BEFORE THE CONTROLLER OF PATENTS, CHENNAI

IN THE MATTER OF:

An opposition under section 25(2) 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 (Amendment) Rules 2005 (“the Rules”)

And

IN THE MATTER OF:

Indian Patent 207232,
Published as granted in the Official Journal
of the Patent Office of June 29th, 2007

M/s F. Hoffman La Roche                 … PATENTEE
v/s
M/s Matrix Laboratories Limited       …OPPONENT

STATEMENT OF OPPOSITION

(i)   The Opposition in brief

1.
The “Opponent” hereby files a post-grant opposition under Section 25(2) of the Patent Act 1970, as amended by the Patents (Amendment) Act, 2005 (the “Act”) against the patent titled:
“2-(2-amino-1, 6-dihydro-6-oxo–purin-9-yl) methoxy-3-hydroxy -1-propanyl –L-valinate”,
granted to F. Hoffman La Roche (the “Patentee”),
on 1st June 2007, bearing the  No. 207232 (the “Patent”). The grant of the Patent was published in the Official Journal of the Patent Office dated 29th June, 2007 and hence the present post-grant opposition is well within the time stipulated under the Patents Act 1970 and the Rules made thereunder. A copy of the relevant extract of the Official Journal dated 29th June, 2007 is attached as [Exhibit 1].
(ii) **The interest of the Opponent**

2.

The Opponent is a registered company, incorporated under the Companies Act, 1956, listed on Indian stock exchanges, having its registered office at 1-1-151/1, 4th Floor, Sai Ram Towers, Alexander Road, Secunderabad – Andhra Pradesh INDIA 500 003.

3.

The Opponent is a leading pharmaceutical company engaged in the manufacture of Active Pharmaceutical Ingredients (APIs) and Solid Oral Dosage Forms. The development and manufacture of quality intermediates, APIs and oral dosage forms have been critical to the Opponent’s success in delivering innovative and affordable products for both the domestic as well as international markets. The Opponent employs more than 2000 employees, including over 200 R&D scientists, and conducts research & development, and manufactures products at its cGMP facilities located near Hyderabad, Visakhapatnam and Nashik in India.

4.

The Opponent is a leading supplier of generic drugs in the anti-viral market on a global level and is also a key component in the US President’s Emergency Plan for AIDS Relief [PEPFAR].

As a part of its commercial plans, the Opponent further plans to manufacture and commercialise the drug, chemically known as

‘L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride’

and commonly known as Valganciclovir Hydrochloride for use/ sale in India as well as export out of India. The granted Indian Patent No. 207232 purportedly has a product claim for this drug, thereby blocking the production, use and sale of this drug within India, by any one other than its Patentee – F Hoffmann la Roche or its licensees.
The Opponent qualifies as a ‘person interested’ as defined in section 2(1)(t) of the Patents Act, 1970 for the purpose of instituting a post-grant opposition under section 25(2) of the Act.

(iii) Jurisdiction of the Patent Office

5. The Application was filed at and subsequently granted a patent by the Patent Office in Chennai; therefore the Patent Controller has the jurisdiction to hear this post-grant opposition in Chennai.

(iv) The Patent under Opposition

6. The product [Valganciclovir] claimed in the present patent is the pro-drug of a known, old anti-viral drug [Ganciclovir]. The present patent’s claims also cover a drug called Valganciclovir hydrochloride or more specifically, the hydrochloride salt of l-valinate ester of Ganciclovir.

Ganciclovir per se has been known since the early 1980s. Ganciclovir is disclosed in US patent 4,355,032 bearing a publication date of 19th October, 1982 [Exhibit 2]. Ganciclovir as well its pro-drug [Valganciclovir, claimed in the present Patent] is used in anti-viral therapy.

(v) Summary of the Claims

7. The Claims in the granted patent can be broadly summarised as follows:

   a. Claim 1 covers a compound - the L-valinate ester of ganciclovir or its pharmaceutically acceptable salts forms, in the form of a diastereomeric mixture.

   b. Claims 2 to 9 are dependent on Claim 1 and add various limitations/embodiments for the compound covered in Claim 1.
c. Claim 10 is an independent process claim for preparing the L-valinate ester of ganciclovir.

d. Claims 11 and 12 are dependent on Claim 10.

I. Opposition of claims 1 to 9 and claim 12

8. The Opponent opposes Claims 1 through 9 and claim 12 of the Patent under section 25(2) on the following [amongst other] grounds:

…

(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:…

(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;

(h): that the Patentee has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any manner was false to his knowledge;

(vi) Lack of Inventive Step

9. The Opponent now will explain its stand for the above Opposition in view of S.25 (2) (e).

S.25 (2) (e) – the claimed invention is obvious and does not involve any inventive
step having regard to publications made in India or elsewhere, in any document. S. 2(j) of the Act defines *invention* as ‘a new product or process involving an inventive step and capable of industrial application;’

S. 2(ja) of the Act defines *inventive step* as ‘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) of the Act defines a *new invention* as ‘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;’

10.

A look at the relevant prior art clearly shows that esterification of drugs having poor absorption is obvious to a person skilled in the art and involves no inventive step, as of the priority date of the present patent. The Opponent states that there is no inventive step involved in creation of an ester of a drug with poor oral absorption/low bioavailability. More specifically, creating the L-valine esters of purine drugs with poor bioavailability does not involve any inventive step nor does it cause technical advancement as compared to the existing knowledge and is obvious to a person skilled in the art.

This will now be demonstrated by means of the following facts and supporting arguments.

11.

Facts:

a) The Patentee, in its specification has stated the compound of the present invention

‘… is an ester derived from ganciclovir and L-Valine’.

Specification page 1, lines 3-4
The principle invention, in simple terms, is the L-valine ester derived from a known drug – Ganciclovir. This ester form is a pro-drug that is hydrolyzed to Ganciclovir through enzymes in the [human] gut mucosa and hepatic cells.

b) The Patentee, in its specification has acknowledged that US patent 4,355,032 discloses Ganciclovir and Ganciclovir being
‘... efficacious against viruses of the herpes family, for example, against herpes simplex and cytomegalovirus.’

Specification page 1, lines 27-29

The parent drug Ganciclovir is already commercially sold in two formulations:
i) an intravenous formulation (IV) in the form of a lyophilized powder of the sodium salt to be reconstituted with water and
ii) an oral tablet formulation.

c) The present Patentee, in its specification has stated that Ganciclovir ‘...has a relatively low rate of absorption...’

Specification page 1, lines 29-30

and
‘...it has been highly desirable to provide ganciclovir with an improved oral absorption profile’.

Specification page 2, lines 6-7

So the alleged invention is ‘the L-valinate ester [pro-drug] of ganciclovir’ and
the alleged inventive step accordingly is the ‘provision of an ester form of ganciclovir for improvement in oral absorption profile.’

d) The present Patent has an Indian filing date of 27/July/1995, with a priority of
12. There is considerable literature on use of esters for increasing bioavailability/improving absorption of poorly soluble drugs, published prior to 28/July/1994. For instance, L. M. Beauchamp et. al., Antiviral Chemistry & Chemotherapy (1992), 3 (3), 157-164 published in 1992, disclose eighteen amino acid esters of the antiviral drug acyclovir and their efficiencies as prodrugs of acyclovir, evaluated in rats by measuring the urinary recovery of acyclovir. Interestingly, according to the authors the L-valyl ester of acyclovir was the best pro-drug of the esters investigated. [Exhibit 3].

13. Esters of other drugs exhibiting poor absorption have been developed and marketed prior to 1994. A representative example is Famciclovir, a drug used for the treatment of various herpes virus infections. It is a pro-drug, in the diacetate ester form, of Penciclovir, itself an anti-viral drug. Penciclovir was disclosed in claim 9 at page 24 of European patent 0141927, with a publication date of 16/Feb/1983 [Exhibit 4]. Famciclovir was disclosed in claim 5 at page 35 of European patent 0182024, with a publication date of 28/May/1986 [Exhibit 5].

14. Another representative example, and more importantly, one which uses the same L-valinate ester route to improve upon poor oral absorption of the parent drug is Valacyclovir. Acyclovir, a purine anti-viral drug was disclosed in US patent 4,199,574; published on 22/April/1980 [Exhibit 6]. The L-valinate ester of Acyclovir [i.e. Valacyclovir] was disclosed in US patent 4,957,924;
published on 18/Sep/1990 [Exhibit 7].

15.

This US ['924] document clearly states that

‘... acyclovir is only poorly absorbed from the gastrointestinal tract after oral administration...

... such low bioavailability requires the administration of large doses of drug in order to achieve and maintain effective anti-viral levels in the plasma.

... the valine ester of acyclovir... surprisingly has improved bioavailability after oral administration...’

Specification column 1, lines 16-33

16.

- The ‘924 patent specifically discloses the L-valinate ester of Acyclovir in claim 1 and the hydrochloride salt of the L-valinate ester of Acyclovir in claim 17.
- The ‘924 patent discloses use of the L-valinate ester of Acyclovir for various viral diseases such as herpes infections, including cytomegalovirus.
- The diseases targeted by the two drugs - L-valinate ester of Acyclovir and L-valinate ester of ganciclovir are similar.
- It is worth keeping in perspective that the ganciclovir is structurally very similar to acyclovir. An addition of hydroxy methyl to acyclovir at the 1st position of hydroxy ethoxy chain results in ganciclovir.
- Consequently the L-valinate esters as well as L-valinate ester salts of these two drugs [Ganciclovir and acyclovir] are structurally very similar to each other. To explain our above point graphically, the detailed structures of the above mentioned drugs and ester salts are juxtaposed as Exhibit [8].

17.
• It is worthwhile to note that the Patentee has further limited the product of claim 1 by adding the words ‘… in the form of its (R)- or (S)- diastereomers, or in the form of mixtures of the two diastereomers’.

• Ganciclovir is a chiral molecule. The compound of present claim 1 is an L-valinate ester of Ganciclovir. A person skilled in the art knows that L-valine is also a chiral compound, hence its derivatives, for e.g. the L-valinate ester of Ganciclovir, inherently will be also be a chiral molecule, i.e. a compound having (R)- or (S)-diastereomers, or a mixture of the two diastereomers. Therefore, adding the above limitation does not bring in any new information or patentable novelty to the product of claim 1; the product of claim 1 must, of necessity, be in the form of its (R)- or (S)-diastereomers or in the form of a mixture of the two diastereomers.

18.
A pro-drug is a camouflaged derivate of a known substance. A pro-drug has no direct effectiveness. Valganciclovir has no therapeutic benefit/efficacy of its own. The therapeutic efficacy of Valganciclovir comes from Ganciclovir which is formed in-vivo upon the metabolism of valganciclovir. The shape-changing valganciclovir is nothing but Ganciclovir in disguise. The Opponents submit that valganciclovir was obvious to a person skilled in the art. In any case, a person skilled in the art would have found it obvious to try the invention.

The jurisprudence on pro-drugs developed by the courts of the Commonwealth clearly indicates that pro-drugs will be regarded as obvious to persons skilled in the art. The Opponent craves leave to refer to case laws on the point at the time of hearing.

A person skilled in the art for this particular field of invention would have a combination of specialised education and work experience in the areas of drug discovery and testing with particular exposure to the design, synthesis and evaluation of pro-drugs. The relevant field of expertise would be pharmaceutical chemistry, bioanalytical chemistry, synthetic
organic chemistry or medicinal chemistry. A skilled person would have the capacity to evaluate the drug-like properties (e.g., bioavailability) of drug and pro-drug candidates using standard in vitro and in vivo studies. Given the molecular structure of Ganciclovir, a person skilled in the art could easily develop its pro-drug, Valganciclovir.

19.
The Opponent submits that a person skilled in the art, when faced with the problem of improving availability of Ganciclovir, would have used the tried and tested technique of ester formation, keeping in view the success of the technique for Acyclovir & Valacyclovir. Hence, there is no inventive step in using the L-valinate ester route for a drug with poor absorption; for increasing oral absorption/bio-availability.

(vii) Lack of Novelty

20.
The Opponent now will explain its stand for the above Opposition in view of S.25 (2) (b) in conjunction with S (2) (l).
S. 2(l) of the Act defines a new invention as ‘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;’
The Opponent states that the claimed invention is not novel in view of US patent document 5,043,339; with an issue date of 27/August/1991 Exhibit [9].

21.
The above ‘339 document discloses various esters of 9-[(2-hydroxy-1-hydroxymethyl ethoxy) methyl] guanine

[i.e. chemical name of ganciclovir].
The document discloses [at column 1, line 39 onwards]:

Page 10 of 25
'According to one feature of the present invention there is provided a compound of formula I:-

\[
\begin{array}{c}
\text{B} \\
\text{CH}_2\text{OCHCH}_2\text{OR}^1 \\
\text{CH}_2\text{OR}
\end{array}
\]

(wherein \( R \) and \( R^1 \) are independently selected from a hydrogen atom and an amino acid acyl residue providing at least one of \( R \) and \( R^1 \) represents an amino acid acyl residue and \( B \) represents a group of formula

\[
\begin{array}{c}
\text{A} \\
\text{or}
\end{array}
\]

in which \( R^2 \) represents a \( C_{1-6} \) straight chain, \( C_{3-6} \) branched chain or \( C_{3-6} \) cyclic alkoxy group, or a hydroxy or amino group or a hydrogen atom) and the physiologically acceptable salts thereof.

A group falling within formula (I) above is where \( R^2 \) represents a hydroxy or amino group or a hydrogen atom.

22.

Specifically, at column 2, line 17, the ‘339 document states:

‘The amino acid acyl residue of the above compounds according to the invention may be derived for example from naturally occurring amino acids, preferably neutral amino acids i.e. amino acids with one amino group and one carboxyl group.

Examples of preferred amino acids include aliphatic acids, e.g., containing up to 6 carbon atoms such as glycine, alanine, valine and isoleucine. The amino
acid esters according to the invention includes the mono- and di-esters of the compound of formula (I). The amino acids may be D-, L- and DL amino acids, with the L-amino acids being most preferred.

The amino acid esters according to the invention includes the mono- and di-esters of the compound of formula (I). The amino acids may be D-, L- and DL amino acids, with the L-amino acids being most preferred.

...The above-mentioned physiologically acceptable salts are preferably acid addition salts derived from an appropriate acid, e.g., hydrochloric ....’

23.
Upon analysis of the above compound 1 and its embodiments, it is clear that compound 1 with substitution ‘B’ and \( R^2 \) being hydroxy group, is Ganciclovir. Moreover, the preferred amino acid option includes valine ester in its mono form. Thus, when \( R \) is hydrogen and \( R^1 \) is the L-valine [or vice versa] we get Valganciclovir. The preferred salt option includes the hydrochloride salt option. The physiologically acceptable salt of above L-valine amino acid ester of ganciclovir, thus includes Valganciclovir hydrochloride. Thus, the ‘339 document clearly discloses the L-valinate ester of ganciclovir hydrochloride, in its entirety.

24.
Since the issue date [27/August/1991] of the US ‘339 document is much before the priority of the present patent [28/July/1994] or its complete specification filing date, the US ‘339 document anticipates the present alleged invention i.e. L-valinate ester of ganciclovir as well as its pharmaceutically acceptable hydrochloride salt.

(viii) Not an invention or not patentable under the Act

25.
The Opponent now will explain its stand for the above Opposition in view of S.25 (2) (f) in conjunction with S (3) (d).

S.25 (2) (f) – allows an Opponent to oppose a granted patent if 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.

S. 3 relates to inventions that are not patentable in India.

S.3 states:

`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 substance, unless they differ significantly in properties with regard to efficacy;`

26.

**Facts:**
The Patentee has admitted that the present invention is an ester of a known substance.

*Prima facie*, such ester or salts of such esters will fall in the not patentable category, unless the ester or salts of such esters differ significantly in properties with regard to **efficacy**. In simple terms, for the present alleged invention [ester form of a known substance] to be treated as an invention, the Patentee must show that the ester so invented/ created has a better therapeutic effect.
27.
The Act does not define ‘efficacy’. Dorland’s Medical Dictionary defines the expression ‘efficacy’ in the field of pharmacology ‘as the ability of a drug to produce the desired therapeutic effect’. Alternatively, efficacy is the ability of a drug to control or cure an illness.

‘Bioavailability’ is the degree to which a drug or other substance becomes available to the target tissue after administration.

Efficacy is not equivalent to or synonymous with bioavailability or oral absorption. Efficacy of a drug is a function of its pharmacodynamic profile – i.e. what a drug substance does to a human body. Absorption or availability of a drug is a function of the drug’s pharmacokinetic profile, i.e. the body’s reaction to the drug.

28.
Efficacy, in the present case for the l-valinate ester form of Ganciclovir, is born out of the previously known therapeutic moiety, i.e. Ganciclovir itself. It is Ganciclovir that is efficacious in the human body and causes the effect of decrease in viral load. The increase in oral absorption arising from the L-valinate ester form of Ganciclovir cannot be termed as an increase in the efficacy of Ganciclovir. The Patentee has allegedly given test results for rats that show an increase in the oral bioavailability of Ganciclovir when its L-valinate ester hydrochloride salt form is administered as compared to Ganciclovir itself. However, the Patentee in the present case has not proven by data or even stated that the ester form causes an increase in efficacy of Ganciclovir itself.

Section 3(d) of the Act requires the patentee to demonstrate enhancement of known efficacy. The patentee ought to have shown how the ‘enhanced efficacy’ of Valganciclovir significantly differs from the ‘known efficacy’ of Ganciclovir. As submitted earlier, Valganciclovir has no therapeutic effect or efficacy in itself. The efficacy of the drug comes from the conversion of Valganciclovir to Ganciclovir in vivo.
29.
Claims 2 through 9 and 12 depend on claim 1. Since the above arguments render the product of claim 1 non-patentable under the Act, all dependent product claims [which merely add limitations to claim 1], are also rendered non-patentable.

30.
In conclusion, as noted above, the Opponents state that using the ester creation route for drugs with poor availability was well known prior to 1994, and specifically that the success of L-valine ester of acyclovir in solving the poor oral availability problems of acyclovir renders the present claimed invention, L-valinate ester of Ganciclovir, obvious and devoid of any inventive step, thereby necessitating the revocation of present patent’s claims 1-9 and 12, in entirety. Alternatively, since efficacy is not the same as availability, and in the present case the Patentee has only shown enhanced availability for an ester form of a known drug, while not satisfying the requirements of Section 3(d), hence the present Patent’s claims 1-9 and 12 should be revoked in entirety.

31.
The Opponent further opposes the Patent’s claims 10 and 11 on the following grounds from S. 25(2) read in conjunction with S.2(ja):

“S. 25(2)
At any time after the grant of patent but before the expiry of a period of one year from the date of publication of grant of a patent, any person interested may give notice of opposition in the prescribed manner on any of the following grounds, namely:--

…
(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:…
(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 specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;
(h): that the Patentee has failed to disclose to the Controller the information required by S.8 or has furnished the information which in any manner was false to his knowledge;

The invention/ process of claim 10 and/ or 11 is anticipated, is not novel, is obvious and clearly does not involve an inventive step, having regard to matter published before the priority date of the present patent.

32. At the outset, the Opponent would like to highlight that process claim 10 is NOT an individual/ single process claim. It encompasses multiple, alternative processes in each of the sub-clauses, which independently could possibly lead to either the L-valinate ester of Ganciclovir or the salt form of the L-valinate ester of Ganciclovir. Each of the sub-clauses, viz a/ b/ c/ d/ e and f independently are aimed at making the L-valinate ester of Ganciclovir or the salt form of the L-valinate ester of Ganciclovir. Importantly, the sub-clauses themselves do not relate/ connect to each other in any sequential order.

33. That said, the Opponent will try to focus its arguments on each of the sub-clauses. Claim 10 with sub-clause [a] reads as follows:
“A process for preparing the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate or a pharmaceutically acceptable salt or diastereomers thereof which process comprises:
(a) removal of an amino- and/or hydroxy-protecting group from a compound with the formula

wherein: \( P^1 \) is a hydroxy-protecting group or hydrogen, \( P^2 \) is an amino-protecting group, and \( P^3 \) is hydrogen or \( P^2 \); to afford the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate or a pharmaceutically acceptable salt thereof;”

34.
US patent 5,043,339 [Exhibit 9, above] having an issue date of 27/Aug/1991 discloses relevant esterification and removal/deprotection of Ganciclovir in Examples 5 (a) and (b) at column 10, lines 01 through 49.
Example 5 (a) discloses esterification of 9-(1,3-dihydroxypropoxymethyl) guanine [i.e. Ganciclovir].
Example 5 (b) discloses de-protection/removal of an amino protecting group from 2-((2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(N-((benzyloxy) carbonyl)-L-valinate) [i.e. bis L-valinate ester of Ganciclovir].

35.
The US ‘339, Example 5 (b) document clearly describes de-protection of an L-valine ester of Ganciclovir.

Claim 10(a) claims a process to make L-valinate ester of Ganciclovir by means of de-protection/removal of an amino protecting group.

Therefore, the Opponent states that the process claimed in claim 10 sub-clause (a) is rendered obvious to a person skilled in the art.

S. 2(ja) of the Act defines **inventive step** as ‘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.’

36.

There is no inventive merit in merely mentioning ‘removal of an amino- and/or hydroxy-protecting group’ without specifically mentioning the specific novel steps involved in such ‘removal’ in the claim. The mere mention of ‘removal of an amino- and/or hydroxy-protecting group’ does not involve any advance in technical knowledge. The Patent’s specification also does not disclose the economic advantage [if any] rendered by using ‘removal’.

Hence, we believe that claim 10(a) of the Patent is liable for revocation.

By using a broad and expansive term - ‘removal’, the Patentee stops all other parties from using any route to remove an amino protected group, whereas the claim should have been specific to the removal steps/process invented by the Patentee.

**Arguendo**, if the claim is deemed patentable, the Opponent states that the claim should have been restricted only to the specific steps/process [if any] invented by the Patentee and not a broad ‘removal of amino groups…’.

37.

Claim 10(b) of the Patent covers a process to convert the L-valinate of Ganciclovir into its pharmaceutically acceptable salts. The claim is presented below:

“A process for preparing the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-
(b) conversion of the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy -3-hydroxyl-1-propanoyl-L-valinate into a pharmaceutically acceptable salt thereof;”

Again, there is no specific sequence of steps mentioned nor is there any mention of the specific reactants involved in the claim.

The above referred US ‘339 document states the following:

“The conversion of an amino acid ester into a physiologically acceptable salt may be effected in conventional manner, e.g., by treatment of the compound with an appropriate acid to form an acid addition salt.”

Column 6, line 57 through 61.

The amino acid ester referred to in the ‘339 document is for amino acid esters of Ganciclovir. Therefore, claim 10(b) is clearly anticipated by the US ‘339 patent.

38.
In addition, there is no inventive merit in merely mentioning ‘conversion of the compound’ [L-valinate ester of Ganciclovir] without specifically mentioning the specific novel steps involved in such ‘conversion’ in the claim.

The broad reference to conversion of the compound to a salt form does not involve any advance in technical knowledge, but rather implies use of presently known methods of salt formation.

Hence, we believe that claim 10(b) is liable for revocation.

By using a broad and expansive term - ‘conversion’, the Patentee attempts to stop all other parties from using any route to make an acid addition salt of L-valinate ester of Ganciclovir, whereas the claim should have been specific/ restricted to the steps/ process [if any] invented by the Patentee and not all types of conversion to salt forms.

39.
We now move to claim 10(c), given below:
“A process for preparing the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate or a pharmaceutically acceptable salt or diastereomers thereof which process comprises:

(c) esterification of 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol (ganciclovir) or a salt thereof, with an activated derivative of L-valine;”

As can be readily seen, Claim 10(c) also claims esterification of Ganciclovir or its salt, generically. However, there is no specific sequence of steps that is covered by the present claim 10(c) which would differentiate it from prior art, for e.g. the US ‘339 process. The US ‘339, Example 5 (a) document discloses esterification of Ganciclovir. That being the case, the process of esterification in claim 10, sub-clause [c] is not novel and is anticipated by virtue of Example 5(a) of the ‘339 document.

40.
Alternatively, if it is argued that claim 10(c) only relates to the mono L-valine ester of Ganciclovir [a limitation that is not found in the language of the present claim] while Example 5(a) of the ‘339 document relates specifically to the bis L-valine ester of Ganciclovir, then too the process of claim 10(c) is rendered obvious to a person skilled in the art, since the ‘339 document clearly illustrates the steps for esterification of Ganciclovir with an amino-protected L-valine. This disclosure renders the process of esterifying Ganciclovir with an amino-protected L-valine to get its mono valinate ester form, obvious to a person skilled in the art.

41.
Importantly, here too the Patentee has not shown any specific steps in his claim for how the esterification is achieved nor has he discussed in his specification the inventive merits or economic merits of his ‘esterification’ vis-à-vis the prior art. Hence, we believe that claim 10(c) is liable for revocation.
Again, since the claim is for broad ‘esterification’ of the compound [i.e. Ganciclovir], the
claim stops all other parties from using any route to esterify ganciclovir.

If the claim is deemed patentable at all [which Opponent maintains would be improper],
the Opponent states that the claim should have been restricted only to the specific
esterification steps/ process [if any] invented by the Patentee.

42.
Claim 10(d) covers a process of condensation of a substituted guanine derivative with a 2-
substituted glycerol to give L-valinate ester of Ganciclovir. It is reproduced below:

“A process for preparing the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-
yl)methoxy-3-hydroxy-1-propanyl-L-valinate or a pharmaceutically acceptable
salt or diastereomers thereof which process comprises:

…

(d) condensation of an optionally substituted guanine of the formula

![Chemical Structure](image)

optionally in persilyated form,

wherein:
P³ is Hydrogen or an amino-protecting group, with an 2-substituted glycerol of
the formula

![Chemical Structure](image)

wherein:
Y¹ and Y² independently are halo, lower acyloxy, lower alkyl oxy, or aryl (lower)
alkoxy groups, and

Z is a leaving group selected from lower acyloxy, methoxy, isopropoxy, benzyloxy, halo, mesyloxy or tosyloxy;

optionally in the presence of a Lewis acid catalyst,

to provide the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate;”

43.
Critical to the disposition of present claim 10 (d) is the fact that the 2-substituted glycerol used in claim 10(d) with the mentioned Y substitutions will not result in L-valinate ester of Ganciclovir or its pharmaceutically acceptable salt – i.e. the subject matter of the present claim.

Since the claimed Y\textsuperscript{1} and Y\textsuperscript{2} substitutions do not cover amino acids, the final product will not be an amino acid ester of Ganciclovir [i.e. L-valinate ester of Ganciclovir] or its salt form. Hence, the Opponent states that the claim is incorrectly drafted and, therefore, invalid.

44.
The Patentee at page 36, lines 30 – 34 of his specification, states that steps for condensation are described in European patent application publication EP 0 187 297 [Exhibit 10, published 16 July 1986] and the same is preferred. The EP ‘297 publication clearly shows a similar set of steps at Page 14 [Reaction scheme III] as is claimed in claim 10 (d) of the present patent.

Reaction scheme III of the EP ‘297 publication [like claim 10 (d) of the patent at issue] discloses condensation of a substituted guanine derivative with a 2-substituted glycerol.

That noted, the Opponent submits that the process of present claim 10 (d) is obvious in view of the EP ‘297 document.

45.
Claim 10(f) is set forth below:

“A process for preparing the compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate or a pharmaceutically acceptable salt or diastereomers thereof which process comprises:

(f) diastereomeric separation of 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate into its (R) and (S) diastereomers.”

It covers a process of diastereomeric separation of 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate into its (R) and (S) diastereomers. Here too there is no specific sequence of steps mentioned nor is there any mention of the specific separation methods involved, in the claim. The Patentee makes a generalized reference to a 1981 text book [Enantiomers, Racemates and Resolutions, John Wiley 1981] in its specification at page 38, line 28-33.

46.

The Opponent states that there is no inventive merit in merely stating ‘diastereomeric separation of [the compound]’ [L-valinate ester of Ganciclovir] without specifically mentioning the specific novel steps or the separation modalities involved in such ‘separation’ in the claim. The broad reference to diastereomeric separation does not involve any advance in technical knowledge, but rather implies using presently known methods of separation from the 1981 text book.

Hence, we believe that claim 10(f) is liable for revocation since the process does not constitute an invention under s. 2(ja).

In addition, by using a broad and expansive term - ‘separation’, the Patentee attempts to stop all other parties from using any route to separate the diastereomers of L-valinate ester of Ganciclovir, whereas the claim, if patentable at all [which Opponent denies], should have been specific to the steps/ process (if any) invented by the Patentee.

47.

Claim 11 [which is dependent on claim 10] adds the limitation that the removal of amino
and/or hydroxy protecting groups is carried out in acidic condition. The US ‘339 document in Example 5(b) discloses removal of amino protecting group [the benzyoloxyl group] from L-valine ester of Ganciclovir in acidic conditions – viz. use of acetic acid. Hence claim 11 is also anticipated and rendered not patentable by the US ‘339 document.

Alternatively, since claim 11 is dependent on claim 10, and because the process claim 10 itself is not patentable, dependent claim 11 is also rendered non-patentable.

In conclusion, the process recited in both claims 10 and 11 is not patentable and liable to be revoked in entirety in view of the arguments mentioned above.

III. OPPOSITION OF CLAIMS 1 TO 12

48. The Opponent also opposes all claims of the present Patent under S. 25(h) pertaining to non disclosure of information required under S. 8 of the Act.

In Europe, the Patentee filed an application on 19/July/1995 for a substantially similar invention in the European patent office (see “2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol derivative”, EP 0 694 547, published 31 January 1996, attached as Exhibit 11. This claimed priority from the same 28/July/1994 US application of the present invention– application number 281,893 – as the present Application. The European Application was made prior to the present Indian Application and was pending at the time of filing the Indian Application, and details of it should have been disclosed under section 8.

49. In USA, the original US application 08/281,893 was later abandoned and a continuation-in-part application 08/453,223 was filed on 30 May 1995 – again, prior to the date of filing in India. US Application 08/453,223 was also subsequently abandoned, and continued in application 08/812,991 filed 4 March 1997. This last application was granted patent on 4 July 2000 as US 6,083,953.
None of these details were submitted by the Patentee.
This is, by itself, an independent ground for revoking the entire Patent, and such action is respectfully requested by the Opponent.

50.
The Opponent submits that based on the above arguments and the evidence attached in Exhibits 1 to 11, the patentee is not entitled to the patent granted in its favour. The Opponent prays that the above patent [207232] be revoked with costs to the Opponent. The Opponent also prays for the following:

- Leave to file further evidence and additional grounds, if necessary;
- Grant of hearing to the Opponent;
- Costs to the Opponent; and
- Grant such relief as the Controller may deem fit.

Dated the 27th June of 2008

For Matrix Laboratories Limited,

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Feroz Ali K.