

**THE PATENTS ACT, 1970  
UNDER SECTION 25 (1)  
REPRESENTATION OF OPPOSITION**

**In the matter of an application for Patent no.  
1647/DELNP/2000 filed on 11/06/2004**

**And**

In the matter of representation of opposition  
u/s 25(1) of the Patents Act, 1970 as amended  
**by Patents (Amendment) Act, 2005**

**And**

**In the matter under rule 55 of the Patent  
rules,2003as amended by the Patents  
(Amendment) rules,2006.**

M/s TIBOTEC PHARMACEUTICALS LTD,.....Applicant

M/s CIPLA LTD, IINDIA.....Opponent

Present:-

Ms. Gowree Gokhale (Nishith Desai Associates).....Agent for Applicant

Ms.Rajeshwari Hariharan(K&S Partner)..... Agent for Applicant

Mr. Sanjeev Tiwari (K&S Partner)..... Agent for Applicant

S.Majumdar (S Majumdar & Co.)..... Agent for Opponent

**Hearing Held on 9th January, 2009**

Order

M/s TIBOTEC PHARMACEUTICALS LTD hereinafter referred as “Applicant” through their Agent filed an application for patent having no. 1647/DELNP/2004, on 11/06/2004 titled “Combination of cytochrome P450 dependent protease inhibitors”.

M/s CIPLA Ltd, hereinafter referred as “Opponent”, an Indian company of LBS Marg, Vujgrol (W) Mumbai, Maharashtra, India through their representative made a representation of opposition under section 25(1) of the Patent Act as amended by Patents ( amendment ) Act,2005 u/r 55 of

the Patents rules,2003 as amended by patents ( Amendment) Rules,2005, on 29<sup>th</sup> august 2007. Accordingly, the Applicant also submitted the reply statement and interlocutory petition on 10<sup>th</sup> November, 2008 with a request of hearing.

### **INTERLOCUTORY PETITION:**

#### **APPLICANT'S SUBMISSIONS:**

The Agent for Applicant filed an interlocutory petition stating as follows:-

The application number 1647/DELNP/2004 for patent was filed on June 11, 2004 and the application was published on November 30, 2007. On March 28, 2008, after following due examination process, the patent office issued the letter of grant to the Applicant. The letter of grant speaks as follows:

"Your above Application for patent has been found in order for grant. However, the Patent Certificate will be issued only after processing of the Application under Section 11(a) and completion of the statutory limit and disposal of pre grant opposition, if any, under section 25(1) of the Act."

According to the Applicant, the patent was granted on March 28, 2008 because of the three conditions, (i) the application was duly processed in accordance with section 11(a) (sic. 11A); (ii) the statutory period (i.e. time under Rule 55 (1-A)) was completed on May 30, 2008; and (iii) there was no pre grant opposition pending or filed (if any) on March 28, 2008 or even May 30, 2008.

Therefore, there was no impediment on May 30, 2008, to the issuance of the Patent Certificate and the Patent Office should have done so within 7 days of May 30, 2008 in accordance with Rule 73(2). Failure by the Applicant's previous agents to pursue to obtain the Patent Certificate or failure by the Patent Office to issue the Patent Certificate within the time stipulated in the Act and/or does not mean that the patent application/ examination process continues, or that the

patent was not granted. M/s Cipla Limited ("Opponent") filed their opposition on June 26, 2008, after a considerable period of time after the date of grant and also expiration of the statutory period.

It was Applicant's submission that the said representation filed by Opponent on June 26, 2008 ought not to have been entertained.

It was the Applicant's further submission that the patent is "granted" by the letter of notification of grant by the Patent Office to the Applicant and not by "the issuance of the Patent Certificate". The Patent Certificate is merely an evidence of the grant. The consequence of the issuance of the letter of notification of the grant is that from the date of the grant, all pre-grant procedures and matters cease to apply. For instance, the Applicant could not further amend the claims or apply for any divisional application. The Patent Office would not allow this. Analogously, after the date of the notification no pre-grant opposition can be admitted or allowed. Any opposition has to be made as a post grant opposition. The Applicant relied upon the provisions of the Act and the case law cited.

They said that this is also consistent with the provisions of Section 25 (2) of the Act which apply to post-grant oppositions. That Section makes it abundantly clear that any application for opposition filed after the date of the notification of grant is a post grant opposition.

Under Section 25 (1) of the Patents Act, 1970 a pre-grant representation is maintainable only if on the date of filing of the pre-grant representation "a patent has not been granted". In the present matter, as specified above, on the date Opponent submitted its alleged pre-grant representation, the patent office had already granted the patent to the Applicant. After such grant, any Opposition as pre grant opposition ought not to be allowed. The Patent Office cannot exercise such discretion under Section 25 or Rule 55(3). This would amount to reversal of its own decision to grant the patent to the Applicant, which is not valid or tenable. They refer to the case of Nokia Mobile Phones (UK) Limited Application [1996] RPC 733. where it was held by the Court that the Patent Office did not have the power to withdraw an application once notification of grant had

been issued. The provisions of section 18 of the English Patent Act 1977 are analogous to the Indian Patents Act 1970 and the Patent Rules.

It was, therefore, submitted by the Applicant Agent that the present patent should be treated as having been granted. The alleged pre-grant opposition filed by Opponent is therefore not valid.

Reference was also made to the cases, (i) ITT Industries Inc's Application [1984] RPC 23, a decision by the English Patent Office and

(ii) Ogawa Chemical Industries Ltd's Application, [1986] RPC 63, a decision from the Patents Court in England and Wales.

The Ogawa case relies upon the ITT Industries matter. In the ITT matter the Applicant was notified by the Patent office by a letter dated March 7, 1983 that its patent application was granted and would proceed for publication in the Official Journal. On March 24, 1983 the Applicant applied for a divisional application. The patent office objected to this on the ground that the earlier patent application had been granted and therefore could not be filed as a divisional application and would be treated as a new patent application. The hearing officer upheld the refusal and stated that the letter of notification was a grant letter and after that date no further pre grant applications could be allowed. The notification of grant letter put a statutory bar on the filing of any new applications.

Similarly, in the Ogawa case the Applicant had sought to amend its application after the letter of notification of grant was issued. The Court held that an application to amend or to divide an application could only be made before the patent office letter of grant had been issued.

Under the provisions of the English patent law (The Patents Act of 1977 and the accompanying rules) and the provisions of the European Patent office, the accepted position is that from the date of the issuance of the letter of notification no further pre grant matters are entertained and the patent is deemed granted for all pre grant matters. . Matters such as revocation and challenge can only commence after the patent is published in the Official Journal. Under English law the patent is granted by issuance of a letter of grant and the notice of grant is to be published

as soon as practicable after the grant (section 24 (1)) and the patent takes effect on the date on which the notice is published (section 25(1)). No pre-grant matters or applications are entertained after the issuance of the letter of grant.

Similarly, under the EPC, if the examining division decides to grant the European patent, it is granted by notification followed by the approval of the text by the applicant, provision of translations and payment of the requisite fees (EPC Art 123(2)). The post grant matters take effect from the date of the publication in the European Patent Bulletin (Art 76, EPC rule 25). In the light of the above, it was the Applicant's humble submission that Section 25 (1) and 43 and Rule 55 cannot be construed differently.

The period between the letter of grant and issuance of certificate is only to allow administrative procedures to be completed and in the light of the above no pre-grant opposition matters can be entertained during that period. Otherwise, the letter of grant will have no meaning. The Hon'ble Controller in his order dated July 4, 2007 delivered in the matter of 537/DEL/1996 has observed that "The time gap between these two activities is actually allowed by the law to complete the official formalities." If the Patent Office had issued the certificate immediately after May 30, 2008, Opponent's representation would have been automatically rejected by the Patent Office. In the present case, the inaction on the part of the Patent Office to issue the Patent Certificate within the prescribed period of 7 days cannot take away the substantive right that has already accrued in favor of the Applicant. The Applicant understands that to avoid the injustice that was being caused due to the delay in issuing the patent certificate. Recently, the Patent Office, has started issuing the patent certificates immediately upon decision taken by the Examiner to grant the patent.

The Applicant referred to the ruling of the Hon'ble Supreme Court of India in various matters, where it has time and again held that "We must always remember that procedural law is not to be a tyrant but a servant, not an obstruction but an aid to justice. It has been wisely observed that procedural prescriptions are the hand-maid and not the mistress, a lubricant, not a resistant in the

administration of justice. It was submitted that, in the present matter, non-issuance of Patent Certificate, which is merely a procedural formality, ought not to take away a substantive right that has accrued to the Applicant for patent upon grant.

It was further submitted that grave prejudice and irreversible loss is being caused to the Applicant by the act of the Patent Office in allowing the Opponent to file an Opposition after May 30, 2008. Particularly as there has been no failure on the part of the Applicant and the failure, if any, is that of the Patent Office which did not issue the patent certificate within the time stipulated in section 43 or even until June 26, 2008 (when the Opposition was filed) or even by August 11, 2008 (when a copy of the Opposition was sent to the Applicant). On the other hand, no prejudice shall be caused to the Opponent who could file a post grant opposition forthwith. Therefore, the Agent for Applicant be granted an early hearing of this matter and in accordance with the provisions of Section 43 read with Rule 73, the Certificate of Patent in relation to the abovementioned Patent Application No. 1647/DELNP/2004 be issued immediately; and the representation filed by Opponent on June 26, 2008 be held as non-maintainable or in the alternative, the representation filed by Opponent on June 26, 2008 be held post-grant opposition; and such other order be passed, as may be deemed fit by the Patent Office.

#### OPPONENT'S SUBMISSIONS:

The opponent submitted as follows:

They drew my attention to the provisions of Rule 24-B (2) (i) which categorically provides that the Controller shall refer an application to an examiner for examination within one month from the date of publication of the application or the request for examination whichever is later.

In the present case the two significant dates which appear from the interlocutory petition and the reply statement are the dates of publication of the application which is November 30, 2007 and the date of the first examination report which is March 14, 2007. While the date of the request for

examination is not indicated but it may be presumed that such a date would be on or prior to March 14, 2007.

Therefore, in the present case, the application was taken up for examination much prior to the publication of the application on November 30, 2007.

It was stated that the examination of the application prior to the notification of the application is clearly in breach of the mandatory provisions of Law and can only be corrected by canceling the first examination report and taking up the impugned applications for examination afresh.

Necessary application is being taken out in this regard and a copy of the application will be duly served on the applicant.

The opponent further proceeded to deal with the interlocutory petition without prejudice to its objection on the maintainability of the examination process, which according to them was clearly in total violation of the provisions of the Act.

It was stated that the aforesaid application was notified under Section 11A on or about November 30, 2008 and the petitioner filed an opposition against the said application on or about June 18, 2008 when the application was still pending. The opposition was taken on record and the applicant filed an interlocutory petition for the rejection of the opposition on the ground of non-maintainability after about three months from the date of the service of the opposition on the applicant. The reply statement was also filed along with. The question of maintainability of any proceeding is a preliminary point to be taken at the first instance but in this case the applicant sat for three months and realizing the weakness of its alleged invention came out with the interlocutory petition so as to divert the attention of the Ld. Tribunal from the key issues. It was stated that the interlocutory petition itself is not maintainable.

Turning to the interlocutory petition it was further stated that the applicant is under the misconception that the letter dated March 28, 2008 from the Patent Office to the applicant is a letter of grant. It appears that neither the applicant nor its patent attorney is involved in the

patenting process on a regular basis and has therefore confused the communication of March 28, 2008 as a letter of grant. The said alleged letter of grant it was categorically mentioning that patent certificate would be issued after the disposal of pre-grant opposition, if any.

The entire case sought to be made out in the interlocutory petition is on the basis of the mistaken interpretation of the letter of March 28, 2008. It was stated that such communications are issued by the Patent Office not under any statutory obligation but only as a good gesture to inform the applicant that the application has been placed in condition for grant. There are several instances where the patent document is directly issued without the issue of such a letter. It is stated that the said letter is an intimation that the application has been found in order for grant and not that a patent has been granted on the application Accordingly the applicant is agitating the matter on an entirely wrong premises and the interlocutory petition is liable to be rejected.

The Agent for opponent further stated that the applicant has relied upon a few authorities based on its mistaken understanding of the said letter from the Patent Office and in the present case the cited judgments are distinguished as under —

Nokia Mobile Phones(UK) Limited Application 119961 RPC 733 —In this case a report under Section 18(4) was issued and later withdrawn and the applicant was invited as the examiner had omitted to consider some relevant prior art. The Patents Court in this case upholding the Section 18(4) Report remitted that Patent office for grant.

In order to appreciate the ratio of the judgment it is important to visit Section 18(4) of the 1977 UK Patents Act which reads as under —

If the examiner reports that the application, whether as originally filed or as amended in pursuance of section 15A, this section or section 19 complies with those requirements at any time before the end of the prescribed period, the Controller shall notify the applicant of that fact and, subject to subsection (5) and sections 19 and 22 and on payment within the prescribed period of any fee prescribed for the grant, grant him a patent.

Under the Indian Law there is no provision for a notice analogous to the provision of 18(4) of the

then UK Act. Section 18(4) makes it mandatory for the Controller to notify the applicant that a patent would be granted upon payment of certain fees and the statute therefore guarantees the grant subject to payment of the fees. The Court in this case disapproves of any further examination process after the 18(4) notice was served. On the other hand, the letter issued by the Controller in the present case is purely complementary in nature and has no statutory binding. Furthermore, such a letter was issued at a point in time when the opposition period was active and it was categorically indicated in the letter that grant would take place only after disposal of pending opposition, if any. The UK Law did not have a parallel provision of concurrent opposition proceedings as is the case in India. These facts of the present case do not apply to the case relied upon by the applicant.

ITT Industries Inc's Application 119841 RPC 23 -

This is a case where the filing of a divisional application was not allowed after the 18(4) notice. Therefore, the 18(4) notice under the 77 Act has the effect of grant subject to fulfilling the precondition of payment of fees while in the case of India the letter of intimation of the fact that the application has been found in condition for grant is not comparable inasmuch as the Controller even after issuing such a notice can issue fresh objection if any new prior art or other circumstances come to his notice. For the appreciation of the same attention is drawn to Section 43 of the local Act which governs the grant of patents and it would be seen that a grant can take place only after the application for patent has been found in order and that the application has also passed the tests provided under Sections 43(1)(a) and (b). Therefore, the provisions of Section 18(4) of the 77 UK Act is closest to Section 43(1) of the Indian Act and the letter in question has not been issued under Section 43(1) but it is only an intimation that the applicant has overcome the objections raised by the examiner. Such a letter is subject to the provisions under Section 43(1)(a) and (b) and the letter from the Controller categorically states that patent would be granted subject to disposal of opposition proceedings, if any.

Ogawa Chemical Industries Ltd's Application 119861 RPC 63 -

In this case the facts are almost identical to the case of ITT Industries Inc's Application [1984] RPC 23 involving the filing of a divisional application after the 18(4) notice. This case and the previous case also go to confirm that 18(4) has the effect of announcing the grant of the patent and thus a divisional application cannot be entertained after the 18(4) notice. On the other hand, under the Indian Law a divisional application can be filed any time before the grant of a patent and unmistakably grant of a patent is governed under Section 43 and not by an intimation by the Patent office that the application is found in order for grant. Therefore it is clear that the said letter of March 28, 2008 cannot have the effect as a 18(4) notice under the UK Act.

As to the corresponding European Laws it is clearly distinct from the Indian Law where the grant takes place under Section 43 followed by a notification of grant which is always subsequent to the actual grant and cannot be equated with the European Law where the intimation of grant cannot be equated with an informal communication from the Patent Office merely informing that the application has been found in condition for grant with the condition that the grant will take place after disposal of any opposition.

It was stated that there has been no delay on the part of the Patent Office because the opposition was entered barely within a month of the expiry of the opposition period of 6 months which, in any event, is open ended and has to be taken on record so long the patent has not been granted.

In the present case the balance of convenience and inconvenience is in favor of the opponent inasmuch as it is not only fighting its own case but a case for the rest of the nation excluding the applicant. If the applicant succeeds there would be a monopoly against all in India while if the opponent succeeds it is not only success for the opponent but for the country at large because all and sundries will have the freedom of using the alleged invention claimed in the impugned application.

It was therefore, respectfully submitted that the interlocutory petition is not maintainable and is liable to be dismissed in toto.

**FINDINGS AND CONCLUSION ON INTERLOCUTORY PETITION:**

Let me go through the relevant sections of "The Patent Act" on grant of Patent and provision for filing of representation of opposition u/s 25(1) to decide this issue as follows:

Section 43. Grant of patents.-(1) where an application for a patent has been found to be in order for grant of the patent and either-

- (a) The application has not been refused by the Controller by virtue of any power vested in him by this Act; or
- (b) The application has not been found to be in contravention of any of the provisions of this Act,

The patent shall be granted as expeditiously as possible to the applicant of, in the case of joint application, to the applicants jointly, with the seal of the patent office and the **date on which the patent is granted shall be entered in the register.**

(2) On the grant of patent, the Controller shall publish the fact that the patent has been granted and thereupon the application, specification and other documents related thereto shall be open for public inspection.

Rule 74. Form of patent. - (1) A patent shall be in the form as specified in the Third Schedule with such modifications as the circumstances of each case may require and shall bear the number accorded to the application under rule 37.

(2) The patent certificate shall ordinarily be issued within seven days from the date of grant of patent under section 43.

After reading through the section 43 of the Act it is quite clear from the provision that the Application may be found in order of grant and this may further proceed to grant with seal of Patent office (Letters Patent) and thereafter date on which the patent is granted shall be entered in the register. This identifies three activities for final grant of Patent which are as follows:

1. Application must be found in order of grant
2. Seal of Patent office must be put or Letters Patent should be generated.
3. Date of grant must be entered in the register.

Therefore, there may be time lag in the application found in order of grant and finally grant of patent.

In this case Patent office has issued letter stating that:

"Your above Application for patent has been found in order for grant. However, the Patent Certificate will be issued only after processing of the Application under Section 11(a) and completion of the statutory limit and disposal of pre grant opposition, if any, under section 25(1) of the Act."

It is clear that there were further conditions of publication and pre grant opposition which were required to be fulfilled by the Applicant.

I agree that there was no impediment on May 30, 2008, to the issuance of the Patent Certificate and the Patent Office should have done so within 7 days of May 30, 2008 as the application was published on November 30, 2007 and six month period was over on May30, 2008.

Now I read through Rule74 (2) which states that the patent certificate shall **ordinarily** be issued within seven days from the date of grant of patent under section 43.

It is agreed that Patent certificate should have been ordinarily issued within seven days of final decision of grant by the controller but it could not happened .The Grant of Patent by the controller and subsequent issue of letters of Patent took more time than it could have taken ordinarily.

But this in my opinion can not jeopardize the right of opponent to file the opposition u/s 25(1) which reads as follows:

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

Therefore the opponent has right to file pre-grant opposition till patent has not been granted and so is the situation here.

The statute is amply clear before me and so as the practice being followed by the office,therefore I do not understand much worth to further go in arguments and counter arguments made by both

parties.

I allow the opposition u/s 25(1) filed by the opponent to the said application on June 18, 2008 to proceed, when the application was still pending for grant.

#### REPRESENTATION UNDER SECTION 25(1)

#### GROUND OF OPPOSITION:

The application is opposed on the following grounds:

1. that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim;
2. that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than the applicant's claim;
3. 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 (a) or having regard to what was used in India before the priority date of the applicant's claim;
4. that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim -  
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  
in India or elsewhere, in any other document;
5. 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;
6. that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;
7. the applicant has failed to disclose to the Controller the information required by

Section 8 or has furnished the information which in any material particular was false to his knowledge.

#### CLAIMS:

The original claims of the application under opposition are as follows:

1. Combination comprising (a) an HIV protease inhibitor of formula (1) or a pharmaceutical acceptable salt or ester thereof and (b) an inhibitor of cytochrome P450, wherein the HIV protease inhibitor of formula (1) has the formula

wherein, L is -C(=O)-, -O-C(=O)-, -NR<sub>10</sub>-C(=O)-, -O-alkanediyl-C(=O)-, -NR<sub>10</sub>-alkanediyl-C(=O)-, -C=S, -S(=O)<sub>2</sub>-, -O-S(=O)<sub>2</sub>-, -NR<sub>10</sub>-S(=O)<sub>2</sub> whereby either the C(=O) group or the S(=O)<sub>2</sub> group is attached to the NR<sub>10</sub> moiety; wherein R<sub>10</sub> is hydrogen, alkyl, alkenyl, aralkyl, cycloalkyl, cycloalkylalkyl, aryl, Het<sub>1</sub>, Het<sub>1</sub>alkyl, Het<sub>2</sub> or Het<sub>2</sub>alkyl; R<sub>1</sub> is hydrogen, alkyl, alkenyl, alkynyl, alkanediyl, alkylcarbonyl, alkyloxy, alkyloxyalkyl, alkyloxycarbonyl, alkanoyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylalkoxycarbonyl, aryl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, Het<sub>1</sub>, Het<sub>1</sub>alkyl, Hetloxy, Hetloxyalkyl, Hetlaryl, Hetlaralkyl, Hetlcycloalkyl, Hetlcarbonyl, Hetlalkoxycarbonyl, Hetloxycarbonyl, Hetlalkanoyl, Hetlaralkanoyl, Hetlaryloxyalkyl, Hetlaryloxycarbonyl, Hetl aralkoxycarbonyl, Hetlaroyl, Het<sub>2</sub>, Het<sub>2</sub>oxy, Het<sub>2</sub>alkyl; Het<sub>2</sub>oxyalkyl, Het<sub>2</sub>aralkyl, Het<sub>2</sub>cycloalkyl, Het<sub>2</sub>aryl, Het<sub>2</sub>carbonyl, Het<sub>2</sub>oxycarbonyl, Het<sub>2</sub>alkanoyl, Het<sub>2</sub>alkoxycarbonyl, Het<sub>2</sub>aralkanoyl, Het<sub>2</sub>aralkoxycarbonyl, Het<sub>2</sub>aryloxycarbonyl, Het<sub>2</sub>aroyl, Het<sub>2</sub>aryloxyalkyl, aminocarbonyl, aminoalkanoyl, aminoalkyl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het<sub>1</sub>, Het<sub>2</sub>, cycloalkyl, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di (alkyl) aminocarbonyl, aminosulfonyl, alkylS(=O)<sub>t</sub>, hydroxy, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, arylaminoalkoxy,

aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, cycloalkyl, cycloalkylalkyl, Het1, Het2, Het1alkyl, Het2alkyl, Hetlamino, Het2amino, Het1 alkylamino, Het2alkylamino, Het1thio, Het2thio, Het1 alkylthio, Het2alkylthio, Hetloxy and het2oxy, OR7, SR7, OS2NR7R8, S02N (OH)R7, CN, CR7=NR8, S (O) R7, S02R7, CR7=N(OR8), N3, N02, NR7R8, N (OH) R7, C (O) R7, C (S) R7, C02R7, C (O) SR7, C (O) NR7R8, C (S) NRR, C (O) N (OH)R8, C (S) N (OH) R7, NR7C (O) R8, NR7C (S) R, N (OH) C (O) R7, N (OH)C (S) R7, NR7C02R8, NR7C (O) NR8R9, and NR7C (S) NR8R9, N (OH) C02R7, NR7C (O) SR8, N (OH) C (O) NR7R8, N (OH) C (S) NR7R8, NR7C(O) N (OH) R8, NR7C (S) N (OH) R8, NR7S02R8, NHS02NR7R8, NR7S02NHR8, P (O) (OR7) (OR8), wherein t is an integer selected from 1 or 2, R7, R8 and R9 are each independently selected from the group comprising H, alkyl, alkenyl, and alkynyl; R2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkyloxycarbonyl, aralkoxy-carbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkyl-alkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, Het1carbonyl, Het2carbonyl, Hetloxycarbonyl, Het2oxycarbonyl, Hetlalkanoyl, Het2alkanoyl, Hetlalkoxycarbonyl, Hetlalkoxycarbonyl, Het1 aralkanoyl, Het2aralkanoyl, Hetlaralkoxycarbonyl, Het2aralkoxycarbonyl, Hetlaryloxycarbonyl, het2aryloxycarbonyl, Hetlaroyl, Het2aroyl, cycloalkyl, aryloxyalkyl, Hetlaryloxyalkyl, Het2aryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono-and disubstituted aminocarbonyl and mono-and disubstituted aminoalkanoyl radicals wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, hetero cycloalkylalkyl radicals, or wherein said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a Het1, Het2, Hetlaryl or Het2aryl radical; R3 is alkyl, aryl, cycloalkyl, cycloalkylalkyl, Het1, Het2, Hetlaryl, Het2aryl, or aralkyl optionally substituted with one or more substituent independently selected from the

group comprising alkyl, halo, nitro, cyano, CF<sub>3</sub>, -OR<sub>5</sub>, and -SR<sub>5</sub>, (CH<sub>2</sub>)<sup>p</sup>R<sub>6</sub>, oR<sub>7</sub>, SR<sub>7</sub>, CN, N<sub>3</sub>, C(O)R<sub>7</sub>, C(S)R<sub>7</sub>, C(O<sub>2</sub>)R<sub>7</sub>, C(O)SR<sub>7</sub>, NOR, NR<sub>7</sub>C(O)R<sub>8</sub>, NR<sub>7</sub>C(S)R<sub>8</sub>, NR<sub>7</sub>C(O<sub>2</sub>)R<sub>8</sub>, C(O)NR<sub>7</sub>R<sub>8</sub>, C(S)NR<sub>7</sub>R<sub>8</sub>, and NR<sub>7</sub>C(O)SR<sub>8</sub>, wherein R<sub>5</sub> is a radical selected from the group comprising hydrogen and alkyl, wherein: p is an integer from 0 to 5; R<sub>6</sub> is cycloalkyl, Het<sub>1</sub>, aryl, or Het<sub>2</sub> in which at least one hydrogen atom is optionally substituted with one or more substituents independently selected from the group comprising a halogen, OH, OCH<sub>3</sub>, NH<sub>2</sub>, NO<sub>2</sub>, SH, and CN, wherein R<sub>7</sub> and R<sub>8</sub> have the same meaning as that defined above;

R<sub>4</sub> is hydrogen, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di (alkyl)-aminocarbonyl, cycloalkyl, cycloalkylalkyl, Het<sub>1</sub>, Het<sub>2</sub>, Het<sub>1</sub>alkyl, Het<sub>2</sub>alkyl, Het<sub>1</sub>cycloalkyl, Het<sub>2</sub>cycloalkyl, Het<sub>1</sub>aryl, Het<sub>2</sub>aryl, alkylthioalkyl, alkenyl, alkynyl, alkyloxyalkyl, haloalkyl, alkylsulfonylalkyl, hydroxyalkyl; aralkyl, aminoalkyl, or alkyl, optionally substituted with one or more substituents independently selected from comprising aryl, Het<sub>1</sub>, Het<sub>2</sub>, cycloalkyl, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di (alkyl) aminocarbonyl, aminosulfonyl, alkylS(=O)<sub>t</sub>, hydroxy, cyano, nitro, thio, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, Het<sub>1</sub>, Het<sub>2</sub>, Het<sub>1</sub>alkyl and Het<sub>2</sub>alkyl.

2. Combination according to claim 1, comprising (a) a HIV protease inhibitor of formula (2) or a pharmaceutically acceptable salt or ester thereof and (b) an inhibitor of cytochrome P450 or a pharmaceutically acceptable salt or ester thereof,

(Formula Removed)

wherein, R<sub>1</sub> is hydrogen, alkyl, alkenyl, alkynyl, alkanediyl, alkylcarbonyl, alkyloxy, alkyloxy-alkyl, alkyloxycarbonyl, alkanoyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylalkoxycarbonyl, aryl, aralkyl, arylalkenyl, aryl-carbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, Het<sub>1</sub>, Het<sub>1</sub>alkyl, Hetloxy, Hetloxyalkyl, Het<sub>1</sub>aryl, Het<sub>1</sub>aralkyl, Het<sub>1</sub>cycloalkyl, Het<sub>1</sub>carbonyl, Het<sub>1</sub>alkoxy-carbonyl, Hetloxycarbonyl, Het<sub>1</sub>alkanoyl, Het<sub>1</sub>aralkanoyl,

Hetlaryloxyalkyl, Hetlaryloxycarbonyl, Hetlaralkoxycarbonyl, Hetlaroyl. Het2, Het2oxy, Het2alkyl ;  
Het2oxyalkyl, Het2aralkyl, Het2cycloalkyl, Het2aryl, Het2carbonyl, Het2oxycarbonyl,  
Het2alkanoyl, Het2alkoxycarbonyl, Het2aralkanoyl, Het2arakoxycarbonyl, Het2aryloxycarbonyl,  
Het2aroyl, Het2aryloxyalkyl, aminocarbonyl, aminoalkanoyl, aminoalkyl, optionally substituted by  
one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl,  
Het1, Het2, cycloalkyl, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono-or di (alkyl)  
aminocarbonyl, aminosulfonyl, alkylS (=0) t, hydroxy, cyano, halogen or amino optionally mono-or  
disubstituted wherein the substituents are independently selected from the group comprising  
alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio,  
alkoxy, aryloxyalkoxy. arylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino,  
arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio,  
arylthioalkylthio, alkylamino, cycloalkyl, cycloalkylalkyl, Het1, Het2, Het1 alkyl, Het2alkyl,  
Hetlamino, Het2amino, Het1 alkylamino, Het2alkylamino, Hetlthio. Het2thio, Hetlalkylthio,  
Het2alkylthio, Hetloxy and Het2oxy, wherein t is an integer between 1 and 2; R is hydrogen or  
alkyl;

R3 is alkyl, aryl, cycloalkyl, cycloalkylalkyl, or aralkyl radical;

R4 is hydrogen, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono-or di (alkyl)-aminocarbonyl,  
cycloalkyl, alkenyl, alkynyl, or alkyl, optionally substituted with one or more substituents  
independently selected from the group comprising aryl, Het1, Het2, cycloalkyl, alkyloxycarbonyl,  
carboxyl, aminocarbonyl, mono-or di (alkyl)

aminocarbonyl, aminosulfonyl, alkylS(=0)t, hydroxy, cyano, halogen or amino optionally mono-or  
disubstituted wherein the substituents are independently selected from the group comprising  
alkyl, aryl, aralkyl, Cycloalkyl, cycloalkylalkyl, Het1, Het2, Het1 alkyl and Het2alkyl.

3. Combination according to claim 1 or 2, comprising (a) an HIV protease inhibitor  
of formula (3) or a pharmaceutically acceptable salt or ester thereof and (b) an inhibitor of  
cytochrome P450,

(Formula Removed)

wherein, R1 is cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylalkoxycarbonyl, aryl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryloxyalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, Het1, Het1alkyl, Hetloxy, Hetloxyalkyl, Hetlaryl, Hetlaralkyl, Hetlcycloalkyl, Hetlcarbonyl, Hetlalkoxycarbonyl, Hetloxycarbonyl, Hetlalkanoyl, Hetlaralkanoyl, Hetl aryloxyalkyl, Hetlaryloxy-carbonyl, Hetl aralkoxycarbonyl, Hetlaroyl, Het2, Het2oxy, Het2alkyl; Het2oxyalkyl, Het2aralkyl, HEt2cycloalkyl, Het2aryl, Het2carbonyl, Het2oxycarbonyl, Het2alkanoyl, Het2alkoxycarbonyl, Het2aralkanoyl, Het2aralkoxycarbonyl, het2aryloxycarbonyl, Het2aroyl, Het2aryloxyalkyl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het1, Het2, cycloalkyl, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di (alkyl) amino- carbonyl, aminosulfonyl, alkylS(=O)t, hydroxy, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, arylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, cycloalkyl, cycloalkylalkyl, Het, Het2, Het1alkyl, Het2alkyl, Hetlamino, Het2amino, Hetlalkylamino, Het2alkylamino, Hetlthio, Het2thio, Hetlalkylthio, Het2alkylthio, Hetloxy and Het2oxy, wherein t is an integer between 1 and 2;

R4 is alkyl, optionally substituted with one or more substituent independently selected from the group comprising aryl, Het1, Het2, cycloalkyl, and amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, Het1, Het2.

4. Combination according to any one of claims 1 to 3, comprising (a) an HIV protease inhibitor as depicted in Table A or Table B or Table C or Table D or Table E or a pharmaceutical<sup>^</sup> acceptable salt or ester thereof and (b) an inhibitor of cytochrome P450.

5. Combination according to any one of claims 1 to 4, comprising (a) an HIV protease inhibitor of formula (4) or a pharmaceutically acceptable salt or ester thereof and (b) an inhibitor of cytochrome P450 wherein the compound of formula (4) has the formula  
(Formula Removed)

6. Combination according to any of claims 1 to 5, wherein said inhibitor of cytochrome P450 is selected from ritonavir, ketoconazole, cimetidine and bergamottin.

7. A combination according to any of claims 1 to 6, characterized by a combination index of about 0.8 or lower.

8. Combination according to any of claims 1 to 7, comprising (a) an HIV protease inhibitor of formula (4) or a pharmaceutically acceptable salt or ester thereof and (b) ritonavir or a pharmaceutically acceptable salt or ester thereof.

9. Pharmaceutical composition comprising a therapeutic amount of a combination according to any of claims 1 to 8 and a pharmaceutically acceptable excipient.

10. Product containing (a) a pharmaceutical composition comprising a therapeutic amount of an HIV protease inhibitor of formula (1), and (b) a pharmaceutical composition comprising a therapeutic amount of an inhibitor of cytochrome P450, as a combined preparation for simultaneous, separate or sequential use in HIV therapy.

11. A combination according to any of claims 1 to 8 for use as a medicament.

12. Use of a combination according to any of claims 1 to 8 in the manufacture of a medicament for treating, preventing or combating infection or disease associated with retrovirus infection in a mammal.

13. Use of a combination according to any of claims 1 to 8 in the manufacture of a medicament for treating or combating infection or disease associated with retrovirus infection in a mammal.

14. Use of a combination according to any of claims 1 to 8 in the manufacture of a medicament for inhibiting a protease of a retrovirus in a mammal infected with said retrovirus. Use of a

15.combination according to any of claims 1 to 8 in the manufacture of a medicament for inhibiting retroviral replication.

16.Use according to any of claims 12 to 15 wherein the retrovirus is a human immunodeficiency virus (HIV).

17.Use according to any of claims 12 to 16, wherein the retrovirus is a multidrug-resistant retrovirus.

18.Use of a combination according to any of claims 1 to 8 for improving the pharmacokinetics of a compound of formula (I) relative to the pharmacokinetics when a compound of formula (I) is administered alone, in the manufacture of a medicament for the inhibition of viral proteases.

19.Use of a combination according to any of claims 1 to 8 in the manufacture of a medicament for the treatment or prevention of HIV or HIV related conditions comprising AIDS in a human, characterized in that said combination is useful for improving the pharmacokinetic variables of a compound of formula (I) relative to the pharmacokinetic variables when a compound of formula (I) is administered alone.

20.Use of a combination according to claim 18, wherein the amount of the cytochrome P450 inhibitor is sufficient for increasing at least one of the pharmacokinetic variables selected from C<sub>min</sub>, C<sub>max</sub>, AUC at 12 hours, relative to the pharmacokinetic variables when a compound of formula (I) is administered alone.

21.Use of a combination according to claim 18, wherein the amount of the cytochrome P450 inhibitor is sufficient for increasing at least one of the pharmacokinetic variables of a compound of formula (I) selected from C<sub>min</sub>, C<sub>max</sub>, C<sub>ss</sub>, *t*<sub>av</sub>, AUC at 12 hours, or AUC at 24 hours, relative to said at least one pharmacokinetic variable when a compound of formula (I) is administered alone.

22.Method for improving the pharmacokinetics of an HIV protease inhibitor of formula (I) comprising administering to an individual in need of such treatment a therapeutically effective amount of a combination according to any of claims 1 to 8. comprising a therapeutically effective amount of each component of said combination.

23. Method for treating HIV infection and AIDS comprising administering to a patient in need of such treatment a combination according to any of claims 1 to 8. Comprising a therapeutically effective amount of each component of said combination.

It is observed that the impugned application for patent 1647/DELNP/2004 was made on June 11, 2004. The impugned application is a national phase application arising out of international patent application number PCT/EP2002/014277 dated December 12, 2002, which claims an earliest priority of European patent application number 01204841.9 dated December 12, 2001. The application having title "COMBINATION OF CYTOCHROME P450 DEPENDENT PROTEASE INHIBITORS" was accompanied by a complete specification containing a statement of 23 claims. After going through the process of examination, the impugned application remained with following 8 no's of final claims, which reads as follows:

Now I shall discuss only relevant grounds in light of 8 no's of final claims.

### **ANTICIPATION (Novelty)**

#### **Opponent's submissions:**

The Agent for opponent submitted that the impugned application concerns combinations of HIV protease inhibitors and cytochrome P450 inhibitors. The HIV protease inhibitors are compounds of formulae 1, 2, 3 or 4 comprising ester functionality between the condensed heterocycles and the sulfonamide function.

The Agent for opponent stated that the subject matter claimed in the impugned application under opposition lacks novelty over the disclosure of WO 00/47551 (herein after DI), which was published on August 17, 2000 i.e. before the claimed priority date of December 12, 2001 and is therefore admissible prior art vis-a-vis the subject matter claimed in the impugned application.

DI discloses, inter alia, a combination therapy involving the administration of an HIV protease inhibitor and one further therapeutic agent including ritonavir. DI discloses certain HIV aspartyl protease inhibitors of formula (I) which covers compounds of formulae 2, 3 and 4. The Agent for opponent further stated that since at least compounds of formulae 2, 3 and 4 are part of the

specific embodiments taught in DI and are disclosed to achieve the same technical effect as the combinations claimed in the impugned application under opposition, it is stated that a skilled person would contemplate using these compounds for the treatment of HIV related conditions. DI further discloses a combination of these compounds of DI with other anti-HIV agents such as ritonavir. It is therefore stated that the alleged invention claimed in the impugned application is anticipated by the disclosure of DI.

The opponent stated that the claims of the impugned application also lack novelty over the disclosure of WO/99/67254 (hereinafter D2), which was published on January 21, 2000 and is consequently admissible prior art vis-a-vis the subject matter claimed in the impugned application under opposition. The opponent further stated that D2 also discloses compounds having formulae which are the same as or covering the compounds of formulae 2, 3 and 4 of the impugned application as having potent HIV protease inhibitory activity.

D2 teaches combinations of the disclosed HIV protease inhibitors with other anti-retroviral compounds such as ritonavir, amprenavir and indinavir. Accordingly, the subject matter claimed in the impugned application is anticipated by the disclosure of D2.

#### **Applicant's Submissions:**

The Agent for Applicant denied that the Application concerns combinations of protease inhibitors and cytochrome P450 inhibitors or that the HIV protease inhibitors are compounds of formulae 1,2,3 or 4 .

The Agent for Applicant disagreed that the application lacks novelty over the disclosure of WO 00/47551 ( DI), which was published on 17 August, 2000. They disagreed that, compounds of formulae 2, 3 and 4 are part of the specific embodiments taught in DI and are disclosed to achieve the same technical effect as the combinations claimed in the Patent that a skilled person would contemplate using these compounds for the treatment of HIV-related conditions.They drew my attention to the fact that DI was considered by the learned Examiner in the Indian Patent

Office and the examiner at the European Patent office. They have both concluded that this application for patent is not anticipated by D1. The novelty and inventive step was acknowledged by the Indian Patent Office as well as the European Examiner. The Applicant craved leave to rely upon the relevant correspondence in this regard.

The Agent for Applicant's submitted that in order for there to be anticipation, the invention as claimed has to be published or used at the priority date. The disclosure has to be an "enabling disclosure". The test of enablement is that the invention as claimed is sufficiently disclosed in the prior art to enable the person skilled in the art to perform the invention. It should be disclosed in such a manner within the alleged prior art that claimed invention would be an infringement of the prior art. The Applicant submitted that there is no such disclosure in any prior art referred to or cited by the Opponent or their expert.

The Agent for Applicant maintained that the Application is not anticipated by the disclosure of D2. The patent as claimed by the Applicant is for a specific combination or composition of one of many HIV protease inhibitors disclosed in WO 99/67254 and one of the many anti retrovirals disclosed therein. D2, in fact, leads away from the claimed compound 4, as it emphasizes compound 32. The Applicant also submitted that D2 does not teach the combination or composition as claimed. The Examiner has withdrawn this objection and even in the EPO office proceedings.

**Findings and conclusion over Novelty:**

The Agent for opponent mentioned two documents WO 00/47551( D1) published on August 17, 2000 and WO00/47551 ( D2) published on 29 December,1999 before the claimed priority date of December 12, 2001of the impugned Application no.1647/DELNP/2004 to establish the ground of anticipation. The Agent for opponent stated that the subject matter claimed in the impugned application under opposition lacks novelty in view of documents D1and D2.

If I read through the document D1,I find that compound of formula (1) of the impugned application

is disclosed in the document D1(published on 17<sup>th</sup> August,2000) having protease inhibiting effect and the said compound may be used in combination with other antiviral Agents refer abstract; lines 23-30 of page 3,lines 12-20 page 87,lines 13-14 page 88 and claims.

I also find that the document D2(published on 29<sup>th</sup> December,1999) teaches a compound of formula (4) of the impugned Application which may be used in combination with other antiviral Agents such as ritonavir for the prevention of or treatment of the retrovirus-infected diseases such as HIV etc refer abstract,lines 9-14 page 6,line 33 page 33 to line 2 page 34,table 4 page 57,lines 9-17 page 54,examples 13 and 15 and claim 1 .

If I analyse the amended set of claims(8no.s) in relation to documents D1 and D2, I find D2 as the most closer prior art to the impugned Application.

I observe that although the document D2 discloses the compound of formula (4) or a pharmaceutically acceptable salt thereof of the amended claim1(dependent claims2-8) of the impugned Application used in combination with ritonavir for treatment of HIV ;but this do not disclose weight ratio's in the range of 40:1 to 1:15.

Therefore, I consider the Amended claims to be novel and are not anticipated by either of the document D 2 or D1.

### **OBVIOUSNESS ( LACK OF INVENTIVE STEP)**

#### **Opponent's submissions:**

The Agent for opponent stated that the applicant of the impugned application was constrained to amend the claims before the examining division of the European Patent Office in order to render the same novel over the cited prior art.

The Agent for opponent stated that the applicant's act of amending the statement of claims on the face of objections to lack of novelty are an implicit admission on the part of the applicant that the claims as currently filed with the Indian application are indeed anticipated by the disclosure of D1 or D2.

The amended claim 1 as remained in the corresponding European application reads as follows:

“Combination comprising (a) an HIV protease inhibitor of formula (4)

(Formula Removed)

or a pharmaceutical acceptable salt thereof and (b) ritonavir or a pharmaceutically acceptable salt thereof”.

The Agent for opponent stated that it is clear from a reading of the above claim that the alleged invention is now intended to cover combination comprising a compound of formula

(4) with ritonavir and the claimed combination of a compound of formula 4 with ritonavir is obvious and does not involve an inventive step over D2 alone.

The opponent further stated that page 57, table 4 specifically discloses the compound of formula 4 of the alleged invention and that the paragraph bridging pages 33 and 34 discloses that the multi-drug resistant retroviral protease inhibitors of D2 (which specifically includes compound of formula (4) of the present impugned application) can be administered in combination with other anti-retroviral compounds such as for example ritonavir, amprenavir, saquinavir, indinavir and the like. D2 specifically teaches the combination claimed in the impugned application under opposition and is therefore anticipated and obvious over D2 alone.

The Agent for opponent further stated that notwithstanding the alleged showing of a synergy existing between the compound of formula (4) of the alleged invention with ritonavir, the claimed combination remains obvious in view of the strong showing of obviousness over D2 constituted by an explicit teaching within D2 of (i) the compound per se of formula (4) and (ii) its possible combination with other anti-retroviral agents specifically including ritonavir in the disclosed list.

That the impugned application is liable to be rejected in toto on this ground alone as selection of the compound of formula (4) from within the table 4 of D2 would certainly require no inventive effort whereas ritonavir is indicated as a choice for the other component of such combinations disclosed in D2.

The Agent for opponent stated that the claimed combination of the compound of formula (4) with

ritonavir would have been obvious in view of the applicant's self admission within the specification that it was known before the priority date of the alleged invention that some anti-retrovirals such as some HIV protease inhibitors including the compound of formula (4) are metabolized by cytochrome P450 leading to sub-optimal pharmacokinetic profile.

Therefore, it would have been obvious for a person skilled in the art to administer such known anti-retroviral agent having sub-optimal pharmacokinetic profiles with a cytochrome P450 inhibitor in order to obtain a favorable pharmacokinetic profile. They further stated that it was well known in the art before the priority date of the alleged invention that ritonavir was a potent cytochrome P450 inhibitor found to be successfully combined with other anti-retroviral agents known before the priority date of the alleged invention.

Therefore, it would have been reasonable to expect ritonavir to "successfully" combine with the compound (4) as well, which is a HIV protease inhibitor having sub-optimal pharmacokinetic profile due to its metabolic degradation caused by cytochrome P450 and it would be reasonable to a person skilled in the art that the pharmacokinetic profile of compound of formula (4) would be improved by coadministering it with a cytochrome P450 inhibitor.

The agent for opponent relied upon document “ Eagling et al, Differential Inhibition of cytochrome P450 isoforms by the protease inhibitors ritonavir, saquinavir and indinavir, Br J Clin Pharmacol, 1997; 44; 190-194” (hereinafter referred to as D3) which compares the inhibitory potential of ritonavir vis-a-vis saquinavir and indinavir against cytochrome catalyzed metabolic reactions in human liver microsomes in vitro. The study concluded that ritonavir was the most potent inhibitor of cytochrome mediated testosterone hydroxylation and that there is an obvious potential for clinically significant drug interactions particularly with ritonavir.

D3 identifies under the introduction that there are important pharmacokinetic issues relating to the use of protease inhibitors wherein the bioavailability appears to be limited with several compounds due to substantial first-pass metabolism by CYP3A4. Thereafter, D3 identifies at several places that ritonavir is the most potent CYP3A4 inhibitor and may be used in conjunction

with other protease inhibitors, which otherwise have unfavorable pharmacokinetic profile due to their metabolism with cytochrome P450. The teachings of D3 identifying ritonavir as the most potent cytochrome P450 inhibitor are as follows:

Ritonavir is a potent inhibitor of CYP3A-mediated reactions showing clinically significant interactions with other co-administered drugs (page 1, column 1);

Ritonavir has recently been reported to increase the area under the plasma concentration time curve of saquinavir by more than 20 fold in a group of HIV+ patients (Introduction, column 2);

Ritonavir is one of the most potent inhibitors of CYP3A ( Paragraph 2);

The potential for clinically relevant drug interactions in HIV+ patients is self-evident, particularly in patients receiving ritonavir and other drugs metabolized by CYP3A4 ( paragraph 4);

On the other hand, it may be possible to gain therapeutic benefit from the metabolic inhibition produced by ritonavir (paragraph 4).

It is therefore clear that D3 motivates the co-administration of ritonavir with other protease inhibitors which are metabolized by cytochrome P450 to improve the pharmacokinetic profile of the protease inhibitor. Accordingly, it is stated that the claimed combination of compound of formula (4), which is a protease inhibitor metabolized by cytochrome P450, with ritonavir would have been obvious to a person skilled in the art before the priority date of the alleged invention under opposition.

The Agent for opponent further relied upon document Kempf et al,

Antimicrobial Agents and Chemotherapy, March 1997, 654-660, Vol. 41, No. 3,

Pharmacokinetic enhancement of inhibitors of HIV protease by co-administration

With Ritonavir (hereinafter referred to as D4) and stated that the alleged invention claimed in the impugned application would have been obvious to a person skilled in the art in view of D4. They stated that the findings of D4 indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors and that combination regimens of ritonavir with other protease inhibitors may play a role in the treatment of HIV infection.

The opening paragraph of D4 admits the problem sought to be solved by way of the alleged invention claimed in the impugned application under opposition. D4 states that because of the peptidomimetic structures of many HIV protease inhibitors, their utility is compromised by modest oral bioavailability resulting from poor absorption and/or rapid hepatobiliary elimination. D4 further reports that the concentrations of various protease inhibitors in plasma are substantially (8- to 46-fold) enhanced in rat and dog following coadministration with ritonavir and that this pharmacokinetic enhancement may have implications for the therapy of HIV infection with combinations of ritonavir and other protease inhibitors.

The opponent stated that D4 motivates co-administration of ritonavir with other protease inhibitors at several places which are compiled as below :

Dual-protease-inhibitor regimens with agents of divergent resistance profiles offer an alternate strategy for increasing the benefit of these agents. The results presented suggest that the elevation and prolongation of the levels of other protease inhibitors in plasma by ritonavir coadministration may produce a composite suppression of viral replication in excess of the sum of that observed with either agent individually.

The results suggest that the bioavailabilities of many peptidomimetic HIV protease inhibitors are limited not by poor absorption but by efficient CYP-mediated metabolism in the intestine or liver. Coadministration with ritonavir may prove to be a powerful tool for the rapid determination of the cause of low oral bioavailability of a variety of classes of pharmaceutical agents. Furthermore, screening for selective CYP inhibition may provide a new approach to the design and development of peptidomimetics as oral therapeutics.

Taken together, these results suggest that several structural features combine to confer high CYP-inhibitory potency upon ritonavir, including direct heme interaction via an unhindered electron-rich atom, extensive hydrophobic interactions with the CYP-active site, and stability toward CYP-mediated oxidative chemistry.

The results suggest that combination therapy with ritonavir and other protease inhibitors may

produce greater clinical benefit and more durable suppression of resistant mutants through higher, sustained plasma drug levels. It is therefore abundantly clear that D4 motivates the co-administration of ritonavir with other protease inhibitors which are metabolized by cytochrome P450 to improve the pharmacokinetic profile of the protease inhibitor. Accordingly, it is stated that the claimed combination of compound of formula (4), which is a protease inhibitor metabolized by cytochrome P450, with ritonavir would have been obvious to a person skilled in the art before the priority date of the alleged invention under opposition.

The opponent denied that the allegedly supporting data evidencing the presence of an unexpected effect leads to a conclusion that the claimed combination of the compound of formula (4) with ritonavir involves an inventive step over the prior arts. The motivation to combine the compound of formula (4) with ritonavir is found not only in the unfavorable pharmacokinetic profile of the said compound due to its metabolism by cytochrome P450 but also from the proven and documented synergism of ritonavir with other protease inhibitors suffering the same problem of unfavorable pharmacokinetic profile due to cytochrome metabolism. There is more than sufficient motivation in the prior art such as D3-D4 cited by the opponent which teaches that similar problems existing within the art relating to the unfavorable pharmacokinetic profile of other protease inhibitors could be solved by combining them with ritonavir. It is well established that by definition, any superior property must be unexpected to be considered as evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, one needs to consider what properties were expected. The opponent states that the evidence of record within the specification of the alleged invention is devoid of any evidence of what the skilled artisan would have expected. That a summary of the advantages demonstrated by the specification of the alleged invention in terms of the properties of the single dosage of the compound of formula (4) compared vis-a-vis the dosage of compound of formula (4) with ritonavir is as below:

C<sub>max</sub>: increases from 3306 ng/ml to 6220 ng/ml i.e. 2 fold increase;

AUC: increases from 10713 ng. h/ml to 98729 ng.h/ml i.e. about 10 fold increase.

The opponent states that the following prior art references demonstrate the increase in C<sub>max</sub> and the area-under-curve values of combination of ritonavir with other protease inhibitors.

Saquinavir pharmacokinetics alone and in combination with ritonavir in HIV infected patients.

Merry et al., AIDS 1997,11:F29-F33 (D5)

C<sub>max</sub> increased from 146 ng/ml to 4795 ng/ml i.e. 33 fold increase; - AUC increased from 470 ng.h/ml to 27 458 ng.h/ml i.e. 58 fold increase.

Pharmacokinetics and safety of amprenavir and ritonavir following multiple-dose, co-administration to healthy volunteers, Sadlera et al, AIDS 2001, 15:1009± 1018 (D6)

Relative to amprenavir alone, ritonavir co-administration resulted in a 3.3- to 4-fold and 10.84 to 14.25-fold increase in the geometric least-square (GLS) mean area under the plasma concentration±time curve (AUC<sub>ss</sub>) and minimum concentration (C<sub>min,ss</sub>);

APV 900 mg with RTV 100 mg resulted in a 2.09-fold and 6.85-fold increase in the GLS mean AUC<sub>ss</sub> and C<sub>min,ss</sub>, respectively;

On day 14, the geometric mean (95% confidence interval) for 450 mg APV AUC<sub>ss</sub> (ng • h/mL) was 23.49 (19.32±28.57) with 300 mg RTV and 35.42 (30.46±44.42) with 100 g RTV, and for the 900 mg APV with 100 mg RTV 47.11 (39.47±61.24);

The 450 mg APV C<sub>min,ss</sub> (ng/ ml) were 1.32 (1.05±1.67) and 2.01 (1.70±2.61), and 2.47 (2.08±3.32) for 900 mg APV.

The opponent stated that it is clear from the above comparison that the increase in the C<sub>max</sub> and area under curve values for a combination of ritonavir - compound (4) is less than that observed for a combination of ritonavir with other protease inhibitors. In fact, the observed increase in C<sub>max</sub> and AUC values would have been expected by a person skilled in the art having read the

results of D5 and D6 .Therefore, the demonstrated advantages of the claimed combination of compound (4) - ritonavir cannot be said to have been unexpected and surprising to a person skilled in the art, which cannot therefore provide the basis for an inventive step.

it was stated that even if it is assumed argue do that the applicant has shown that the claimed combination exhibits unexpectedly superior results then this secondary consideration does not overcome the strong showing of obviousness in this case. It is well settled law that although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. The record establishes such a strong case of obviousness that the applicant's allegedly unexpectedly superior results are ultimately insufficient.

### **Applicant's Submissions:**

The Applicant denied that the amendments to the statement of claims in the corresponding European Patent Application EP 02 793 018.9 are an implicit admission on the part of the Applicant that claims filed with the Indian application are anticipated. There is no basis for such an argument.

The Agent for Applicant denied that the invention lacks an inventive step or is obvious. They went on submitting that the Opponent has erred in its interpretation and construction of the definition of "inventive step". As defined in the Act, an "inventive step" means a feature of an invention that involves technical advance as compared to the existing knowledge, or a feature having economic significance (or both), and that makes the invention not obvious to a person skilled in the art. An inventive step must involve technical advance and non-obviousness. Obviousness must be judged in the light of what was publicly known or used at the priority date. The priority date of this patent is 12<sup>th</sup>December 2001 and obviousness is to be judged at this date in the light of the existing common general knowledge and prior art. It must be tested objectively with reference to individual claims without the benefit of hindsight. That the obviousness cannot be judged without a full disclosure of the state of the art and all the relevant facts circumstances and evidence being

adduced. To succeed on this ground in this Opposition, the Opponents must prove that the invention as claimed "*clearly and prima facie*" does not involve any inventive step. The Opponent has failed to discharge its burden in this respect.

It was submitted that the Opponent's reference to the amended claims in the equivalent EPO application has no relevance to the grounds of this Opposition.

In any case, it is a matter for the relevant tribunal or court to assess the obviousness of the Patent, and to suggest that the Applicant's response to such assessment by the European Patent Office is an implicit admission of anticipation is to misrepresent the process by which the relevant authority assesses the merits of an application.

The main ground upon which the Opponents and their expert have based their objections on obviousness is that all of the cited documents on obviousness including D2-D6 disclose and teach the use of the combination of a protease inhibitor including ritonavir with at least a second compound and that is sufficient to establish obviousness. The Applicant submitted that none of these documents can be considered to render any of the claims obvious whether in the unamended form or in the Patent as granted. The Applicant referred to page 2 lines 16-34 of the specification of the application and claimed that they disclose and cite various documents, (including documents referred to as D1 and D2 in the Opposition), which make reference to the combination of a protease inhibitor including ritonavir with a second compound. None of these have been held to make the claimed invention obvious. That documents cited in the Opposition disclose no more than those disclosed in the Specification of the Patent and do not render the claims in the Patent as granted obvious.

They said that the Opponent has failed to appreciate the scope of the Patent and effects of the combination of formula (4) with ritonavir. First, the invention claimed concerns a specific combination and this purposive selection out of various possibilities is narrow in scope and has favorable characteristics that could not have been derived from the various cited prior art

documents by a person skilled in the art. Second, the claimed combination showed synergy with ritonavir. This synergetic effect is the inventive step in the Patent and has been acknowledged as such by both, the Examiner of the Indian Patent Office as well as the European Patent Office.

This synergy was demonstrated in Example 3 in the Specification of the Patent (page 43 lines 5-25). The combination index (CI) for the combination was determined. A CI value between 0.8 and 1.2 reflects additive inhibition of the combined compounds and a value below 0.8 indicates a synergy between the two molecules. The compound of formula (4) showed synergy with ritonavir at all molar ratios.

Example 2 (pages 39-43) shows that when ritonavir is given in combination with the compound of formula (4), it increased the C<sub>min</sub> (minimum serum concentration) of such HIV protease inhibitor of formula (4) showing reduction of the dose and dosing frequency compared to the sole administration of the compound.

The safety profile of the compound of formula (4) in combination with low doses of ritonavir was good. The combination resulted in a reduced the adverse side effects, which was not expected. The combination has an improved safety and tolerability profile compared to the therapy with the compound of formula (4) administered alone. No maculopapular rash was seen on the volunteers. This was an unexpected technical advance because the average and C<sub>min</sub> plasma concentrations of the compound of formula (4) in combination were generally higher than those after the compound of formula (4) was administered alone.

They further argued that the Opponent overlooked the fact that the learned Examiner in the Indian Patent Office, after raising the queries of obviousness and lack of inventive step on very similar grounds, accepted the Patent to be granted, after considering the submissions tendered by the Applicant before her.

The Applicant craved leave to rely upon the evidence of its own expert in rebuttal to Mr Natu's

statement.

#### Obviousness over Annexure 2 to Mr. Natu's Affidavit

The Agent for Applicant submitted that WO/99/67254 was considered by the learned Examiner and was satisfied that claims in this application are inventive over and not obvious.

It was denied that D2 specifically teaches the combination or composition of formula (4) and ritonavir and does highlight the synergy between formula (4) and ritonavir. Whilst D2 states that the compounds described therein can be used in conjunction with an anti-retroviral compound, but this does not teach the use of the compound formula (4) and ritonavir as specified in the claims, nor does it highlight the effects described in the specification and in the present response . The purposive selection out of a list of possibilities is narrow in scope and has favorable features that could not have been derived from D2 by a person skilled in the art. On the contrary D2 leads away from the granted claims, which considers compound 32 as more favorable.

it was denied that it would be obvious for a person skilled in the art, to administer the compound formula (4) with a cytochrome P450 inhibitor to obtain a favourable pharmacokinetic profile. Furthermore, it would not be reasonable to expect ritonavir to combine with formula (4) and produce the enhanced effects described in the Specification and in the present response.

Applicant submitted that D2 does not teach or disclose the composition as claimed.

The Agent for Applicant denied that it would be obvious to a person skilled in the art to know that if some HIV protease inhibitors including the compound of formula (4) are metabolised by cytochrome P450, leading to sub-optimal pharmacokinetic profile, then administering such an anti-retroviral agent with cytochrome P450 inhibitor would result in a favourable pharmacokinetic profile.

It was denied that D3 discloses the co-administration of ritonavir with other protease inhibitors

metabolised by cytochrome CYP3A4. D3 does not teach use of ritonavir with formula 4 and certainly not in what ratio. D3 merely teaches and high lights the potential interactions ritonavir may have with other drugs both beneficial and harmful. D3 only highlights the need to perform further drug interaction studies.

It was submitted by the Agent for the Applicant that D4 discusses the usefulness of combination therapy with ritonavir and suggests the need for further investigation to establish safe regimens for clinical applications. D4 does not even remotely provide any teaching or direction to person skilled in the art towards the Patent. That the selected combination or composition of protease inhibitor of formula (4) and ritonavir clearly demonstrates significant synergistic effect and results in considerably reduced incidence of adverse effects. The results are also illustrated in Figure 3 where the isobolograms for the combinations/compositions are plotted. Whereas a straight line represents additive inhibition by two inhibitors, a curve towards the origin of the axes indicates synergy. Also, as provided in Example 3, the combination index (CI) between 0.8 and 1.2 reflects additive inhibition of the combined compounds and the value below 0.8 indicates a synergy between the two molecules. As stated , the compound of formula (4) showed synergy with ritonavir at all molar ratios (0.66-0.81).

Further, the person skilled in the art may perhaps recognize the specific dose level. Frequency of dosage for any particular patient will depend upon a variety of factors including activity of the compound, metabolic stability and length of action of that compound among others. A number of possible weight ratios, dosage regimen and exemplary combinations with different dosage and frequencies are disclosed on pages 33-37 of the specification. It is the Applicant's humble submission that the claimed combination as such and the composition as claimed in claims 1-8 are inventive in

view of any one or combination of references discussed above and none of these teach or suggest the specific combination as claimed as such or the composition as claimed in claims 1-8, with demonstrated synergistic effect and reduced side effects with lowered Cmin dose.

It was also denied that the impugned application is obvious in the light of D5 and D6.

D5 does not disclose the combination or composition as claimed, comprising compound of formula (4) and ritonavir for which a synergistic effect and reduced side effect is demonstrated at all molar ratios, in the experiment section. None of these references, including those made to D5 either alone or in combination thereof provide any suggestion to the person skilled in the art to render the synergistic effect and reduced side effect of the claimed combination or composition, obvious. D5 discloses increase in the maximum plasma concentration of Saquinavir (SQV) when used in combination with Ritonavir (RTI). D5 also discloses the issue that administration of protease inhibitors in combination does not raise important pharmacokinetic issues in particular clinically relevant drug interactions and demonstrates the ability of RIT to inhibit SQV metabolism leading to exposure of patients to SQV toxicity. D5 does not imply or provide any suggestion about the claimed composition with demonstrated advantages.

D6 discloses studies to evaluate safety and pharmacokinetic interaction between amprenavir (APV) and ritonavir (RTV) and demonstrates statistically and clinically increase in APV plasma concentrations when APV is co-administered with RTV in specific concentration and doses. D6 does not provide any teaching or suggestion to arrive at combination or composition as claimed for which a synergistic effect and reduced side effect is demonstrated at all molar ratios.

**Findings and conclusion over obviousness (lack of inventive Step):**

The Agent for opponent referred to following documents to establish the ground of lack of inventive step on amended claims(8 no's):

1. WO/00/47551 (D1)
2. WO/99/67254 (D2)
3. Eagling et al.,Differential inhibition of cytochrome P450 isoforms by the protease inhibitors ritonavir,saquinavir and indinavir,Br J clin pharmacol.,1997;44;190-194 (D3)
4. kempf et al.,Antimicrobial agents and chemotherapy,march 1997,654-660,Vol.41,no.3,Pharmacokinetic enhancement of inhibitors of HIV protease by co administration with retonavir(D4)
5. saquinavir pharmacokinetics alone and in combination with ritonavir in HIV infected patients,Merry et al.,AIDS 1997 11:F29-F33(D5)
6. Pharmacokinetics and safety of amprenavir and ritonavir following multiple-dose,co-administration to healthy volunteers,sadlera et al.,AIDS 2001,1009+1018(D6)

After reading through the document D2(published on 29<sup>th</sup> December,1999),I find that document D2 teaches a compound of formula (4) of the impugned Application, which may be used in combination with other antiviral Agents such as ritonavir for the prevention of or treatment of the retrovirus-infected diseases such as HIV etc refer abstract,lines 9-14 page 6,line 33 page 33 to line 2 page 34,table 4 page 57,lines 9-17 page 54,examples 13 and 15 and claim 1 .

I agree to the statement made by Agent for opponent that document D2 at page 57, table 4 specifically discloses the compound of formula 4 of the alleged invention and that the paragraph bridging pages 33 and 34 discloses that the multi-drug resistant retroviral protease inhibitors of D2 (which specifically includes compound of formula (4) of the present impugned application) can be administered in combination with other anti-retroviral compounds such as for example ritonavir, amprenavir, saquinavir, indinavir and the like.

If I analyse the amended set of claims(8no.s) in relation to documents D1 and D2, I find D2 as the most closer prior art to the amended claims of impugned Application.

I refer to the introduction of document D3 which states that :

“Initial clinical studies suggest that the protease inhibitors are very potent anti-HIV drugs with three compounds licensed for use ritonavir, saquinavir and indinavir all reported to produce marked reductions in plasma viral load, particularly when used in combination with nucleoside analogue reverse transcriptase inhibitors. However, there are important pharmacokinetic issues relating to the use of protease inhibitors. For example, bioavailability appears to be limited with these several compounds”.

I also agree that Eagling et al, Differential Inhibition of cytochrome P450 isoforms by the protease inhibitors ritonavir, saquinavir and indinavir, Br J Clin Pharmacol, 1997; 44; 190-194 (D3) compares the inhibitory potential of ritonavir vis-a-vis saquinavir and indinavir against cytochrome catalyzed metabolic reactions in human liver microsomes in vitro. D3 further identifies that there are important pharmacokinetic issues relating to the use of protease inhibitors wherein the bioavailability appears to be limited with several compounds due to substantial first-pass metabolism by CYP3A4. D3 identifies ritonavir as the most potent CYP3A4 inhibitor and may be used in conjunction with other protease inhibitors, which otherwise have unfavorable pharmacokinetic profile due to their metabolism with cytochrome P450. Ritonavir is a potent inhibitor of CYP3A-mediated reactions showing clinically significant interactions with other co-administered drugs (page 1, column 1);

Ritonavir has recently been reported to increase the area under the plasma concentration time curve of saquinavir by more than 20 fold in a group of HIV+ patients (Introduction, column 2);

Ritonavir is one of the most potent inhibitors of CYP3A ( Paragraph 2);

D3 motivates the co-administration of ritonavir with other protease inhibitors which are metabolized by cytochrome P450 to improve the pharmacokinetic profile of the protease inhibitor.

I also observe that D4 indicate that ritonavir can favorably alter the pharmacokinetic profiles of other protease inhibitors and that combination regimens of ritonavir with other protease inhibitors

may play a role in the treatment of HIV infection.

I also refer to at page 658 document D4 that the AUC values of each of the four inhibitors above, after co-dosing with ritonavir, were similar to or greater than that of ritonavir given separately,

It is also noted and as admitted by the Agent for applicant that compound of formula 4 and ritonavir shows synergy at all molar ratios. Therefore, it is not clear how this specific combination having weight ratios 40:1 to 1:15 shall be purposive selection which can give unexpected results.

Keeping in view the above, it is concluded that a person skilled in the art having knowledge of document D2 shall be motivated to arrive at the invention claimed in amended set of claims when taught by the document D3 or D4.

Therefore, this leaves me no doubt that the amended claims (8 no's) submitted by the agent for applicant lacks inventive step defined u/s 2(1)(ja) because the Applicant can easily arrive at the invention claimed in amended claims, when teachings of document D2 is combined with the teachings of either D3 or D4.

I agree that these amended claims have been allowed in the Indian patent office and proceedings; but upon perusal of records I found that document D2 has not been understood along with document D3 or D4 as herein above. Furthermore, EPO proceedings have no binding upon me.

Having arrived at conclusion upon inventive step, I do not understand worth going further in to other grounds of oppositions.

Both parties produced expert evidences to support their claims over novelty and inventive step,

which are declined for consideration due to their contradictory statements.

In view of my findings and conclusion drawn above over inventive step, I refuse to grant patent on this patent application no. **1647/DELNP/2004** on the ground of lack of inventive step section 25(e) read with section 2(1)(ja).

This opposition is disposed off with no cost to either party.

Dated this 30<sup>th</sup>. Day of march, 2009

( N .R. MEENA)

ASSTT. CONTROLLER OF PATENTS & DESIGNS

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