FORM 7A

THE PATENTS ACT, 1970

(39 OF 1970)

AND

THE PATENT RULES, 2003

NOTICE OF OPPOSITION

(See section 25(1); rule 55-A)

We, DR. REDDY'S LABORATORIES LIMITED, an Indian Company having its Office at IPDO, Innovation Plaza, Bachupally, Hyderabad- 500090, India, hereby give representation by way of opposition to grant of patent in respect of Patent Application No. **4412/DELNP/2007** dated November 8, 2006 made by **NOVARTIS AG**, having office at Lichtstrasse 35, CH 4056, Basel Switzerland and published on August 24, 2007 under Section 11A in the Official Journal of Indian Patent Office on the following grounds:

1. **Section 25(1)(e)**: that the invention so far as claimed in any claim of the complete specification is obvious and 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.
2. **Section 25(2)(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.

3. **Section25(2)(g)**: that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed

Our address for service in India is:

Singh & Singh Law Firm, C-139, Defence Colony, New Delhi -110024;

Phone: 011-49876099, 011-49876005-6099;

e-mail: bitika@singhandsingh.com

Dated this 13th day of June, 2019

Ms. Bitika Sharma, Ms. Anusuya Nigam, Ms. Nitya Sharma (INPA-3522)

Of **Singh & Singh Law Firm**

Opponent's Agent

To,

The Controller of Patents,

The Patents Office,

At Delhi

FORM 7A

THE PATENTS ACT, 1970

(39 OF 1970)

AND

THE PATENT RULES, 2003

NOTICE OF OPPOSITION

(See section 25(1); rule 55-A)

We, DR. REDDY'S LABORATORIES LIMITED, an Indian Company having its Office at IPDO, Innovation Plaza, Bachupally, Hyderabad- 500090, India, hereby give representation by way of opposition to grant of patent in respect of Patent Application No. **4412/DELNP/2007** dated November 8, 2006 made by **NOVARTIS AG**, having office at Lichtstrasse 35, CH 4056, Basel Switzerland and published on August 24, 2007 under Section 11A in the Official Journal of Indian Patent Office on the following grounds:

1. **Section 25(1)(e)**: that the invention so far as claimed in any claim of the complete specification is obvious and 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.
2. **Section 25(2)(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.

3. **Section25(2)(g)**: that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed

Our address for service in India is:

Singh & Singh Law Firm, C-139, Defence Colony, New Delhi -110024;
Phone: 011-49876099, 011-49876005-6099;
e-mail: bitika@singhandsingh.com

Dated this 13th day of June, 2019

Ms. Bitika Sharma, Ms. Anusuya Nigam, Ms. Nitya Sharma (INPA-3522)
Of **Singh & Singh Law Firm**
Opponent's Agent

To,
The Controller of Patents,
The Patents Office,
At Delhi

BEFORE THE PATENTS OFFICE, DELHI

In the matter of a representation under Section 25(1) read with Rule 55 of The Patents Act, 1970

IN THE MATTER OF:

Application No.: **4412/DELNP/2007**

Date of Filing of Application: **08.06.2007**

IN THE MATTER OF:

Dr. Reddy's Laboratories Ltd. .....Opponent

VERSUS

Novartis AG. .....Applicant

REPRESENTATION BY WAY OF OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970 ON BEHALF OF THE OPPONENT/PETITIONER, DR. REDDY'S LABORATORIES LTD.

1. It is submitted that the present representation is being filed by the Opponent, Dr. Reddy's Laboratories (hereinafter referred to as the 'Opponent') opposing the grant of the Indian patent no. 4412/DELNP/2007 (hereinafter referred to as 'IN '412' or the 'impugned application') in favor of Novartis AG. (hereinafter referred to as the 'Applicant' or 'Respondent'). The present representation has been signed by Dr. Poonam Raghuvanshi on behalf of the Opponent. Dr. Poonam Raghuvanshi is the Vice President and Head of

Intellectual Property Management of the Opponent and is duly authorized to sign the present representation.

ABOUT THE OPPONENT: DR. REDDY'S LABORATORIES LIMITED

2. Dr. Reddy's Laboratories Ltd., the Opponent herein named, is a company incorporated in the year 1984, under the Companies Act, 1956. The Opponent is a pharmaceutical company that works on the principle that "good health can't wait". Dr. Reddy's Laboratories fosters a culture of scientific research aimed at accelerating access to affordable and innovative medicines by:

a) Bringing expensive medicines within reach of patients;
b) Addressing the unmet patient needs;
c) Helping better management of diseases; and,
d) Ensuring that medicines are available where needed.

3. The Opponent has immense reputation for its medications, APIs, diagnostic kits, critical care and biotechnology products. The opponent is driven by drug development and research with a patient-centric approach which helps in developing differentiated products. The Research and Development is mainly carried out in a state-of-the-art R&D Center spread over 300,000 sq. ft. and houses over 70 laboratories and more than 800 research scientists working on various projects in conjunction with several research centers across the globe. For industry consumers, the Opponent offers starting materials, intermediates, active pharmaceutical ingredients and finished-dosage forms.

4. The Opponent has to its credit over 200 Abbreviated New Drug Applications (ANDAs), over 750 Drug Master Files with the US FDA and more than 86 patents applications in the last five years alone.

LOCUS STANDI

5. As per Section 25(1) any person may, in writing, file an opposition to the Ld. Controller against the grant of patent on any of the grounds, available after the publication of the said application and before the grant thereof.

ABOUT THE IMPUGNED PATENT APPLICATION

6. It is submitted that the Applicant has filed for the Indian Patent Application No. IN 4412/DELNP/2007 on June 08, 2007. The details of the said patent are as under:

Application Number	4412/DELNP/2007
Applicant Name	Novartis AG.
Title of Invention	PHARMACEUTICAL COMBINATIONS OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND AN NEP INHIBITOR
Priority Date	November 09, 2005
Date of Filing of PCT Application (PCT/US2006/043710)	November 08, 2006
Date of Filing / Entry to National Phase	June 08, 2007
Date of Publication of Application u/s 11 A	August 24, 2007
Date of filing Request for Examination before the IPO	November 06, 2009

Date of Filing Response to First Examination Report	November 27, 2015

7. The impugned application contains the following 17 claims, after the amendment of claims as filed on which are being challenged by the Opponent:

Claim 1:

A compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na1-3 • x H2O, wherein x is 0 to 3.

Claim 2:

The compound as claimed in claim 1 having the formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na3 • x H2O, wherein x is 0 to 3.

Claim 3:

The compound as claimed in claim 2, wherein the compound is in crystalline or amorphous form.

Claim 4:

The compound as claimed in claim 2 or 3, wherein x is 2.5.

Claim 5:

The compound as claimed in claim 4, which is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate.

Claim 6:

The compound as claimed in claim 5, wherein the compound is in crystalline form.

Claim 7:

The compound as claimed in claim 6 characterized by an Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum having the following absorption bands expressed in reciprocal wave numbers (cm-1) (± 2 cm-1): 1711 (st), 1637 (st), 1597 (st), 1401 (st).

Claim 8:

The compound as claimed in claim 7 wherein the Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum has the following absorption bands expressed in reciprocal wave numbers (cm-1)(± 2 cm-1): 2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942 (w), 907 (w), 862 (w), 763 (st), 742 (m), 698(m) 533 (st).

Claim 9:

The compound as claimed in any of claims 6 to 8, characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals:

d in [A] (± 0.1 A): 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w).

Claim 10:

A pharmaceutical composition comprising the compound as claimed in any one of claims 1 to 9; and at least one pharmaceutically acceptable additive.

Claim 11:

The pharmaceutical composition as claimed in claim 10, wherein the pharmaceutically acceptable additive is selected from the group consisting of diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and combinations thereof.

Claim 12:

A method of preparing the compound as claimed in any of claims 1 to 9, said method comprising the steps of:

(a) dissolving (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine or a salt thereof and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester or a salt thereof in a suitable solvent;

(b) dissolving a basic Na compound in a suitable solvent;

(c) combining the solutions obtained in steps (i) and (ii);

(d) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(ivb) re-dissolving the solid in suitable solvent;

(ivc) precipitation of the solid and drying same to obtain the compound.

Claim 13:

The method as claimed in claim 12 wherein the suitable solvent in steps (i) and/or (iva) is acetone.

Claim 14:

The method as claimed in 12 or 13, wherein the basic Na compound is NaOH, Na2Co3, NaHCO3, NaOMe, NaOAc or NaOCHO.

Claim 15:

A pharmaceutical composition comprising

(a) the compound as claimed in any one of claims 1 to 9;

(b) a therapeutic agent selected from an anti-diabetic, a hypolipidemic agent, an anti-obesity agent and an anti-hypertensive agent; and

(c) At least one pharmaceutically acceptable additive.

Claim 16:

16. The pharmaceutical composition as claimed in claim 15 wherein the therapeutic agent is amlodipine besylate.

Claim 17:

The pharmaceutical composition as claimed in claim 15, wherein the therapeutic agent is hydroclorothiazide.

8. It is submitted that a perusal of the aforesaid claims reveals that monopoly is being sought by the Applicant/Respondent qua [((S)-N-valeryl-N-{[2"-(1-H-tetrazole-5-yl)-biphenyl4-yl]-methyl}-valine) [(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester) Na1-3.x H2O where x = 0-3, which is a combination of an angiotensin receptor antagonist valsartan and a neutral endopeptidase inhibitor (NEPi) (2R,4S)-5-biphenyl4-yl~5-(3-carboxypropionylamino)-2-methyl-pentanoic acid ethyl ester. It is submitted that the patent entails such compounds achieved by formation of supramolecular structure/ co crystals of the already known compounds being valsartan and sacubitril. Therefore, it is most respectfully submitted that the present patent intends to claim merely a new form of the already known and claimed compounds.

9. It is submitted that the impugned patent fails to provide any new or novel compound that is not merely a derivative of the compounds already known in the art and is clearly barred under Section 3(d) of the Patents Act, 1970 (hereinafter referred to as the 'Act') as the same is not an invention as per the provisions of the Act. By way of the impugned application, the Patentee/Respondent is indulging in evergreening, and attempting to circumvent the very intent of the Legislature which is to prevent grant of patents that result in repeated and extended monopolies being

granted in respect of the same compounds with known activity and use in different forms.

10. The impugned patent application was published by the Patent Office on 24.08.2007. As per Section 25(1) of the Act, any "person" may give a notice of Opposition to the Ld. Controller of Patents with respect to a patent, at any time after the publication but before the grant of patent. Therefore, the Opponent submits its opposition by way of representation under Section 25(1) of the Indian Patents Act, 1970 (hereinafter the Act) in respect of the Patent Application IN 4412/DELNP/2007. The present Opposition is being filed within the stipulated time period. Further, locus standi is not a condition precedent for an opposition under Section 25(1). The grounds of the opposition under Section 25(1) of the Act are as follow:

GROUND I

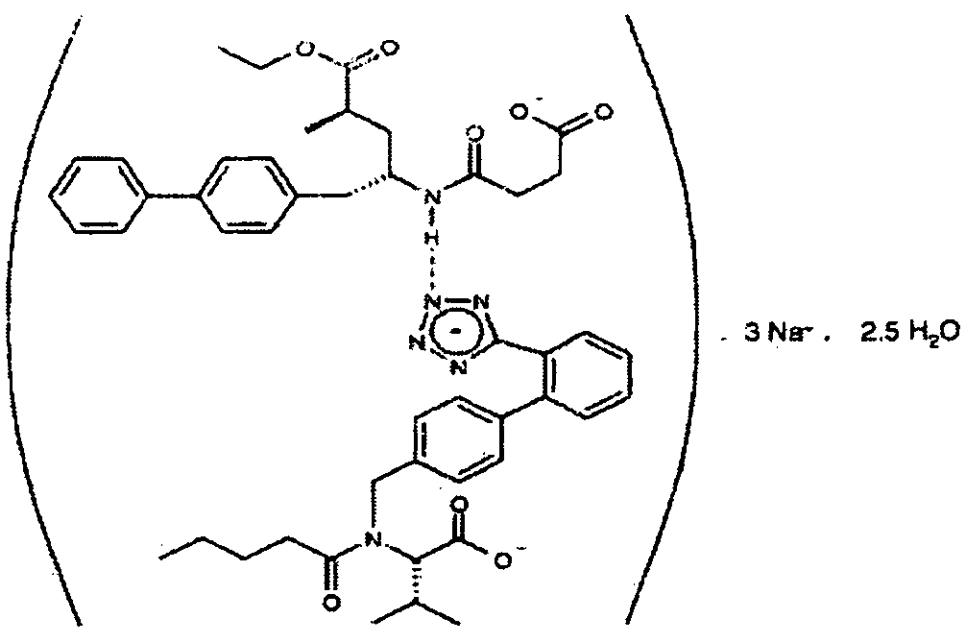
A. Section 25(1)(e): that the invention so far as claimed in any claim of the complete specification is obvious and does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim:

11. It is most respectfully submitted that the compounds/complexes as claimed in the impugned application along with its pharmaceutically acceptable salts

were obvious to a person skilled in the art on the basis of knowledge that was prevalent in the relevant field prior to the filing of the impugned application.

12. It is humbly submitted that the impugned patent relates to compounds which are used as inhibitors of angiotensin receptor and neprilysin. It is submitted that the combination of valsartan and sacubitril is known to be used in the treatment of heart related diseases such as hypertension. It is pertinent to note that other NEP inhibitors and angiotensin receptor inhibitors along with their use in treatment of heart related diseases were known in the prior art.

13. It is most respectfully submitted that the Applicant/Respondent in claim 1, claims a compound of the following general structural formula:



14. It is most respectfully submitted that the compounds as claimed in the impugned patent along with their pharmaceutically acceptable salts were obvious to a person

skilled in the art on the basis of the prior arts as detailed hereinbelow.

15. **WO 2003/059345 titled as "Pharmaceutical Compositions Comprising Valsartan and NEP Inhibitors" filed on 16 January, 2003 and published on 24 July, 2003 (D1)** (*a copy whereof is being filed with the present representation and marked as Annexure A*)

16. It is submitted that the present prior art D1 is directed to a pharmaceutical composition comprising a combination of (i) the AT1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier. It is also directed to a method for the treatment or prevention of different cardio-vascular condition or diseases including hypertension, heart failure such as (acute and chronic), congestive heart failure.

17. It is submitted that D1 teaches that NEP inhibitor is preferably N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester being sacubitril or a pharmaceutically acceptable salt thereof. It is submitted that D1 teaches that the preferred salt of sacubitril is sodium salt. The relevant portion of the prior art is reproduced below for ready reference:

"...

With respect to N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R- methylbutanoic acid ethyl

ester, preferred salts include the sodium salt disclosed in U.S. Patent No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt.

....." (Page 6, Para5)

18. It is submitted that D1 also discloses that the combination of valsartan and sacubitril achieves better therapeutic effect than administration of valsartan alone or sacubitril alone. The relevant portion of the prior art is reproduced below for ready reference:

"...

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).

....." (Page 7, Para 3)

19. **Research Article titled as "Hydrogen-bond directed cocrystallization as a tool for designing acentric organic solids" by Etter et al. published in January 1989, Chemistry of Materials, Vol 1 , 12 -14 (D2)** (*a copy whereof is being filed with the present representation and marked as Annexure B*)

20. It is submitted that D2 teaches a process for preparing a 1:1 co-crystalline complex of 4-aminobenzoic acid (4-ABA) and 3,5-dinitrobenzoic acid (3,5-DNBA) via a hydrogen bonding.

21. The present prior art also discloses that co-crystal of 4-aminobenzoic acid is made with 4-chloro-3,5-dinitrobenzoic acid, 4-nitrobenzoic acid, and 3,4-dinitrobenzoic acid. It is submitted that D2 teaches two methods of production of same co-crystal of two anions: (i) solution co-crystallization, and (ii) solid-state grinding.

22. It is submitted that though, in their reply to the FER, the Applicant sought to distinguish the claimed compound of the impugned application in relation to the pharmaceutical composition of D1, the fact is that the claimed compound is a combination of valsartan and sacubitril having 3 moles of sodium 2.5 moles of water in the form of a complex, towards which, ample teaching and suggestion exists in the art.

23. It is submitted that D1 is the closest prior art which teaches a combination of valsartan and sacubitril having superior therapeutic effect than the individual components thereof. It is submitted that a complex formation of two anionic moieties are known in the art for a long time, especially between two anionic moieties as already disclosed in D2.

24. Therefore, a person having ordinary skill in the art will be motivated to form a complex with valsartan and sacubitril

since both of them are anions and combination of these two agents have better therapeutic profile than the individual components in light of the combined teachings of D1 and D2.

25. It is submitted that a person of ordinary skill in the art would know of at least two processes, as entailed in D2, to make the complex of the impugned application.

26. It is submitted that in view of D1, combined with the teachings of D2, the complex of the impugned application is rendered obvious and therefore lacks an inventive step and fails to meet the requirement of Section 2(1)(ja) of the Act.

27. Further, it is submitted that the compound as contained in the impugned application has no advantages/ technical advancement over the over the combination, as taught in D1, as elaborated hereinbelow:

(i) One of the advantages as claimed by the Applicant is a fixed 1:1 molar ratio of sacubitril and valsartan. It is submitted that D1 covers a pharmaceutical composition comprising valsartan and Sacubitril in 1:1 ratio. Therefore, the fixed 1:1 dose ratio of valsartan and sacubitril is already known and achieved in the prior art and hence does not provide any advantageous property of the complex.

(ii) Second advantage as claimed by the Applicant is the simplification in compounding and manufacturing of drug

product. It is submitted that the Applicant is indulging in fraudulent behavior by indicating so. It is submitted that many combination products have been approved and are being manufactured routinely by a person having ordinary skill in the art in a manufacturing unit. Hence, this should not be treated as an advantage/ technical advancement over what is already known in the art. Further, it is submitted that the applicant has exemplified in the examples of D1 the method of manufacture of a drug product which is a combination of Sacubitril and Valsartan. It is therefore submitted that a person having ordinary skill in the art would know how to prepare a drug product which is a combination of Sacubitril and Valsartan from D1.

(iii) The third advantage, as per the applicant is better physical properties of the complex like less hygroscopicity and better solubility. It is submitted that the applicant is trying to imply that valsartan is so hygroscopic that it is not easy to formulate valsartan in to a drug product. However, valsartan tablet is available in India since long and many companies in India have been manufacturing valsartan tablet for a long period. It is submitted that D1 provides many examples of making the combination of valsartan and sacubitril and a person having ordinary skill in the art can make the combination as per the examples of D1 without solving the problem of hygroscopicity and hence hygroscopicity does not play any role in making the complex advantageous over the combination. It is submitted that the applicant has only mentioned that the

complex has better solubility, but does not provide any data to further its claim. Hence, the advantage regarding solubility is also questionable herein by because of lack of data/evidence.

28. It is submitted that the complex of the impugned application is obvious over the combination of valsartan and sacubitril as disclosed in D1 and there is no advantage of the complex over the combination. It is submitted that due to lack of any advantage of the complex over the combination, as known in D1, the complex lacks inventive step.

29. It is submitted that Claim 6 of the impugned application covers a process for preparation of the claimed complex which comprises dissolving valsartan or salt thereof and sacubitril or salt thereof in a suitable solvent; dissolving basic sodium in a suitable solvent; combining both the solutions and precipitation and drying the resulting complex.

30. It is submitted that the process for synthesizing the complex in claim 6 is a general process since the process, according to the claim, operates in any condition, i.e. in presence of any solvent, at any temperature and pressure, in presence of any sodium base etc. It is submitted that the claimed process is obvious and lacks inventive step in view of the teachings of D2. It is submitted that D2 discloses two processes for preparing a complex between two anionic species and one of them is solution co-crystallization, same as covered in the impugned application.

31. It is submitted that D2 provides important roadmap to the production of supramolecular structure. It motivates and teaches a person skilled in art to develop a supramolecular form of pharmaceutical compound disclosed in D1. It is submitted that D2 provides various reasons to develop a supramolecular form of a compound.

32. It is submitted that the process for synthesizing the complex is so general and vague that as per the Claims of the impugned application it takes place without any exact reaction conditions and it takes place in any solvent, in presence of any sodium base or starting material and at any temperature and pressure. It is submitted that in view of the fact that the process of synthesizing the complex becomes obvious over D2 inasmuch as no clear and unambiguous advantage of the claimed process over the known process for synthesizing a complex is shown by the Applicant. Moreover, a person skilled in the art reading the claims and specification of the impugned patent would be unable to follow the invention without undue experimentation.

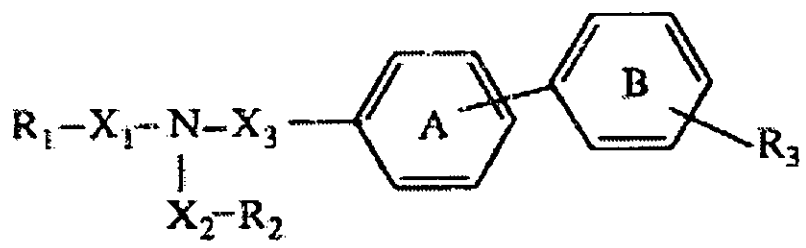
33. It is submitted that the present application is liable to rejected on basis of lack of inventive step over combined teachings of D1 and D2.

34. **EP 0443983 titled as "Acyl Compounds" filed on 16 January, 2003 and published on 24 July, 2003 (D3)** (*a*

copy whereof is being filed with the present representation and marked as Annexure C)

35. It is submitted that D3 discloses and claims valsartan for the first time. It is submitted that the compound valsartan as disclosed in the present prior art has the IUPAC name (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine).

36. It is submitted that the present application relates to the compound having general structure:



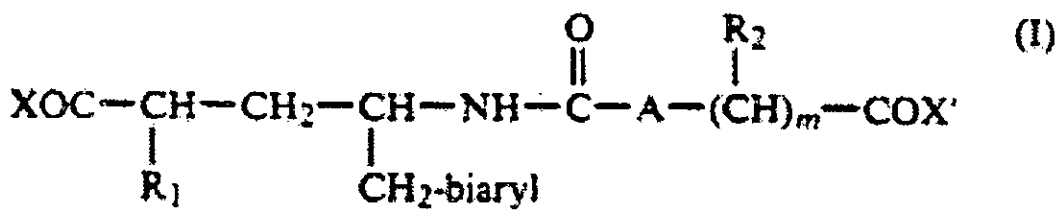
(I),

37. It is submitted that the present prior art also discloses the method of manufacture of the claimed compounds and specifically valsartan.

38. **US 5217996 titled as "Biaryl substituted 4-amino-butyric acid amides" filed on 22 January, 1992 and granted on 08 June, 1993 (D4)** (*a copy whereof is being filed with the present representation and marked as Annexure D*)

39. It is submitted that D4 discloses the compound which acts as NEP inhibitor and which can be used as antihypertensive

or saluretic agents. It is submitted that the present prior art specifically teaches the compounds which are biaryl substituted 4-amino-butyric acid amide derivatives having the following general structure:



(I)

40. It is submitted that the present prior art in the examples 7 and 8 and claim 6, particularly teaches the sodium salt of the sacubitril [N-(3-Carboxy-1-oxopropyl)-(4S)-p-phenyl phenyl methyl)-4-amino2R-methyl butanoic acid, ethyl ester].

41. Therefore, it is submitted that admittedly NEP inhibitors like (2R,4S)-5-biphenyl4-yl~5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester (Sacubitril) and its salts were known to be useful as anti-hypertensive agents.

42. **WO 02/06253 titled as "Valsartan Salts" filed on 17 July, 2001 and published on 24 January, 2002 (D5)** (*a copy whereof is being filed with the present representation and marked as Annexure E*)

43. The invention as disclosed in D5 relates to new salts of valsartan or crystalline, also partly crystalline and amorphous salts of valsartan, the respective production and

usage, and pharmaceutical preparations containing such a salt. It discloses disodium salt of valsartan, specifically.

44. It is submitted that the present prior art specifically intends to meet the need in the art for more stable crystalline forms of valsartan. It is submitted that D5 specifically teaches towards salts of valsartan which are selected from the group consisting of the monosodium salt, the disodium salt, the monopotassium salt, the dipotassium salt, the magnesium salt, the calcium salt, the bis-diethylammonium salt, the bis-dipropylammonium salt, the bis-dibutylammonium salt, the mono-L-arginine salt, the bis-L-arginine salt, the mono-L-lysine salt and the bis-L-lysine salt, as well as salt mixtures, or respectively, an amorphous form, a solvate, especially hydrate, as well as a polymorphous form thereof, the respective production and usage, and pharmaceutical preparations containing such salts.

45. It is submitted that D5 discloses that the preferred salts of valsartan are selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

46. Further, the present prior art also teaches salt mixtures are (i) single salt forms from different cations selected from the above group or (ii) mixtures of those single salt forms which exist for example in the form of conglomerates. Moreover, the present prior art also teaches the equilibrating crystallisation process for producing hydrates of valsartan.

47. Therefore, in view of the above-mentioned prior art, any person skilled in the art will be motivated to crystallise di-sodium salts of valsartan for use as angiotensin receptor inhibitors.

CONCLUSION:

48. On the basis of the teachings and disclosures contained in the various prior art documents as discussed by the Opponent, it would be obvious for a person skilled in the art to develop the compounds as disclosed and claimed in the impugned patent since it was already known that:

- Angiotensin receptor and NEP inhibitors can be used for treatment of heart failure/diseases;
- Valsartan and sacubitril can be used in combination as Angiotensin receptor and NEP inhibitors respectively for the treatment of heart failure/diseases;
- Valsartan and sacubitril are respectively most stable in their salt form;
- Crystals of valsartan and sacubitril are superior in as much as they are more stable than amorphous forms thereof.

49. Moreover, it is submitted that all the features of the present alleged invention as claimed in the impugned patent find sufficient motivation/ teachings in the art. As a result, it was obvious for a person skilled in the art to arrive at the compounds as claimed in the impugned patent.

50. It is most respectfully submitted that every new form cannot be rewarded with a patent unless there is a genuine and enforceable development (which was not obvious to a person skilled in the art in view of what was already known/prevalent/used in the art). In the present case, based on the disclosures contained in the prior art documents cited hereinabove, it was worthwhile for a person skilled in the art to study the efficacy of the different substituents by trial and error method which does not warrant the grant of a patented monopoly. Thus, the impugned patent application is liable to be dismissed on this ground alone.

GROUND II

B. SECTION 25(2)(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

Claims not patentable under Section 3(d):

51. It is most respectfully submitted that the impugned patent application does not constitute an invention and is not patentable in view of the Section 3(d) of the Act. It is submitted that the compounds claimed in the impugned patent application fall within the purview of Section 3(d) of the Act as the same are nothing but derivatives of previously

known angiotensin receptor inhibitors and NEP inhibitors. Section 3(d) of the Act provides that:

> ***"Section 3: -***
>
> ***What are not inventions:***
>
> .....
>
> *(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 for 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;*
> *....."*
>
> (emphasis added)

52. It is submitted that the compound as claimed and disclosed in the impugned patent application is nothing but an alleged new form, i.e. supramolecular structure of the already known compound as claimed and disclosed in D1 to D5 which has been discussed hereinabove.

53. Although the applicants argue that the impugned application covers a new compound/ supramolecular structure, the fact is that the claim covers a complex between valsartan and sacubitril having 2.5 moles of water and 3 moles of sodium.

54. It is most respectfully submitted that the compound Valsartan is known from the prior art D3 and sacubitril is known from D4. Further, the use of these compounds in combination as a treatment for heart failure is also already known and disclosed before the filing of the present application. Additionally, as discussed herein above D5 specifically discloses disodium salts of valsartan and D3 discloses sodium salt of sacubitril.

55. It is submitted that both the components/ compounds/crystals of the claimed complex are known and claimed in the prior art. Further, it is submitted that a complex is defined as a derivative of its individual components.

56. It is submitted that as per Section 3(d) of Indian Patents Act, 1970 and the settled law, a complex is deemed to be patentable in India only when the complex shows enhanced therapeutic efficacy over its individual components i.e. the complex as disclosed in the impugned application ought to have enhanced efficacy over valsartan and valsartan disodium as known from D3 and D5 respectively and also over sacubitril and sacubitril sodium as known from D4. It is submitted that D1 and D2 discloses a combination of valsartan and sacubitril and methods of production of their co-crystals, as already detailed hereinabove.

57. It is submitted that the complex of the impugned application is not patentable in view of section 3(d) of Indian Patents

Act, 1970 until and unless the same shows better therapeutic efficacy in comparison with the combination/ conjugation of valsartan and sacubitril as already known in D1 and D2.

58. It is submitted that the Applicant is trying to mislead the Hon'ble Indian Patent Office by stating that the compound as contained in the impugned application is a "new substance" and hence the test of Section 3(d) shall apply to the alleged invention as contained in the impugned application.

59. It is submitted that merely forming a complex between two known moieties, a "new substance" cannot be obtained. The explanation of Section 3(d) clearly and unambiguously points out to the fact that a complex of two known substances attracts 3(d). Moreover, in the present case D1 among others, already discloses a combination of valsartan and sacubitril.

60. It is submitted that complexes of known substance do not stand the test of obviousness much less the stricter criteria of Section 3(d).

61. It is reiterated that in the present case, not only are the individual compounds of the complex so contained in the impugned application but their combination and use and method of production is also already known in the art. Hence, it is submitted that the complex of the impugned application attracts Section 3(d) of the Act.

62. It is submitted that the Applicant has taken a stand before the Hon'ble Indian Patent Office that Section 3(d) excludes its applicability to combinations/compositions/complexes of two active agents since combinations/complexes of two active agents cannot be considered as simple derivatives of either of the active agent. It is submitted that this is nothing but a mala fide attempt on the part of the Applicant to mislead the IPO. It is submitted that the complex of any two known agents are "mere new form" of the two agents, as per Section 3(d). it is submitted that the complex of the impugned application is a "mere new form" of valsartan as known in D3 and sacubitril as known in D4; also it is a "mere new form" of valsartan disodium as known in D5 and sacubitril sodium as known in D4; further it is a "mere new form" of a combination of valsartan and sacubitril.

63. It is submitted that even if, arguendo, the complex of the impugned application is not a "mere new form" of valsartan and sacubitril; it cannot be denied that the compound as contained in the impugned application is a "mere new form" of valsartan disodium, as known in D5, sacubitril sodium, as known in D4

64. It is submitted that the Applicant has provided comparative study showing that the complex of the impugned application is having higher therapeutic efficacy for reduction in blood pressure over valsartan. However, it is imperative to note that the applicant has not shown any data to prove that the

complex of the impugned application has higher therapeutic efficacy over valsartan disodium, over sacubitril, over sacubitril sodium and/or over the combination of the said compounds.

65. It is most respectfully submitted that the impugned patent does not constitute an invention and is not patentable in view of the Section 3(d) of the Act. It is humbly stated that the impugned patent discloses and claims a derivatives of valsartan/ valsartan disodium and sacubitril/ sacubitril sodium for use as inhibitors of angiotensin receptor and neprilysin. As evident from the above analysis, the claimed compounds were already known and subject matter of sufficient patent applications, research and were within public domain. In such circumstances, the patentee had the responsibility to show the improvement in the properties with regard to therapeutic efficacy.

66. It is a well settled principle in law that new forms of known substances including salts, esters and other derivatives are not considered as an invention under the Patents Act. Further, even new uses of known substances are excluded from the meaning of an invention by virtue of Section 3(d).

67. It is most respectfully submitted that if any patent which includes subject matter specifically excluded under Section 3(d) is inadvertently granted by the Indian Patent Office, it shall not only lead to an illegal monopoly over a known substance in favour of the Patentee, but shall also be

counterproductive to the intention of the Legislature in including the said provision in order to ensure that after a substance has been used exclusively by a patentee for the full term, it must necessarily fall into public domain. Thereafter, no exclusivity can be granted to a person/entity to claim monopoly over that which is already public domain.

68. Thus, no patent can be legally granted *qua* the claims in the impugned patent and the impugned application stands liable to be rejected and not be granted a patent under the Indian Patent Law.

GROUND III

Section 25(1)(g) that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed

69. It is submitted that the compete specification of the impugned patent does not sufficiently and fairly describe the invention and the method by which it is to be performed, that is to say, that the description of the method or the instructions for the working of the invention as contained in the complete specification are not themselves sufficient to enable a person in India possessing average skill in, and average knowledge of, the art to which the invention relates, to work the invention, or that it does not disclose the best method of performing it which was known to the Patentee and

for which he was entitled to claim protection and in light of the same the impugned patent is not patentable.

70. It is submitted that Section 10(4) of the Act states that "*Every complete specification shall—*

(a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed;

(b) disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection; and

(c) end with a claim or claims defining the scope of the invention for which protection is claimed.

(d) be accompanied by an abstract to provide technical information on the invention."

71. It is of importance to note that the Patentee has failed to describe and disclose sufficiently in the complete specification:

- The best methods of developing the preferred embodiments of the compounds as claimed in claims 1 - 5;
- The compounds comprising valsartan and sacubitril having 1 – 3 moles of sodium and 0 -3 moles of water;
- The synthesis of the complex as claimed in Claim 6 – 8 is too vague and will not teach a person skilled in the art to arrive at the claimed supramolecular structure;
- No clarity as regard to how the water molecules are associated to the compounds valsartan and sacubitril;
- The choice of alkali being Na+ finds no disclosure in the complete specification;
- The best dosage compositions of the preferred compounds inasmuch as the Patentee have provided only

a generic composition of the effective drug containing any compound in claims 1-5. The Patentee has further failed to provide any ratios of the compound and excipients, failed to provide the effective dosage form and composition;

- The Patentee has also failed to provide the best methods of use of the said compounds. Further, the administration forms mentioned in the description are vague and too wide so as to include all possible routes of administration.

72. The Opponent submits that a complete specification should sufficiently and clearly describe the invention and not leave a person skill in the art in a state where he has to conduct undue experimentation to perform the invention. There is no data and examples in the complete specification of the impugned application to show the best mode of working of the invention. Accordingly, it is not known as to what is the exact and actual workable method of arriving at the compound, methods of using the compounds and the workable and effective dosage compositions of the compounds claimed in the impugned application. It is therefore submitted that the impugned patent is not patentable on this ground under Section 25(1)(g) of the Act, for being lacking sufficient description and also being vague and ambiguous.

PRAYER

73. In the facts and circumstances of the case the Opponent prays as follows:

a) That the present pre-grant opposition allowed, and the Application No. IN 4412/DELNP/2007 and claims thereof be rejected under Section 25(1) of the Indian Patent Act, 1970;

b) The Opponent may be allowed to file further documents as evidence if necessary to support their averments;

c) The Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

d) Any other reliefs considering the facts and circumstances may be granted in favor of the Opponent in the interest of justice.

SINGH AND SINGH LAW FIRM LLP
ATTORNEYS FOR THE OPPONENT

Dated: New Delhi

To,
The Controller of Patents
The Patents Office, Delhi