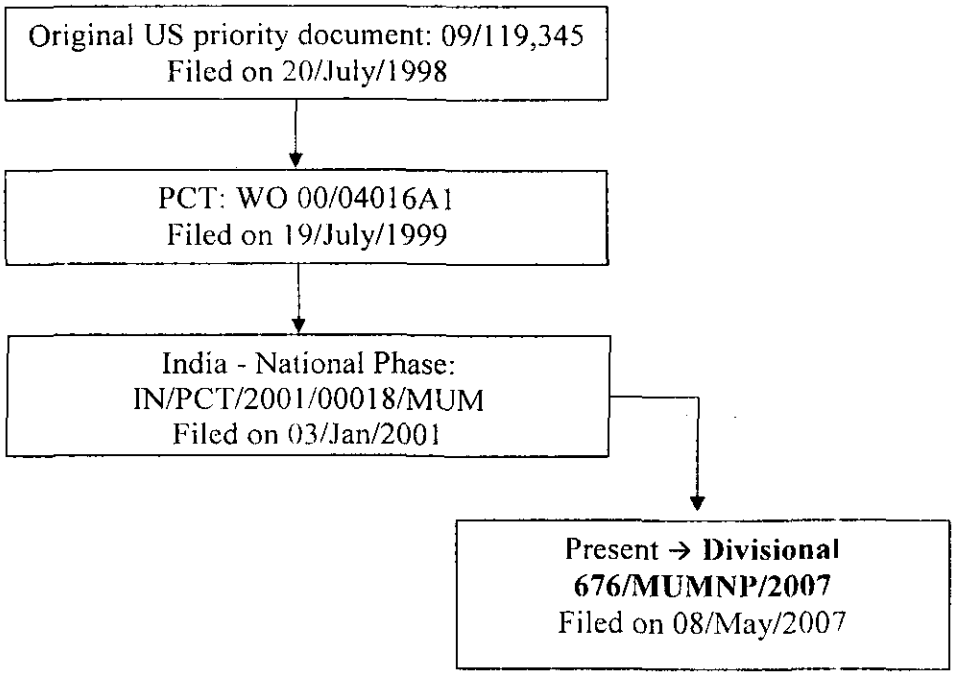
Ritonavir: In Brief

Ritonavir is a chiral molecule having the following chemical nomenclature: (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L-valinyl)amino)-2-(N-((5thiazolyl) -methoxycarbonyl)amino)-1, 6-diphenyl-3-hydroxyhexane [Merck Index, **Exhibit 1**]. Ritonavir is also refered to as ABT-538.

One of the early patents disclosing Ritonavir is US 5541206, published on 30/July/1996. The United States Food and Drug Administration (US FDA) first approved Ritonavir as an oral solution in March 1996 and later approved a capsule dosage form of Ritonavir in June 1999. It is sold commercially under the brand name Norvir™.

The Opposed Application – Filing details:

The Application principally claims 'substantially pure amorphous Ritonavir' and 'a composition comprising amorphous Ritonavir' through its eight claims. The Application was filed as a divisional from an earlier Indian application bearing number IN/PCT/2001/00018/MUM. Its genesis is graphically represented below:



Priority Date

The priority date of the application under opposition is July 20, 1998. Thus publications and/or public use prior to July 20, 1998 will be operate as prior art in the present opposition.

The alleged invention – in brief:

The alleged invention in the Application principally relates to a substantially pure amorphous form of Ritonavir and a composition containing amorphous Ritonavir.
The description discloses multiple processes to prepare substantially pure amorphous Ritonavir. The specification defines the term "substantially pure" in the context of amorphous ritonavir as follows:

> '"substantially pure", when used in reference to amorphous ritonavir refers to amorphous ritonavir which is greater than about 90% pure. This means that the amorphous ritonavir does not contain more than about 10% of any other compound and, in particular, does not contain more than about 10% of any other form of ritonavir. More preferably, the term "substantially pure", when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than about 95% pure. This means that the amorphous ritonavir does not contain more than about 5% of any other compound and, in particular, does not contain more than about 5% of any other form of ritonavir.'

The specification also goes on to disclose methods for analysis of Ritonavir polymorphs as well as the amorphous form. However, the Application does not provide any data/ working example/ guidance for making a composition comprising amorphous Ritonavir.

The Application contains the following eight claims:

1. Substantially pure amorphous ritonavir.
2. The substantially pure amorphous ritonavir of Claim 1 characterized by a glass transition from about 45°C to about 49°C.
3. A solid composition comprising amorphous ritonavir.
4. The composition of claim 3, wherein said amorphous ritonavir is substantially pure.

5. The composition of claim 3, wherein greater than about 90% of ritonavir in said composition is amorphous ritonavir.
6. The composition of claim 3, wherein greater than about 95% of ritonavir in said composition is amorphous ritonavir.
7. The composition of claim 3, wherein greater than about 97% of ritonavir in said composition is amorphous ritonavir.
8. The composition of claim 3, wherein said amorphous ritonavir is prepared from ritonavir crystalline Form II.

Grounds of Opposition

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

(a) 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:...

(b) 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) of Section 25(1) or having regard to what was used in India before the priority date of the applicant's claim;

(c) 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;

(d) that the complete application does not sufficiently and clearly describe the invention or the method by which it is to be performed;

(e) 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;

Discussion of above grounds for opposition:

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

S. 25(1)(b): Prior publication of the invention in any document:

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)

The Applicant has, over the years, published a number of papers/ articles on the development of Ritonavir and its formulation into pharmaceutical compositions. Martin D. *et al.* (1996) *Pharmaceutical Research Supplement* 13(9): page S-351 PDD 7474 published in September, 1996 **[Exhibit 2]** is one such publication. In view of this date of publication, this article is clearly prior art to the Application. Martin D. *et al.* discloses methods of preparing an orally bioavailable solid formulation of ABT-

538 – as a coprecipitate with PVP. The authors, Martin D., Al-Razzak L., Dias L., Eiden E., Gao R., Kaul D., Lechuga-Ballesteros D., Marsh R., and Poska R., are connected to Abbott Laboratories [the Applicant]. The article is a sanctioned disclosure made by Abbott in a widely distributed, prestigious scientific journal. Lines 18-22 of Martin D. *et al.* disclose a formulation comprising Ritonavir.

> *"The coprecipitate formulation were qualitatively studied using X-ray powder diffraction and differential scanning calorimetry. ABT-538 was shown to exist in the amorphous state and remained as such far up to 6 months at uncontrolled ambient conditions, and for up to four weeks in a dry oven at 40°C. (emphasis ours)"*

It is stated that Exhibit 2 discloses that ABT-538/ Ritonavir was analysed and found to exist in amorphous state by both X-ray powder diffraction and scanning thermal calorimetry.

Thus, the Martin *et al* document clearly discloses that Ritonavir in an amorphous state was produced, recognized, analyzed and studied. Additionally, the pharmaceutical composition made therein had Ritonavir in the amorphous state. Hence, both the principal claimed components of the Application namely amorphous Ritonavir and a pharmaceutical composition containing Ritonavir are clearly and unmistakably disclosed in the prior art Martin document.

Additionally, Exhibit 2 also includes another public disclosure from Abbott relating to Ritonavir as claimed in the application. Dias L. *et al.* (1996) *Pharmaceutical Research Supplement* 13(9): page S-351 PDD 7475 discloses an Abbott project relating to the evaluation of ABT-358: PVP co-precipitates. The Dias publication discloses a Ritonavir-containing composition, as shown below:

> *"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.*
>
> ...
>
> *Several ratios of drug to PVP and various molecular weights 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.

[lines 1-12 (emphasis, ours)]"

Like the *Martin* publication, the *Dias* publication also discloses that ABT-538/ Ritonavir was shown to exist in the amorphous state by both X-ray powder diffraction and scanning thermal calorimetry. Thus, the Dias *et al* publication also discloses both claimed aspects of the Application, namely "substantially pure amorphous Ritonavir" of the Application's Claim 1 as well as a pharmaceutical composition containing Ritonavir [claim 3].

i) The Opponent has shown that ABT-538 is Ritonavir (Exhibit 1);

ii) The above Martin and Dias publications both were published in September 1996 while the Application has an earliest priority of 20/July/1998 of U.S.A.;

iii) Both the Martin and Dias publications clearly disclose that compositions of ABT-538/ Ritonavir were prepared; and in such compositions ABT-538 [i.e. Ritonavir] was shown to exist in amorphous state, that the amorphous nature of ABT-538 was confirmed by analytical testing and that it remained in the amorphous state for up to six months.

The Opponent states that the alleged invention recited in claims 1 through 8 of the Application was published before the earliest priority date of the Application. It is further stated that the Martin and Dias publications individually and independently render claims 1 through 8 of the Application, unpatentable in India and warrant rejection on this ground alone.

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

The Opponent states that the claims being anticipated by prior art are also obvious and lack an inventive step on the face of the cited document. The Opponent reiterates the

arguments under the ground of prior publication to highlight the lack of inventive merit in the alleged invention.

It is further stated that the disclosure of Exhibit 2 establishes beyond doubt that the amorphous form of ritonavir and a composition comprising the same was known in the art. The Opponent states that the Application does not claim a new product but a polymorph of a known product. It is stated that such forms can be deemed within the prior art - and therefore obvious. It is stated that the Application warrants rejection on this ground.

S. 25(1)(f): Not an invention / Not patentable

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 entitled 'Inventions not patentable' specifically enumerates categories of developments that are, by statute, not considered to be patentable inventions. Claims 1 and 2 as well claims 3 through 8 of the Application fall squarely within such categories and hence are not patentable in India. The relevant section is set forth below:

> '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' (emphasis ours)

The present Application states:

'invention relates to a novel crystalline polymorph of....'

[page 1, first para]

'invention also relates to an amorphous form of ... (Ritonavir)

[page 1, first para]

'Ritonavir and processes for its preparation are disclosed in U. S. Patent No. 5,541,206, issued July 30, 1996. This patent discloses processes for preparing ritonavir which produce a crystalline polymorph of ritonavir which is termed crystalline Form I.'

[page 2, second para]

'Substantially pure amorphous Ritonavir is prepared from the Form I crystalline polymorph...' *[page 5, third para]*

'As used herein, the term "substantially pure" when used in reference to amorphous ritonavir, refers to amorphous ritonavir which is greater than 90% pure. This means that the amorphous ritonavir does not contain more than about 10% of any other compound and, in particular, does not contain more than about 10% of any other form or ritonavir '

[page 17, third para]

The Application, as noted previously, claims 'substantially pure amorphous ritonavir' and 'a composition containing amorphous ritonavir'. The Applicant has acknowledged that Ritonavir *per se* was known from the US '206 patent. Hence, the alleged invention of claims 1 and 2, is nothing but merely a new form of a previously known substance. Also, a composition containing amorphous ritonavir was disclosed and the same is evident from the earlier discussion under the ground of anticipation.

It should also be noted that the Application does not contain any data regarding the efficacy of substantially pure amorphous ritonavir; much less any comparative data on enhanced efficacy of 'substantially pure amorphous ritonavir' versus its earlier known form [Form I]. The Opponent also states that the Applicant has not submitted any

such data/comparative data to the Controller since filing of the Application. Section 3(d) requires that the new form of a known substance should show improvement in the therapeutic efficacy [i.e. demonstrate difference in therapeutic efficacy of the new entity versus known entity], which has not been proved/ clarified by the Applicant in the present instance.

Arguendo, even if the present claims are considered a case of selection invention – i.e. selecting a particular form of Ritonavir within the various possible forms of Ritonavir, then too there is no support data showing any enhancement in the known efficacy of this selected 'substantially pure amorphous ritonavir' vis-à-vis the earlier known forms; hence the Opponent respectfully submits that the claims 1 and 2 of Application fall squarely within the ambit of 'inventions not patentable' as contemplated in S. 3(d) read in conjunction with S.25(1)(f). Hence, the claims 1 and 2 are unpatentable and must be rejected as efficacy for these claims has not been substantiated.

The Opponent states that the subject matter of claims 3 through 8 in the Application do not cover an invention under the premises of the Act. The Dias as well as the Martin publications are valid prior art against the Application. Since they disclose compositions containing amorphous Ritonavir, their publication anticipates claims 3 through 8. Additionally, since claims 3 through 8 relate to a composition containing this 'new form' of ritonavir, they too are liable to be rejected in entirety as there is no data/ comparative data showing enhanced efficacy for amorphous ritonavir compositions vis-à-vis compositions containing prior art/ crystalline Ritonavir compositions.

Hence, the claims 1 through 8 of present 676 application cannot be held to cover an 'invention' [i.e. a <u>new</u> product] as envisaged in S.2(j) and must be rejected in their entirety.

<u>S. 25(1)(g)</u>: <u>Invention not sufficiently and clearly described</u>

The Opponent states that features claimed in claims 3 through 8 are not enabled. Ritonavir is a class IV compound under the Bio Pharmaceutics Classification system. Drugs in class IV are not well absorbed by gastro intestinal mucosa. Class IV drugs

are very difficult for formulation in solid compositions. Ritonavir is characterised by low aqueous solubility, low membrane permeability, and a lack of bioavailability when given in the solid state, instability once in solution under ambient conditions and a metallic taste. The Applicant markets Ritonavir [under the trade name Norvir] in two different types of compositions – an oral solution and a soft gel capsule. The Applicant also released its data on a third type of Ritonavir-containing composition (a heat stable tablet composition) in August 2008[1] and submitted its documentation for such composition to the US FDA in January 2009[2].

These compositions and their development by the Applicant have had a long and eventful journey. The approved oral solution is extremely unpleasant to taste. The next in line – soft gel capsule formulation – needs refrigeration and so cannot be distributed in many parts of the world. This soft gel capsule was introduced because the manufacturing facility in which a previous capsule form was made had problems related to the formation of an undesired crystalline form of Ritonavir. This issue escalated to a level that Abbott recalled the entire capsule product from the market and even shut down the manufacture of Ritonavir capsules in the U.S. for some months.

This undesired crystalline Ritonavir form in the capsules effected how the Ritonavir dissolved following its administration. Countless articles have been devoted to highlight the Ritonavir capsule recall. At the time of recall, the Applicant itself was not sure of how long the recall would continue or when an alternative solid oral Ritonavir formulation would be approved for sale. Finally, a soft gel capsule formulation was developed and received US FDA approval in 1999.

As seen from above discussion, Ritonavir-containing compositions are tricky to formulate and require a lot of effort in their development, to prevent crystalline conversion. With this background, it is expected that any patent application

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[1]http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0645.htm annexed hereto as Annexure 1.

[2]http://www.aidsmeds.com/articles/hiv_norvir_ritonavir_1667_16021.shtml annexed hereto as Annexure 2.

containing a composition claim for Ritonavir would certainly contain sufficient and extensive formulation development data and examples in the specification. However, the Application does not provide any data or even a single working example or other guidance for making a composition comprising amorphous Ritonavir.

The premise of patent law is that the inventor discloses sufficient and complete scientific knowledge to make the invention available to the public at large, in return for a limited time monopoly, so that the public can utilise the invention, post expiry of the patent.

In the present specification, the inventor has not disclosed any data/guidance/ technical method to make a feasible / practical composition of amorphous ritonavir leave alone the best method of preparing the claimed invention which is a requirement of the Patents Act. The lack of description/ method to prepare the amorphous ritonavir composition [for claims 3-8] renders the present specification completely insufficient to enable a person in India possessing average skills in, and average knowledge of, the art of formulation development in making a feasible amorphous Ritonavir composition – considering the difficulty noted above in relation to development of other Ritonavir-containing compositions. Granting a monopoly for such a non-enabled, but claimed invention, goes against the very foundation of patent law.

Based on the complete lack of data/ examples/ guidance of making a composition containing solid amorphous Ritonavir in the Application, the Opponent contends that present claims 3 through 8 are not patentable in India on the ground of claimed invention not being sufficiently and clearly described in the specification and hence liable for outright rejection.

S. 25(1)(h): SECTION 8

The Applicant is required to provide all the information regarding the prosecution of his equivalent applications till the grant of his Indian application to the Controller in writing from time to time and also within the prescribed time which the applicant has failed to do.

The Opponent states that the details of National phase entries and prosecution details of the foreign counterparts were not submitted by the applicant. This is, by itself, an independent ground for rejecting the present application in its entirety, and such action is respectfully requested by the Opponent.

Thus the Applicant has failed to furnish statement and undertaking under section 8, therefore the Applicant has failed to comply with the requirements of the section 8 of the act and the Application warrants rejection on this ground also.

RELIEF SOUGHT

The Opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Ld. Controller for the following relief(s).

1) Take the representation on record;
2) Leave to file additional evidence;
3) Leave to file supplementary representation in the event that such amendments are made to the application which are not adequately covered in the present representation;
4) grant of hearing;
5) refusal of the application in toto;
6) such other relief or reliefs as the Controller may deem appropriate.

Dated this 24th Day of April 2009.

Mythili Venkatesh
Of S. Majumdar & Co.
Opponent's Agent

To:

The Controller of Patents

The Patent Office,

Mumbai.

Enclosures:

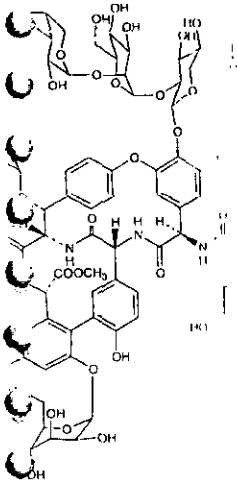
- Exhibit 1;
- Exhibit 2;
- Annexure 1;
- Annexure 2.

Exhibit-1

16

...DMF + 2-propanol, mp ... and pharmacokinetics: P. Timmerman *et al.*, ...ds. dogs (mg/kg): ... *Mass Spectrom.* **18**, 498 (1989). Clinical ...1, 63.1, 113, 56.6, 18.3, 18... *et al., Headache* **30**, 439 (1990); G. Bersani ... Antipsychotic.

Ristocetin. [1404-55-3] ... peptide antibiotic complex ... *ta furida.* Ristocetin A and ... in the number of gluc... *ose groups in their sulf...* properties: J. E. Philp *et al.* ... *Chem.* **US 2990329** (1961 ... tocetin A: Fehlner *et al.*, *J...* 72); C. M. Harris *et al.*, *J. ...* Sztaricskai *et al.*, *ibid.* 10... ermn of ristocetin A: D. H. Willi... 979, 906; J. R. Kalman ... 3, 897 (1980). Identity ... D. H. Williams *et al.*, *J. ...* ^{13}C-NMR studies: P. Sztaric... 1, 2983 (1980); M. P. Williams... *Chem. Soc. Perkin Trans. 1* 1981, ... J. M. Harris, T. M. Harris, *J. ...* osynthesis: S. J. Hammond *et al.* ... 1986. *Review:* D. C. Jordan, ... Shaw, Eds. (Springer-Verlag, ...



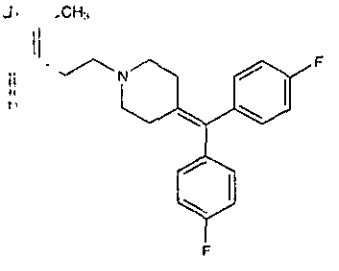
sulfates. Sol in acidic ... ral pH range. Generally ... ments show good stability ... vated above pH 7.0 ... both with >90% ristocetin ... n A. Ristomycin A. $C_{...}$ ... −133° (water).

3. Ristomycin B. ... ter).

... for investigation of platelet ... *Diath. Haemorrh.* **26**, ...

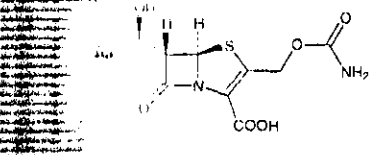
AT: Antibacterial.

Ritanserin. [87051-43-2] ... methylene]-1-piperidinyl]... 477.58. C 67.90%, ... 71%. Selective serotonin ... m: L. E. J. Kennis *et al.*, *J. ...* 4, 1985 both to Janssen ... *et al., Drug Dev. Res.* **15**, ...



...nitrile, mp 145.5°. LD_{50} in male, female ... mg/kg): 28.2, 28.2, 20.0, 22.2, 24.1, 33.2 i.v.; ... 280, 640-1280 orally (Awouters). ... *Review:* D. C. Jordan, ... Shaw, Eds. (Springer-Verlag, ... $C_{29}H_{25}F_2N_3OS.C_4H_4O_4$. Solid ... mp 198.7°.

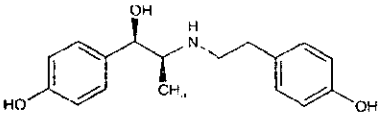
... lytic; antidepressant.



...lfates. [84845-57-8] (5*R*,6*S*)-3-[[(Aminocar... ...-[(1*R*)-1-hydroxyethyl]-7-oxo-4-thia-1-... ...ene-2-carboxylic acid; (5*R*,6*S*,8*R*)-6-... ...moyloxymethyl-2-penem-3-carboxylic ... ...-(1-hydroxyethyl]-3-(hydroxymethyl)-7-... ...]3.2.0]hept-2-ene-2-carboxylic acid, 3-... ...$_6$S; mol wt 288.28. C 41.66%, H 4.20%, ... S 11.12%. Prepn: M. Alpegiani *et al.*, ...ano *et al.*, US **4482565** (1983, 1984 both ... ...thesis: G. Franceschi *et al.*, *J. Antibiot.* **36**, ...nthesis: W. Cabri *et al.*, *Tetrahedron Let...* ... Toxicity study: M. Brughera *et al.*, *J. ...medica.* **23**, Suppl. C, 129 (1989). Series of ... *in vitro* activity, metabolism: *ibid.*, 1-204 ... pharmacokinetics of acid and ester forms: S. ... *Ibid.* **25**, 371 (1990); A. M. Lovering *et al.*, ... HPLC determn in serum and urine: R. ... *Chromatog.* **579**, 115 (1992).

Rituximab. [174722-31-7] Anti-(human CD20 antigen) immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ_1-chain) disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer; IDEC-C2B8; Mabthera; Rituxan. Genetically engineered chimeric murine-human monoclonal antibody directed against the CD20 antigen found on normal and malignant B lymphocyte surfaces. Contains murine light and heavy-chain variable regions and γ_1 heavy-chain and κ light chain human constant regions. Composed of 2 heavy chains of 451 amino acids and 2 light chains of 213 amino acids; approx mol wt 145 kD. Prepn: D. R. Anderson *et al.*, **WO 94 11026**; *eidem*, **US 5736137** (1994, 1998 both to IDEC); M. E. Reff *et al.*, *Blood* **83**, 435 (1994). HPLC determn of product purity: K. G. Moorhouse *et al.*, *J. Pharm. Biomed. Anal.* **16**, 593 (1997). Clinical pharmacokinetics: N. L. Berinstein *et al.*, *Ann. Oncol.* **9**, 995 (1998). Clinical trial in lymphoma: P. McLaughlin *et al.*, *J. Clin. Oncol.* **16**, 2825 (1998); in combination with CHOP chemotherapy: M. S. Czuczman *et al.*, *ibid.* **17**, 268 (1999). Review of clinical studies: C. A. White, *Cancer Biother. Ra...*

Clinical investigations: Coutinho *et al.*, *Am. J. Obstet. Gynecol.* **104**, 1053 (1969); Landesman *et al.*, *ibid.* **110**, 111 (1971); Wesselius-De Casparis *et al.*, *Brit. Med. J.* **3**, 144 (1971). Clinical efficacy in treatment of preterm labor: J. F. Larsen *et al.*, *Obstet. Gynecol.* **67**, 607 (1986).

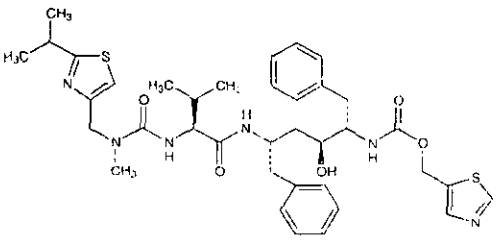


Base. Resinous mass, mp 88-90°.

Hydrochloride. [23239-51-2] DU-21220; Miolene; Prempar; Pre-Par; Utemerin; Utopar; Yutopar. $C_{17}H_{21}NO_3.HCl$; mol wt 323.82. mp 193-195° (*dec*) from ethanol-ether. uv max: 267.5 nm (ε 3310).

THERAPCAT: Tocolytic.

8321. Ritonavir. [155213-67-5] (5*S*,8*S*,10*S*,11*S*)-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; (2*S*,3*S*,5*S*)-5-[*N*-[[*N*-methyl-*N*-[(2-isopropyl-4-thiazolyl)methyl]amino]carbonyl]valinyl]amino]-2-[*N*-[(5-thiazolyl)methoxycarbonyl]amino]-1,6-diphenyl-3-hydroxyhexane; A-84538; Abbott 84538; ABT-538; Norvir. $C_{37}H_{48}N_6O_5S_2$; mol wt 720.96. C 61.64%, H 6.71%, N 11.66%, O 11.10%, S 8.90%. Peptidomimetic HIV-1 protease inhibitor. Prepn: D. J. Kempf *et al.*, **WO 94 14436**; *eidem*, **US 5541206** (1994, 1996 both to Abbott). Antiretroviral spectrum, pharmacokinetics: *idem et al.*, *Proc. Nat. Acad. Sci. USA* **92**, 2484 (1995). Structural model for drug resistance: M. Markowitz *et al.*, *J. Virol.* **69**, 701 (1995). HPLC determn in biological fluids: R. M. W. Hoetelmans *et al.*, *J. Chromatog. B* **705**, 119 (1998). Review of clinical experience: A. P. Lea, D. Faulds, *Drugs* **52**, 541-546 (1996). Clinical trial with nucleoside analogs in HIV-infected children: S. A. Nachman *et al.*, *J. Am. Med. Assoc.* **283**, 492 (2000).



THERAPCAT: Antiviral.

Exhibit-2

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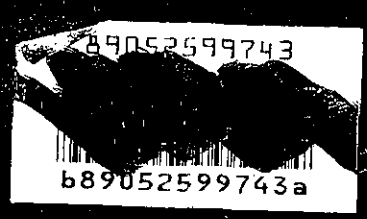

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PDD 7473

ORAL ABSORPTION OF XR543, A NEUROTRANSMITTER RELEASE ENHANCER, IN DOGS FROM VARIOUS FORMULATIONS - IN VITRO AND IN VIVO CORRELATION. Shiew-Mei Huang*, Lei-Shu Wu, Maria D. Ribadeneira, Cecilia L. Chi, Philip L. Saxton, Benjamin M. Chien, and Check Y. Quon. The DuPont Merck Pharmaceutical Company, Newark, DE 19714

XR543 is a drug candidate for improvement of cognitive performance in patients with Alzheimer's-type dementia. The purpose of this study was to determine the oral bioavailability of XR543 in dogs from various formulations. *In vitro* dissolution (in 0.1% Na dodecyl sulfate [SDS] aqueous solution, at 100 rpm, for 60 min) and Caco-2 permeation (passage 32, non-stagnant conditions) were also determined. XR543 (0.3 mg/kg) in 0.25% MC suspension or capsule formulations were administered to groups of male beagle dogs (n=4/group) under fasting conditions. XR543 levels in plasma were determined by LC/MS/MS (QL=0.1 ng/mL). The results indicate that the dry mix of XR543 and lactose was ~60% as bioavailable as the suspension formulation. The formulations prepared by dissolving XR543 in ethanol or Tween 80/ethanol solution prior to spraying on lactose showed comparably good bioavailability (absolute % F: 25-40%) to the suspension formulations. In vitro studies showed the dissolution and Caco-2 flux rates of the suspension ≥ Tween 80/ethanol = ethanol > dry lactose. Formulations containing dry blending or wet granulation with SDS, which did not improve the dissolution rate, also showed the lowest Caco-2 flux rates *in vitro*. Results of the study indicate that XR543 has a good membrane permeability and its bioavailability *in vivo* appears to be dissolution-limited.

PDD 7474

METHOD OF PREPARING AN ORALLY BIOAVAILABLE SOLID FORMULATION OF AN INSOLUBLE PROTEASE INHIBITOR AS A COPRECIPITATE WITH PVP AND OTHER EXCIPIENTS. D. Martin*, L. Al-Razzak, L. Dias, E. Eiden, R. Gao, D. Kaul, D. Lechuga-Ballesteros, K. Marsh and R. Poska, Pharmaceutical and Analytical R&D, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois, 60064.

In order to enhance the oral bioavailability of a poorly soluble antiviral compound, a coprecipitate with polyvinylpyrrolidone (PVP) was deposited onto a solid substrate. Granulations containing a variety of excipients were prepared using a prototype high shear granulator. A granulating solution (ABT-538, PVP and ethanol), was slowly applied onto a solid substrate followed by drying. The oral dog bioavailability of ABT-538 in the resulting formulations was improved, however, it was highly variable. The *in vivo* variability observed was thought to be related to either poor formation of the coprecipitate due to the lack of process control during drying or enhanced wettability due to the presence of residual solvent. A fluidized bed coating technique (using a STREA-1 fluidized bed coater) was found to be an effective means of controlling the formation and drying of the coprecipitate in the formulation. Spherical particles containing sugar spheres NF and granules consisting of either lactose or microcrystalline cellulose were coated with a *ca.* 10-50 μm film of ABT-538 & PVP coprecipitate. The coprecipitate formulation were qualitatively studied using X-ray powder diffraction and differential scanning calorimetry. ABT-538 was shown to exist in the amorphous state and remained as such for up to 6 months at uncontrolled ambient conditions, and for up to four weeks in a dry oven at 40 °C. Liquid surfactants and solid additives were incorporated into the films to improve wetting and ABT-538 solubility. The oral dog bioavailability was improved at least 10 fold as compared to the unformulated ABT-538.

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.

PDD 7476

CYCLODEXTRINS AS POTENTIAL EXCIPIENTS IN TABLET DOSAGE FORMS

Priyashri Nayak* and Sunil Jambhekar, Division of Pharmaceutical Sciences, Massachusetts College of Pharmacy/A.H.S., 179 Longwood Avenue, Boston, MA 02115

The purpose of this study was to evaluate cyclodextrins (CYDs) as excipients with potential for enhancing the dissolution of poorly soluble drugs. Ketoprofen (KPF), a poorly water soluble drug, was selected as a model. Tablets were prepared by wet granulation using β-CYD, hydroxypropyl β-CYD, conventional diluents like lactose and M.C.C., and several combinations of conventional diluents with CYDs. The particle size, bulk and tap density, and the angle of repose of the granules were determined. Tablets were evaluated for the in-vitro dissolution of KPF using a modified reverse phase HPLC method and other parameters such as weight variation, content uniformity, friability, hardness, and disintegration. The dissolution results indicated that the rate and cumulative amount of KPF dissolved from all formulations containing CYDs was greater than those containing lactose and/or M.C.C. alone. It is postulated that the presence of CYDs may improve the wettability of KPF which increases the effective surface area available for dissolution. Alternatively, faster dissolution may be attributed to the formation of a complex between KPF and CYD. [Supported by Zeneca Pharmaceuticals, Inc.]

ANNEXURE- I

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Press Release

Abbott Study Shows Investigational Heat-Stable Norvir® Tablet Provides Similar Drug Levels to Current Norvir Capsule

Pivotal Study of Norvir Tablet Bioavailability Will Form the Basis of Request for Priority Regulatory Review

August 7, 2008

Mexico City — Abbott (NYSE: ABT) presented pivotal data at the XVII International AIDS Conference (AIDS 2008) in Mexico City today showing that its investigational Norvir® (ritonavir) tablet and the current soft-gelatin capsule provide similar levels of drug in the blood.

The heat-stable Norvir tablet will not require refrigeration, making it more convenient for patients to use, particularly in developing countries where the majority of people with HIV live.

The heat-stable formulation of ritonavir may help to further expand protease inhibitor-based HAART (highly active antiretroviral therapy) in regions where the need for refrigeration of HIV medicines is a major barrier to treatment and care," said Pedro Cahn, M.D., Ph.D., president, International AIDS Society.

The study compared the bioavailability of the 100mg ritonavir tablet to that of a 100mg soft-gelatin capsule under non-fasting conditions. The ritonavir tablet demonstrated similar bioavailability to the current soft-gelatin capsule, and was generally well tolerated. In this study performed in 93 healthy adult volunteers, the safety profiles of the two formulations were similar, with no serious adverse events reported.

Several formulations were evaluated, and the final formulation evaluated in the bioavailability study is the product of significant testing and formulation work. The data presented are the basis of upcoming regulatory submissions.

Abbott has confirmed its intention to submit registration applications for the tablet and request priority review by US and EU authorities before the end of the year.

>Abbott intends to register the new Norvir tablet as broadly worldwide as lopinavir/ritonavir, the most widely registered PI worldwide, according to the World Health Organization. The lopinavir/ritonavir tablet is approved for sale, available (in countries where no regulatory approval is needed), or has been submitted for registration in 157 countries around the world.

The Norvir tablet was developed using the Meltrex® technology, which was also used in the development of Abbott's Kaletra® tablets, which combine ritonavir and lopinavir However, ritonavir on its own required a different formulation to ensure that the tablets remain stable over time and that the body can absorb the drug.

About Abbott's Commitment to Fighting HIV/AIDS

HIV/AIDS is a global problem that demands shared commitment and shared responsibility. Abbott is committed to working with governments, multilateral organizations, nongovernmental organizations and patient groups to expand access to HIV treatments around the world. Abbott has also made significant investments in expanding manufacturing capacity to meet the growing demand for HIV treatment in developing countries.

Abbott's lopinavir/ritonavir formulations are among the lowest-priced protease inhibitors in the developing world. Abbott has been providing its HIV medicines at a price of US$500 per adult patient per year in all African and least developed countries since 2002, making these medicines more affordable than any generic copies.

Abbott and the company's philanthropic foundation, Abbott Fund, have invested more than US$100 million in the fight against HIV/AIDS in Africa and the developing world. Abbott Fund-supported programs have served more than 700,000 children and families. In addition, more than 250,000 patients have been tested through Abbott Fund-supported voluntary counseling and testing programs, with thousands being referred to treatment programs. Abbott also has donated more than eight million rapid HIV tests to help prevent mother-to-child HIV transmission.

Abbott and Abbott Fund have announced several efforts to expand access to treatment and care for children living with HIV/AIDS, including an additional investment of US $12 million in grants and product donations this year.

For more information about Abbott's commitment to fighting HIV/AIDS, please visit http://www.abbott.com/global/url/content/en_US/40.45:45/general_content/General_Content_00320.htm.

About Norvir

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Indication

NORVIR (ritonavir) is a class of medicines called HIV protease (*PRO-tee-ase*) *inhibitors*. NORVIR is used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. NORVIR is for adults and for children age one month and older.

Important Safety Information

NORVIR does not cure HIV infection or AIDS and does not reduce the risk of passing HIV to others.

NORVIR must not be taken in patients who have had a serious allergic reaction to NORVIR or any of its ingredients.

Taking NORVIR with certain medicines can cause serious or life-threatening problems such as irregular heartbeat, breathing difficulties or excessive sleepiness. Norvir must not be taken with Cordarone® (amiodarone); ergotamine, ergonovine, methylergonovine, and dihydroergotamines such as Cafergot®; Migranal®; D.H.E. 45® and others; *Halcion® (triazolam)*; *Hismanal®* (astemizole); Orap® (pimozide); Propulsid® (cisapride); Quinidine®, also known as Quinaglute®; Cardioquin®; Quinidex®; Rythmol® (propafenone); Seldane® (terfenadine); Tambocor®; (flecainide); Uroxatral® (alfuzosin hydrochloride); Vascor® (bepridil); Versed® (midazolam); and Vfend® (voriconazole).

NORVIR must not be taken with St. John's Wort (*hypericum perforatum*), Mevacor® (lovastatin) or Zocor® (simvastatin).

There are drug-drug interactions with the potential for risk of serious or life-threatening side effects. Alterations in dose, increased monitoring of drug levels in the blood or increased observations for side effects may be recommended when NORVIR is taken with: Lipitor® (atorvastatin), Crestor® (rosuvastatin), Viagra® (sildenafil), Cialis® (tadalafil), Levitra® (vardenafil), oral contraceptives ("the pill") or the contraceptive patch, Mycobutin® (rifabutin), rifampin, also known as Rimactane®, Rifadin®, Rifater® or Rifamate®; inhaled Flonase® *(fluticasone), metronidazole or disulfiram.*

Rifampin and saquinavir should not be taken together with NORVIR. Patients should tell their doctor if they are taking rifampin and saquinavir.

The above lists of medicines are not complete. Patients should discuss all medicines, including those without a prescription and herbal preparations they are taking or plan to take, with their doctor or pharmacist.

The most commonly reported side effects are: feeling weak or tired, nausea, vomiting, diarrhea, loss of appetite, abdominal pain, changes in taste, tingling feeling or numbness in hands or feet or around the lips, headache, and dizziness. This is not a complete list of reported side effects.

Pancreatitis and liver problems, which can be fatal, have been reported in patients receiving NORVIR. Patients should tell their doctor if they have nausea, vomiting, or abdominal pain, which may be signs of pancreatitis, or if they have or have had liver disease such as Hepatitis B or C

Some patients have had large increases in triglycerides and cholesterol. Changes in body fat have been seen in some patients taking anti-HIV therapy. The long-term health effects of these conditions are not known at this time.

Diabetes and high blood sugar have occurred in patients taking protease inhibitors, such as NORVIR.

Some patients with hemophilia have increased bleeding with protease inhibitors.

The effects of NORVIR on pregnant women or to their unborn babies are not known. Mothers taking NORVIR should not breastfeed.

Refrigeration of NORVIR soft gelatin capsules by the patient is recommended, but not required if used within 30 days and stored below 77°F (25°C). Avoid exposing NORVIR soft gelatin capsules to excessive heat or cold. Store in the original container.

Store NORVIR oral solution at room temperature. Do not refrigerate NORVIR oral solution. Avoid exposing NORVIR oral solution to excessive heat or cold. Store in the original container.

About Kaletra

Indication

KALETRA (lopinavir/ritonavir) is a human immunodeficiency virus-1 (HIV-1) protease inhibitor. KALETRA is always used in combination with other anti-HIV-1 medicines for the treatment of HIV-1 infection. KALETRAis a combination of two medicines, lopinavir and ritonavir. KALETRA is for adults and for children age six months and older.

Important Safety Information

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KALETRA does not cure HIV-1 infection or AIDS and does not reduce the risk of passing HIV-1 to others.

KALETRA must not be taken by patients who have had an allergic reaction to KALETRA or any of its ingredients.

Taking KALETRA with certain drugs can cause serious problems or death. KALETRA must not be taken with dihydro ergotamine, ergonovine, ergotamine or methylergonovines such as Cafergot® , Migranal® , D.H.E. 45® , ergotrate maleate, and methergine, as well as Halcion® (triazolam), Orap® (pimozide), Propulsid® (cisapride), or Versed® (midazolam).

KALETRA must not be taken with rifampin, also known as Rimactane® , Rifadin®, Rifater®, or Rifamate®; St. John's Wort (*Hypericum perforatum*); Mevacor® (lovastatin), or Zocor® (simvastatin).

There are drug-drug interactions with the potential for risk of serious or life-threatening side effects. Alterations in dose, increased monitoring of drug levels in the blood, or increased observations for side effects may be recommended when KALETRA is taken with: Lipitor® (atorvastatin), Crestor® (rosuvastatin), Viagra® (sildenafil), Cialis® (tadalafil), Levitra® (vardenafil), oral contraceptives ("the pill") or the contraceptive patch, Mycobutin® (rifabutin), inhaled Flonase® (fluticasone), metronidazole, or disulfiram. Patients should talk with their doctor about all medicines they are taking or planning to take, including those without a prescription and herbal products.

KALETRA should not be given once-daily in combination with Sustiva® (efavirenz), Viramune® (nevirapine), Agenerase® (amprenavir), fosamprenavir, Viracept® (nelfinavir), phenobarbital, Dilantin® (phenytoin) or Tegretol® (carbamazepine).

Patients and/or their care providers should pay special attention to accurate administration of the KALETRA dose to reduce the risk of accidentally giving too much or too little medicine.

The most commonly reported side effects of moderate severity that are thought to be drug related are abdominal pain, abnormal bowel movements, diarrhea, feeling weak/tired, headache and nausea. Children taking KALETRA may sometimes get a skin rash. Other side effects may occur.

Pancreatitis and liver problems, which can be fatal, have been reported in patients receiving KALETRA. Patients should tell their doctor if they have nausea, vomiting, or abdominal pain, which may be signs of pancreatitis, or if they have or have had liver disease, such as hepatitis B or C.

Some patients have had large increases in triglycerides and cholesterol. Changes in body fat have been seen in some patients taking anti-HIV therapy. The long-term health effects of these conditions are not known at this time.

Diabetes and high blood sugar have occurred in patients taking protease inhibitors such as KALETRA.

Some patients with hemophilia have increased bleeding with protease inhibitors.

The effects of KALETRA on pregnant women or their unborn babies are not known. Mothers taking KALETRA should not breast-feed.

All strengths of KALETRA tablets should be swallowed whole and not chewed, broken, or crushed.

KALETRA tablets should be stored at room temperature. Exposure of this product to high humidity outside the pharmacy container for longer than two 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 two months.

Avoid exposure to excessive heat.

Abbott and HIV/AIDS

Abbott has been a leader in HIV/AIDS research since the early years of the epidemic. In 1985, the company developed the first licensed test to detect HIV antibodies in the blood and remains a leader in HIV diagnostics. Abbott retroviral and hepatitis tests are used to screen more than half of the world's donated blood supply. Abbott has developed two protease inhibitors for the treatment of HIV.

About Abbott Fund

Abbott Fund is a philanthropic foundation established by Abbott in 1951. Abbott Fund's mission is to create healthier global communities by investing in creative ideas that promote science, expand health care and strengthen communities worldwide.

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About Abbott

Abbott (NYSE: ABT) is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritionals, devices and diagnostics. The company employs more than 68,000 people and markets its products in more than 130 countries.

For more information on Abbott's HIV/AIDS programs, please visit http //www.abbott.com/global/url/content/en_US/40.45:45/general_content/General_Content_00326.htm and http://www.abbottglobalcare org/.

ANNEXURE-2 24

January 28, 2009

New Heat-Stable Norvir Tablet Sent to FDA for Approval

Paperwork for a new heat-stable tablet formulation of Norvir (ritonavir) has been submitted to the U.S. Food and Drug Administration (FDA) for approval, according to an announcement by the drug's maker, Abbott Laboratories. Unlike the current Norvir capsules, the new tablet will not have to be refrigerated.

Norvir is a protease inhibitor that is primarily used to boost the blood levels of other antiretroviral (ARV) drugs. Abbott used the same technology to produce the new tablet that it used to make a tablet version of its drug Kaletra (ritonavir plus lopinavir). The company first released data about how the body absorbed the new Norvir tablet, compared with the old capsule, at the International AIDS Conference in Mexico City in August 2008.

Abbott commented that the new tablet will be a boon for patients in developing countries, who often don't have access to refrigerators. They did not, however, announce the price for the new tablet, which will likely affect how widely the drug will be used. There was a great deal of controversy when Abbott raised the price of the capsule form of Norvir several years ago by 400 percent.

Search: Norvir, heat-stable, ritonavir, Kaletra, lopinavir, Abbott, protease inhibitor

24 APR 2009