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- Patents

- Trademarks

- Designs

- Copyrights

- Contractual
Agreements

- Technology
Search,
Sourcing and
Transfer

- Licensing

- Prior Art
Search

- Infringement
Analysis

- Patentability
Opinion

- Pre & Post
Grant
Opposition

- Revocation

- IP Enforcement
and Legal
Services

GNA/AF/133/16-17

To,

The Controller of Patents

The Patent Office,

Government of India,

Boudhik Sampada Bhavan,

Plot No. 32, Sector-14, Dwarka,

New Delhi - 110075

10th February, 2017

Dear Sir,

**Sub: Pre-grant Representation/Opposition to the Patent
Application under Section 25(1) of the Patents Act,
1970 and Rule 55(1) of the Patents Rules, 2003
(amended upto 2014)**

**Reg: Patent Application No. 6148/DELNP/2011A published
under Section 11A on 3rd February, 2012.**

We are filing this Pre-grant representation/Opposition under Section 25(1) of the Patents Act, 1970 read with Rule 55(1) of the Patents Rule, 2003 on Form 7A. The Written Statement and evidence (attached herewith as Annexures/Exhibits) are enclosed herewith in duplicate.

As per provision of the Patent Act, 1970, we are entitled to file this Pre-grant Opposition any-time before grant of patent. As per the status available under inPASS, the Official website of the Indian Patent Office, the Application is awaiting Examination. The Request for Examination was filed on 1st February, 2013.

Pune (Mrs. Srividya Ravi - Mobile: 09860010252)

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Gopakumar Nair Associates

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Fax : 91-22-28462455
Mobile : 093211 52272 (Dr. Nair); 09869011185 (Mr. Sajeev)
09892583300 (Dr. Aruna)

- Patents
- Trademarks

This pre-grant opposition is being filed by us on behalf of C Mr. D Sankar Rajkumar. We request you to take this Pre-grant Opposition on record and process the same accordingly.

- Designs
- Copyrights
- Contractual Agreements

We further request you to provide to us a copy of the Reply Statement and evidence and further claim amendments, if any, filed by Patent Applicant. We also request you to grant us a personal hearing under Rule 55(1).

- Technology Search, Sourcing and Transfer

Also, please find enclosed herewith Form 26 (Power of Attorney), in original.

- Licensing

Thanking you in anticipation.

- Prior Art Search

Kindly acknowledge receipt.

- Infringement Analysis

With best regards,

- Patentability Opinion

Dr. Gopakumar G. Nair

Regn. No: IN/PA 509

Gopakumar Nair Associates

Encl : as above

- Pre & Post Grant Opposition

C.C. Anand and Anand B-41, Nizamuddin East, New Delhi 110013, India

- Revocation

P.S.: File size of the Exhibits exceeds limit. Hence, only the representation has been filed online. The Representation & Exhibits are being filed as hard copy at Patent Office, Delhi & served on the Agents of the Patent Applicant.

- IP Enforcement and Legal Services

Pune (Mrs. Srividya Ravi - Mobile: 09860010252)

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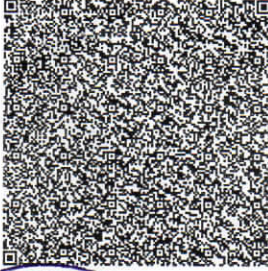


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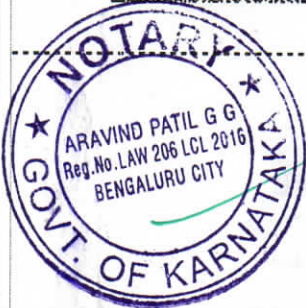
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FORM 26

THE PATENT ACT, 1970
(39 of 1970)

FORM OF AUTHORISATION OF A PATENT AGENT / OR ANY PERSON
IN A MATTER OR PROCEEDING UNDER THE ACT

[See sections 127 and 132 and Rule 135]

... 2

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1. The authenticity of this Stamp Certificate should be verified at "www.scshestamp.com". Any discrepancy in the details on this Certificate and as available on the website renders it invalid.
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D.S. Raja

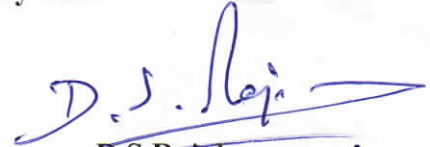
I, D.S.RAJAKUMAR Indian Inhabitant, residing at 114/5, 2nd Main, 9th Cross, Chamarajpet Bangalore-18. India, hereby authorize Ms. Veena Johari, Advocate, Courtyard Attorneys, Ms. Julie George, Advocate, and Dr. Gopakumar G. Nair, Dr. Aruna Sree, Ms. Andreyra Fernandes and Ms. Kavita Rao Parmar, of Gopakumar Nair Associates having office at 3rd Floor, 'Shivmangal', Akurli Road, Kandivli (East), Mumbai - 400 101, Maharashtra, India, all Indian inhabitants, to act on my behalf in relation to pursuing representation by way of opposition, post-grant patent opposition and revocation related matters under the Patents Act, 1970 pertaining to the National Phase Patent Application No. 6148/DELNP/2011 filed at the Patent Office, Delhi.

I request that all notices, requisition and communication relating thereto may be sent to such persons at the above address unless otherwise specified.

I hereby revoke all previous authorization, if any, made in respect of the same matter or proceedings.

I hereby assent to the action already taken by the said persons in the above matter.

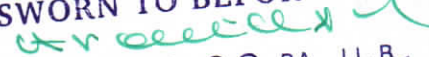
Dated this 04/02/2017 day of February 2017


D.S. Rajakumar

**To
The Controller of Patents
The Patent Office
At Delhi**

:: 2 ::



SWORN TO BEFORE ME

**ARAVIND PATIL .G.G, BA., LL.B.,
ADVOCATE & NOTARY
4, K.M. Layout, Basavanagudi
Bangalore - 560 004.**

- 6 FEB 2017

FORM 7-A
THE PATENTS ACT, 1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[Rule 55]

I, Mr. D Sankar Rajkumar, hereby give representation by way of opposition to the grant of patent in respect of application no. 6148/DELNP/2011 dated 12th August 2011 made by Boehringer Ingelheim International GMBH and published on 3rd February, 2012 on the ground of

1. Section 25(1)(b),
2. Sections 25(1)(c),
3. Section 25(1)(e),
4. Section 25(1)(f) and
5. Section 25(1)(g).

Our address for service in India is

Gopakumar Nair Associates
3rd floor, Shivmangal, Next to Big Bazaar,
Akurli Road, Kandivli (East), Mumbai-400101
Maharashtra, India. Phone: 91-22-40895454
E-mail address: gopanair@gnair.net

Dated this 10th day of February, 2017



Dr. Gopakumar G. Nair
(Reg No. IN/PA 509)
(Agent for the Opponent)
Gopakumar Nair Associates

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

BEFORE THE PATENT CONTROLLER AT DELHI

IN THE MATTER OF Section 25(1) of
The Patents Act, 1970, as amended up to
the Patents (Amendment) Act, 2005

AND

IN THE MATTER OF Rule 55 of the
Patents Rules, 2003, as amended up to
the Patents (Amendment) Rules, 2016

AND

IN THE MATTER OF National Phase
Patent Application No.
6148/DELNP/2011 bearing title
“Pharmaceutical composition comprising
linagliptin and optionally a SGLT2
inhibitor, and uses thereof” filed by
Boehringer Ingelheim International
GMBH on 12 August 2011 and claiming
priority of 13 February 2009

... Applicant

AND

IN THE MATTER OF pre-grant
representation by way of opposition filed
by D Sankar Rajkumar, Indian Inhabitant
of adult years, having his residence at

114/5, 2nd Main, 9th Cross, Chamrajpet,
Bengaluru 560 018.

... Opponent

STATEMENT OF FACTS/ EVIDENCE

1. The Opponent is an adult Indian citizen. He is a trained social worker and has been working on social issues for the last 20 years. The Opponent, who has been diagnosed with Type 2 diabetes and takes medication for the same, hereby makes a representation by way of opposition against the grant of patent application, titled “Pharmaceutical composition comprising linagliptin and optionally a SGLT2 inhibitor, and uses thereof” bearing Indian Patent Application No. 6148/DELNP/2011 (hereinafter referred to as “the present Application”) filed by Boehringer Ingelheim International GmbH (hereinafter referred to as “Patent Applicant”), having its office at Binger Strasse, 173, 55216 am Rhein Ingelheim, Germany.
2. The Opponent submits as follows.
3. The representation by way of opposition is being filed on Form-7A under section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 (hereinafter referred to as “the Patents Act”) and Rule 55 of the Patents Rules, 2003 as amended by the Patents (Amendment) Rules, 2016. Any submission made or evidence adduced with specific reference to any clause of section 25(1) may be treated as being made without prejudice to other submissions made elsewhere in this representation by way of

opposition or any other opposition proceeding before the Indian Patent Office.

4. The Opponent submits that he is opposing the grant of a patent to the impugned present Application reciting Claims 1 to 20 by availing strong and valid grounds provided under section 25(1) of the Patents Act and is consequently filing the present representation by way of opposition to the impugned present Application.

I. LOCUS STANDI

5. That representation by way of opposition can be made by any person in writing under section 25(1) of the Patents Act. Notwithstanding this, the Opponent submits that he is a “person interested” under section 2(1)(t) in the field of the present invention and has *locus standi* to initiate the present representation by way of opposition. Being a diabetic, the Opponent has a real and substantial interest in the aforesaid patent application being opposed.

II. JURISDICTION

6. The present Application has been filed by the Patent Applicant at the Patent Office in Delhi. Therefore, the Patent Controller has the jurisdiction to hear this representation by way of opposition in Delhi.

III. BACKGROUND

7. The present Application claims a mere combination of two known anti-diabetic molecules—*linagliptin* and *empagliflozin*. Both these drugs are admittedly known prior to the priority date of the present Application.
8. As of 2014, there are an estimated 422 million people with diabetes. The global prevalence of diabetes is 8.5 per cent. The prevalence of diabetes in India is 7.8 per cent [WHO Diabetes Country Profiles 2016, India, available at http://www.who.int/diabetes/country-profiles/ind_en.pdf?ua=1].
9. There are two types of diabetes—Type 1 and Type 2. Type 1 is a result of complete or near total insulin deficiency and occurs due to destruction of pancreatic islet beta cells, predominantly due to an autoimmune process. Type 2 is a heterogeneous group of disorders characterised by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production, impaired response of liver and peripheral tissues to insulin, loss of beta cell function, impaired regulation of glucagon secretion and disturbed incretin physiology. Incretins are involved in maintaining glucose homeostasis along with other hormones such as insulin, glucagon and amylin.
10. Patients with insulin resistance do not develop hyperglycaemia until their beta cells are unable to meet the demands for insulin. Thus, enhancement of insulin secretion from the islet beta cells is a practical target for treatment of patients with Type 2 diabetes. However, as noted by Lebovitz, insulin secretagogues, including sulfonylureas and glitinides, frequently exhibit a secondary failure

and may cause hypoglycaemia in patients with Type 2 diabetes [Lebovitz, “Insulin secretagogues: old and new” (1999) *Diabetes Reviews* 7: 139–53 (abstract)]. Therefore, there was an interest in identifying agents that enhanced insulin secretion in a sustained glucose-dependent manner in patients with Type 2 diabetes.

11. Glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the two major incretin hormones released after meals by the enteroendocrine cells in the intestine to enhance glucose-stimulated insulin secretion.
12. As noted by Holst and Gromada, patients with Type 2 diabetes are characterised by two defects related to incretin effect: (i) while secretion of GLP-1 is decreased, its insulintropic effect is preserved and (ii) while secretion of GIP is near normal, its insulintropic effect is reduced [Holst and Gromada, “Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans” (2004) *American Journal of Physiology Endocrinology and Metabolism* 287:E199–206].
13. GLP-1 was targeted as a mechanism for treating Type 2 diabetes. In addition, GLP-1 represented a more attractive treatment option for Type 2 diabetes because of its multiple effects, including the stimulation of satiety in the central nervous system by crossing the blood-brain barrier. GLP-1 was known to stimulate glucose-dependent insulin secretion [Mojsov, *et al.*, “Insulintropin: Glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas” (1987) *The Journal of Clinical Investigation* 79:616–19] and insulin gene expression [Drucker, *et al.*, “Glucagon-like peptide I

stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line” (1987) *Proceedings of the National Academy of Sciences of the United States of America* 84: 3434–38], inhibit glucagon secretion [Matsuyama, *et al.*, “Glucagonlike peptide-1 (7-36 amide): a potent glucagonostatic and insulintropic hormone” (1988) *Diabetes Research and Clinical Practice* 5:281–84 (abstract)] and delay gastric emptying [Wettergren, *et al.*, “Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man” (1993) *Digestive Diseases and Sciences* 38: 665–73 (abstract)]. *In vitro* and *in vivo* data showed that GLP-1 increases beta cell mass by stimulating islet cell neogenesis and inhibiting apoptosis of islets [Li, *et al.*, “Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis” (2003) *The Journal of Biological Chemistry* 278:471–78].

14. As noted by Chyan and Chuang, due to the short circulating half-life of GLP-1, which is degraded by dipeptidyl peptidase IV (DPP-IV), two approaches were undertaken. One was to develop long-acting GLP-1 analogs, such as exendin-4, that would be resistant to degradation. The second approach was to develop DPP-IV inhibitors. They also noted that DPP-IV inhibitors are used either as a monotherapy or in combination with other anti-diabetic agents for treatment of Type 2 diabetes, as well as metabolic syndrome, osteoporosis and arthritis [Chyan and Chuang, “Dipeptidyl Peptidase-IV Inhibitors: An Evolving Treatment for Type 2 Diabetes from the Incretin Concept” (2007) *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* 1: 15–24]
15. Similarly, Pratley and Salsali found that DPP-IV inhibitors were effective as monotherapy in patients suffering from diabetes and

- also as add-on therapy in combination and were a promising new treatment [see Prateley and Salsali, “Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes” (2007) *Current Medical Research and Opinion* 23(4): 919–31 (abstract)].
16. Levetan too concluded that oral DPP-IV inhibitors offered potential for significant improvement in glycaemic control without hypoglycaemia or weight gain [Levetan, “Oral antidiabetic agents in type 2 diabetes” (2007) *Current Medical Research and Opinion* 23(4): 949–52 (abstract)].
 17. Gupta, *et al.*, concluded that DPP IV inhibitors had an advantage over other anti-diabetic agents such as long-acting GLP-1 analogs, thiazolidinediones, sulfonylureas, biguanides, etc (TZD) and glycosidase inhibitors [Gupta, *et al.*, “Emerging Drug Candidates of Dipeptidyl Peptidase IV (DPP IV) Inhibitor Class for the Treatment of Type 2 Diabetes” (2009) *Current Drug Targets* 10: 71–87].
 18. Thus, DPP-IV inhibitors and their use for treatment of diabetes, both as a monotherapy and in combination with other anti-diabetic agents, were well-known prior to the priority date of the present Application.
 19. Another mechanism of action that is targeted for treatment of diabetes is sodium-glucose co-transporter-2. Sodium-glucose cotransporter-2 is present in the kidney and reabsorbs blood glucose filtered by the glomeruli of the kidneys, thus preventing glucose excretion through urine. Competitive inhibitors of sodium-glucose cotransporter-2 (hereinafter referred to as “SGLT2 inhibitors”), which would provoke glucose excretion through urine,

were identified as a treatment option for diabetes and several SGLT2 inhibitors were discovered [(i) Jabbour and Goldstein, “Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes” (2008) *International Journal of Clinical Practice* 62(8): 1279–84 (abstract) and (ii) Idris and Donnelly, “Sodium-glucose co-transporter-2 inhibitors: an emerging new class of oral anti-diabetic drug” (2009) *Diabetes, Obesity and Metabolism* 11(2): 79–88 (issued online on 29 December 2008)]. SGLT2 inhibitors were known to enhance renal glucose excretion and consequently lower plasma glucose levels. A principle behind the development of SGLT2 inhibitors was the improvement of diabetic conditions without increasing body weight or the risk of hypoglycaemia [Isaji, “Sodium-glucose cotransporter inhibitors for diabetes” (2007) *Current Opinion in Investigational Drugs* 8(4): 285–92 (abstract)].

20. Thus, SGLT2 inhibitors and their advantages were also known prior to the priority date of the present Application.
21. Patent documents such as WO 2008/055870, titled “Glucopyranosyl-substituted benzyl-benzonitrile derivatives, medicaments containing such compounds, their use and process for their manufacture” and published on 15 May 2008, disclosed pharmaceutical compositions comprising SGLT2 inhibitors with other anti-diabetic agents including DPP-IV inhibitors, *inter alia*, for treatment of metabolic diseases.
22. In light of this and as will be shown below, the composition of a DPP-IV inhibitor and SGLT2 inhibitor claimed in the present

Application is not new, is obvious to a person skilled in the art, lacks inventive step and does not meet the standards of invention or patentability set out under the Indian patent law.

IV. PATENT APPLICANT'S CONTENTION

23. The present Application, which was filed in India on 12 August 2011 and published in India on 3 February 2012, is the national phase application of WO 2010/092124. The WO application was filed on 11 February 2010, claiming a priority of 13 February 2009. Thus, the priority date for the present Application is 13 February 2009. The complete specification of WO 2010/092124, is enclosed herewith as **Annexure 1**.
24. As originally filed, the present Application had 26 claims. On 29 January 2013, the claims were amended. As of today, the present Application has 20 claims. The bibliographic page along with amended claims of the impugned present Application, as retrieved from the website of the Indian Patent Office website, is enclosed herewith as **Annexure 1.1**.
25. The present Application claims a patent for a pharmaceutical composition, more particularly a solid oral dosage form, comprising *linagliptin*, *empagliflozin* and excipients.
26. *Linagliptin*, i.e. 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, which was also identified as BI 1356, is a DPP-IV inhibitor. The Patent Applicant admits that *linagliptin*, its preferred crystalline forms and its pharmaceutical composition are known [*see* Complete Specification, internal pages 1, 2, 18 and 34].

27. 1-Chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, i.e. *empagliflozin*, is an SGLT2 inhibitor. The Patent Applicant also admits that *empagliflozin* and its preferred forms are known [see Complete Specification, internal pages 2 to 3, 18 and 20].
28. The Patent Applicant describes the alleged problems of incompatibility and degradation of DPPIV inhibitors with a primary or secondary amino group, including *linagliptin*, with excipients due to the presence of amino groups. It characterises this as an unforeseen difficulty for potent DPPIV inhibitors, such as *linagliptin* [see Complete Specification, internal pages 1 to 2] and also sets out the preferred excipients [see Complete Specification, internal pages 27 to 33]. Interestingly, the Patent Applicant admits that the degradation can be tested in standard tests [see Complete Specification, internal page 27].
29. Though the Patent Applicant discusses the combination of *linagliptin* with various SGLT2 inhibitors, it prefers and subsequently claims *empagliflozin* [see Complete Specification, internal pages 2 to 3, 5 to 6 and 18 to 20].
30. The Patent Applicant also discloses the preferred particle size and particle size distribution for the compounds [see Complete Specification, internal pages 5 to 7 and 23 to 27].
31. The Patent Applicant sets out the various diseases and conditions that can be treated, including diabetes, and various treatment outcomes [see Complete Specification, internal pages 3 to 4, 7 to 11 and 48 to 54].

32. Interestingly, while it sets out at least nine pharmacological examples, the Patent Applicant provides data for only one example to show an alleged improved glucose excursion [*see* Complete Specification, internal pages 54 to 58].
33. Essentially, the Patent Applicant is claiming a patent for a combination of two known drugs which are independently patented in India and elsewhere. The Patent Applicant has not shown significantly enhanced efficacy for the combination as required under section 3(d) of the Patents Act. Further, the Patent Applicant has not shown synergistic effect for the combination of the two drugs as required under section 3(e) of the Patents Act. The Patent Applicant itself admits that *linagliptin* can be administered combined or alternately with the SGLT2 inhibitor [*see* Complete Specification, internal page 48].
34. Without prejudice to pleadings in this or any other proceeding before the Indian Patent Office, the Opponent submits that *linagliptin* is, *inter alia*, covered by Indian Patent No. 243301 which is set to expire on or about 18 August 2023. *Empagliflozin* is, *inter alia*, covered by Indian Patent No. 268846, which is set to expire on or about 11 March 2025. Incidentally, both these patents are owned by the Patent Applicant. The Patent Applicant is now attempting to obtain a patent on a pharmaceutical dosage form of a composition comprising these two known molecules. If granted, the Patent Applicant would extend its monopoly until about 11 February 2030, thereby obtaining a monopoly for an additional five years.

35. Diabetes is one of the most highly prevalent diseases in India and it is essential that drugs for treating it should be made available at competitive and low prices so that people are able to avail of treatment at affordable rates.
36. The Opponent states that the right to health guaranteed under Article 21 of the Constitution of India is paramount and that the medicines required for diabetes treatment ought to be made available at affordable and low costs, so that the maximum people can benefit from the treatment, and lives can be saved. The wrongful grant of a patent to the Patent Applicant would be a breach of the fundamental right to health of a large number of patients with diabetes who ought to be able to obtain medicines at competitive prices and not monopolistic prices.

V. SUMMARY OF CLAIMS

37. The claims as amended on 29 January 2013 may be summarised as follows:
- (i) Claim 1 relates to a pharmaceutical composition comprising *linagliptin* or a pharmaceutically acceptable salt thereof as a first active pharmaceutical ingredient and *empagliflozin* as a second active pharmaceutical ingredient and one or more excipients.
 - (ii) Claim 2 is dependent on Claim 1 and provides a limitation for the particle size distribution of *linagliptin*.
 - (iii) Claim 3 is dependent on Claim 1 and provides a limitation for the particle size distribution of *empagliflozin*.

- (iv) Claims 4 to 6 are dependent on Claim 1 and relate to a pharmaceutical composition as claimed in Claims 1, 2 or 3, wherein the excipients comprise (i) one or more diluents, (ii) one or more diluents and binders and (iii) one or more diluents, binders and disintegrants respectively.
- (v) Claim 7 relates to a pharmaceutical composition as claimed in one or more of the previous claims in terms of percentages by weight of the total composition of the various ingredients of the composition.
- (vi) Claims 8 relates to a pharmaceutical composition as claimed in one or more of Claims 1 to 7 in the form of a granulate, capsule, a tablet or a film-coated tablet.
- (vii) Claims 9 and 10 relate to a pharmaceutical dosage form and a solid pharmaceutical dosage form (more particularly a capsule or tablet) respectively of the pharmaceutical composition claimed in one or more of the Claims 1 to 8.
- (viii) Claim 11 relates to the pharmaceutical dosage form claimed in Claim 9 or Claim 10 comprising *linagliptin* or its pharmaceutically acceptable salt in an amount of 0.1 to 30 mg.
- (ix) Claim 12 relates to the pharmaceutical dosage form claimed in Claim 9, Claim 10 or Claim 11 comprising *empagliflozin* in an amount from 0.5 to 100 mg.
- (x) Claims 13 and 14 depend on Claims 9 to 12 and describe the dissolution test results and disintegration test results of the pharmaceutical dosage form respectively.

- (xi) Claim 15 relates to a process for preparing a pharmaceutical dosage form claimed in Claims 9 to 14 comprising one or more granulation processes.
- (xii) Claim 16 relates to a claim for the pharmaceutical composition claimed in Claims 1 to 8 for manufacture of a medicament to treat various conditions that are listed therein and to achieve certain outcomes in a patient.
- (xiii) Claims 17 to 20 are dependent on Claim 16 and describe the conditions present in a patient to whom the pharmaceutical composition claimed in Claim 16 is to be administered.

VI. GROUNDS

38. The Opponent raises the following amongst other grounds, which are without prejudice to one another.

- (i) Claims 1 to 14 and 16 are anticipated by the claims of either of at least two other Indian patent applications—Indian Application No. 1006/DELNP/2010 (Exhibit A) and Indian Application No. 4811/DELNP/2011 (Exhibit C)—which have an earlier priority date. Therefore, Claims 1 to 12 and 16 ought to be rejected under section 25(1)(c) of the Patents Act.
- (ii) Claims 1 to 10, 12 to 14 and 16 are anticipated by the disclosures of either or both of at least two other previously-published patent documents—Indian Application No. 4844/DELNP/2006 (Exhibit E) and WO 2007/093610 (Exhibit F). Therefore, they ought to be rejected under section 2(1)(j) read with section 25(1)(b) of the Patents Act.

(iii) Claims 1 to 16 are obvious to a person skilled in the art in light of the disclosures contained in the following prior art documents:

- WO 2007/128724 published on 15 November 2007 (Exhibit G)
- WO 2006/078593 published on 27 July 2006 (Exhibit H)
- WO 2007/033350 published on 22 March 2007 (Exhibit I)
- IN 01092/DELNP/2003 published on 12 January 2007 (Exhibit J)
- IN 567/DELNP/2005 published on 23 January 2009 (Exhibit K)
- US 2007/0281940 published on 6 December 2007 (Exhibit L)
- Katsuno, *et al.*, “Sergliflozin, a Novel Selective Inhibitor of Low-Affinity Sodium Glucose Cotransporter (SGLT2), Validates the Critical Role of SGLT2 in Renal Glucose Reabsorption and Modulates Plasma Glucose Level” (2007) *The Journal of Pharmacology and Experimental Therapeutics* 320:323–30 (Exhibit M)
- WO 2008/055940 published on 15 May 2008 (Exhibit N)
- Tim Heise, *et al.*, “Treatment with BI 1356, a Novel and Potent DPP-IV Inhibitor, Significantly Reduces Glucose Excursions after an oGTT in Patients with Type 2 Diabetes” (2007) *Diabetes* Jun 2007

Supplement 1, 56: A156 (abstract) (Exhibit O-1) ::
American Diabetes Association 67th Scientific
Sessions (2007) Abstract No. 0588-P (Exhibit O-2)

- Thomas, *et al.*, “(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a Novel Xanthine-Based Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors” (2008) *The Journal of Pharmacology and Experimental Therapeutics* 325:175–82 (Exhibit P)
- Thomas *et al.*, “Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor BI 1356 [(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione] Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models” (2009) *The Journal of Pharmacology and Experimental Therapeutics* 328:556–63 (published on 1 February 2009) (Exhibit Q)
- Fiese and Hagen, “Preformulation”, in Lachman and Lieberman (eds), *The Theory and Practice of Industrial Pharmacy* (1987) (Exhibit R)
- WO 2006/117359 published on 9 November 2006 (Exhibit S)

Further, the Claims do not involve a technical advance. They therefore do not involve an inventive step and ought to be

rejected under section 2(1)(ja) read with section 25(1)(e) of the Patents Act.

- (iv) Claims 1 to 14 and 16 to 20 are hit by section 3(d), which prohibits the patenting of new forms of known substances, unless they exhibit significant enhanced efficacy. The Patent Applicant has not demonstrated significant enhanced efficacy for the claimed composition or dosage form or the various limitations. Therefore, Claims 1 to 14 and 16 to 20 ought to be rejected under section 3(d) read with section 25(1)(f) of the Patents Act.
- (v) Claims 1 to 14 and 16 to 20 are hit by section 3(e), which prohibits the patenting of mere admixture of two or more substances that results only in the aggregation of the properties of the components thereof. The Patent Applicant has not demonstrated any alleged synergistic effect for the claimed admixture. Further, Claim 15 which is a process claim is also hit by section 3(e). Therefore, Claims 1 to 20 ought to be rejected under section 3(e) read with section 25(1)(f) of the Patents Act.
- (vi) Claim 16 is essentially a claim related to a process of treating various conditions listed therein and achieving certain outcomes. Therefore, Claim 16 ought to be rejected under section 3(i) read with section 25(1)(f) of the Patents Act.
- (vii) Claims 17 to 20 of the present Application essentially claim human patients with certain conditions and, as such, are contrary to morality. They therefore ought to be rejected under section 3(b) read with section 25(1)(f) of the Patents Act.

- (viii) Claims 17 to 20 are directed to human patients with certain conditions and, as such, are not capable of industrial application. They therefore ought to be rejected under section 2(1)(j) and section 2(1)(ac) read with section 25(1)(f) of the Patents Act.
- (ix) Claims 16 to 20 are not supported by the Complete Specification and ought to be rejected under section 10 read with 25(1)(g) of the Patents Act.
39. The Opponent states that none of the claims of the Applicant should be deemed accepted, unless the same are specifically admitted / accepted herein, and that the Opponent opposes all the claims of the Applicant as amended on 29 January 2013.

VI.A. SECTION 25(1)(c): ANTICIPATION BY PRIOR CLAIMING

40. Section 25(1)(c) provides a ground of opposition on the ground that the claimed invention is claimed in a claim of complete specification filed in pursuance of an application for a patent in India and having a priority date earlier than that of the present application even though it may have been published on or after the priority date of the Applicant's claim.

Claims 1 to 14 of the present Application are anticipated by the claims of IN '1006

41. Indian Application No. 1006/DELNP/2010 (hereinafter referred to as "IN 1006") titled "Pharmaceutical composition comprising a glucopyranosyl-substituted benzene derivative" was published on 27 August 2010 but claims a priority of 16 August 2007. As such,

though published after the priority date of the Applicant's claim, it has an earlier priority date than that of the present Application. The bibliographic page and relevant extracts of the Complete Specification and claims of 'IN 1006, as retrieved from the website of the Indian Patent Office, are hereto annexed and marked as "**Exhibit A**". A tabular comparison of the claims of IN '1006 and the present Application is hereto annexed and marked as "**Exhibit B**".

Claim 1 and dependent Claims 2 to 7 and 11 to 12

42. The claims of IN '1006 are directed to a pharmaceutical composition of *linagliptin* or its pharmaceutically acceptable salt and *empagliflozin*, both generally and in an oral dosage form.
43. It is understood that a pharmaceutical composition would be a composition having ingredients of optimal particle size and particle size distribution.
44. The complete specification of IN '1006 states that the claimed pharmaceutical composition and dosage forms preferably comprise "*one or more pharmaceutically acceptable carriers which must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof*" [see 'IN 1006, internal page 44]. The complete specification further states that "*[t]ablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents*" [see 'IN 1006, internal page 44]. It also states that "*[e]xamples of pharmaceutically acceptable carriers are known to one skilled in the art*" [see 'IN 1006, internal page 45].

45. Claim 1 of '1006 claims a pharmaceutical composition comprising *empagliflozin* in combination with the DPP IV inhibitor or a pharmaceutically acceptable salt thereof wherein the amount of *empagliflozin* is from 5 mg to 50 mg. and wherein the amount of the DPP IV inhibitor is from 0.5 mg to 10 mg.
46. Therefore, Claim 1 of the present Application is anticipated by claim 1 of IN '1006. Dependent Claims 2 to 3 (relating to particle size distribution), Claims 4 to 7 (relating to a pharmaceutical composition comprising *linagliptin*, *empagliflozin* and excipients) and Claims 11 and 12 (preferred dosage strength) of the present Application are also anticipated by claim 1 of IN '1006 read with its complete specification.

Claims 8 to 10 (pharmaceutical dosage form)

47. The complete specification of IN '1006 states that the pharmaceutical compositions can be formulated for oral, rectal, nasal, topical, transdermal, vaginal or parenteral administration and sets some of these formulations out in further detail [see 'IN 1006, internal pages 39 and 44–45].
48. The complete specification of IN '1006 also states that “[t]he pharmaceutical composition may be formulated in the form of tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, -dry syrups, chewable tablets, troches, effervescent tablets, drops, suspension, fast dissolving tablets, oral fast-dispersing tablets, etc.” [see IN '1006, internal page 44]. It further states that “[t]he tablets may be coated according to methods well known in the art.” [see 'IN 1006, internal page 44].

49. Claim 1 of IN '1006 thus includes a pharmaceutical composition of *linagliptin*, *empagliflozin* and excipients in the form of granules, capsules, tablets and film-coated tablets as well as all pharmaceutical dosage forms, including solid pharmaceutical dosage forms. Claim 2 of IN '1006 relates to a pharmaceutical composition claimed in claim 1 thereof wherein the two active ingredients are present in a single dosage form. Claim 8 of IN '1006 relates to a pharmaceutical composition formulated for oral administration in solid form.
50. Therefore, Claim 8 (pharmaceutical composition in the form of a granulate, capsule, tablet or film-coated tablet), Claim 9 (pharmaceutical dosage form) and Claim 10 (solid pharmaceutical dosage form, in particular a capsule or tablet) of the present Application are anticipated by claims 1, 2 and 8 of IN '1006.

Claims 11 to 12 (dosage strength)

51. In addition to the above and without prejudice to the above contention, a substantial part of the limitations relating to the dosage strength are anticipated by the claims of 'IN 1006.
52. Claim 1 of 'IN 1006 claims a pharmaceutical composition of *linagliptin* and *empagliflozin*, wherein the amount of *linagliptin* is 0.5 mg to 10 mg. Claims 6 and 7 of 'IN 1006 claim a pharmaceutical composition of *linagliptin* and *empagliflozin*, wherein the amount of *linagliptin* is 1 mg to 5 mg (claim 6) and 5 mg (claim 7) respectively. To the extent that Claim 11 (0.1 to 30 mg of *linagliptin* or its pharmaceutically acceptable salt) of the present Application claims a pharmaceutical dosage form

comprising 0.5 to 10 mg of *linagliptin*, it is anticipated by claims 1, 6 and 7 of 'IN 1006.

53. Claim 1 of 'IN 1006 claims a pharmaceutical composition of *linagliptin* and *empagliflozin*, wherein the amount of *empagliflozin* is from 5 mg to 50 mg. Claim 3 (5, 10, 15, 20, 25 or 50 mg), claim 4 (10 mg) and claim 5 (25 mg) of 'IN 1006 claim some further specific amounts of *empagliflozin*. To the extent that Claim 12 (0.5 to 100 mg of *empagliflozin*) of the present Application claims a pharmaceutical dosage form comprising 5 mg to 50 mg of *empagliflozin*, it is anticipated by claims 1, 3, 4 and 5 of 'IN 1006.

Claims 13 to 14 (properties)

54. Because Claim 1 and Claims 9 to 12 are anticipated, Claims 13 and 14 which describe their properties in terms of dissolution test results and disintegration test results respectively are inherently anticipated.

Summary

55. For the aforementioned reasons, the claims of IN '1006 anticipate Claims 1 to 14 of the present Application by prior claiming.

Claims 1 to 11, 13, 14 and 16 of the present Application are anticipated by the claims of IN '4811

56. Additionally, the claims of the present Application are anticipated by the claims of Indian Application No. 4811/DELNP/2011 (hereinafter referred to as "IN '4811") titled "Salt forms of organic

compound” which was published on 27 September 2013 but claims a priority date of 23 December 2008. The bibliographic page and relevant extracts of the complete specification and claims of IN ’4811, as retrieved from the website of the Indian Patent Office, are hereto annexed and marked as hereto annexed and marked as **“Exhibit C”**. A tabular comparison of the claims of IN ’4811 and the present Application is hereto annexed and marked as **“Exhibit D”**.

57. IN ’4811 discloses and claims salt forms of *linagliptin* and its combination with other anti-diabetic drugs, including SGLT2 inhibitors by means of which improved treatment results can be obtained [*see* IN ’4811, internal pages 10 and 17 to 18, claims 9 to 11]. It discloses that the dosage form of such a pharmaceutical composition would contain excipients such as diluents, fillers, binders, carriers, lubricants, disintegrants, glidants and / or coating agents and discloses that the preferred form would be a tablet [*see* IN ’4811, internal pages 10 and 12 to 16].
58. Therefore, Claim 1 (pharmaceutical composition) and dependent Claims 2 and 3 (particle size limitation), dependent Claims 4 to 6 (pharmaceutical composition with excipients), Claim 7 (percentage by weight) and Claims 8 to 10 (pharmaceutical dosage form) of the present Application, to the extent that they claim pharmaceutical compositions comprising the salt forms of *linagliptin*, are anticipated by claims 9 to 11 of IN ’4811 read in light of the disclosures of the complete specification thereof.
59. Further, the complete specification of IN ’4811 discloses the preferred dosage strength range for *linagliptin* of 0.1 to 100 mg,

more preferably 0.5 mg to 10 mg or 2.5 to 10 mg or 1 mg to 5 mg per patient per day and preferred dosage strengths of 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg [*see* IN '4811, internal pages 16 to 17]. Claims 9 to 11 of IN '4811 thus cover pharmaceutical compositions of *linagliptin*, including those involving combinations with SGLT2 inhibitors where *linagliptin* is in an amount of 0.1 to 100 mg. Therefore, Claim 11 (0.1 to 30 mg of *linagliptin* or its pharmaceutically acceptable salt) of the present Application is anticipated by the claims 9 to 11 of IN '4811 read in light of the disclosures of the complete specification thereof.

60. With respect to the diseases or conditions to be treated, IN '4811 discloses that the salt form of *linagliptin* can be used for treatment and / or prevention of metabolic diseases, particularly diabetes type 2 mellitus and lists several other treatment outcomes such as preventing or slowing down progression of metabolic disorder, improving glycaemic control, etc [*see* IN '4811, internal pages 10 to 11]. This is very similar, if not identical, to the list of diseases and conditions that can be treated and / or prevented by the present Application. Therefore, Claim 16 (pharmaceutical composition for manufacture of medicament to treatment to treat various conditions that are listed therein and to achieve certain outcomes in a patient) is anticipated by claim 12 of IN '4811 read in light of the disclosures of the complete specification thereof.
61. Because Claim 1 and Claims 9 to 11 are anticipated, Claims 13 and 14 which describe their properties in terms of dissolution test results and disintegration test results respectively are inherently anticipated.

62. For the aforementioned reasons, the claims of IN '4811 anticipate Claims 1 to 11, 13, 14 and 16 of the present Application by prior claiming.

Conclusion

63. As set out above, Claims 1 to 14 and 16 of the present Application are anticipated by prior claiming by the claims of either IN '1006 or IN '4811 and ought to be rejected under section 25(1)(c) of the Patents Act.

VI.B. SECTION 25(1)(b): NOT NEW AND ANTICIPATION BY PRIOR PUBLICATION

64. Section 25(1)(b) provides a ground of opposition on the ground, *inter alia*, that the invention so far as claimed in a claim of complete specification has been published before the priority date of the claim in India or elsewhere, in any other document.

Claims 1 to 10, 12 to 14 and 16 are not new and are anticipated by the disclosures of IN '4844

65. The claims of the present Application are anticipated by publication by the disclosures of WO 2005/092877 (hereinafter referred to as "WO '877"), titled "Glucopyranosyl-substituted benzol derivatives, drugs containing said compounds, the use thereof and method for the production thereof" which was published on 6 October 2005. Because WO '877 is in German, reference is being made to its Indian national phase equivalent, i.e. Indian Application No. 4844/DELNP/2006 published on 10 August 2007 (hereinafter referred to as "IN '4844"), which was granted a

patent in India, being IN 268846, on 18 September 2015. The bibliographic page, relevant extracts of the Complete Specification, claims as originally filed and claims as filed on 22 May 2015 (also referred to in the Controller's decisions dated 18 September 2015) of 'IN 4844, as retrieved from the website of the Indian Patent Office, are hereto annexed and marked are hereto annexed and marked as "**Exhibit E**".

66. IN '4844 discloses SGLT-2 inhibitors, more particularly glucopyranosyl-substituted benzene compounds of formula I, including 1-Chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, i.e. *empagliflozin* [see IN '4844, internal pages 1 to 8 and page 29 and granted claim 5].
67. IN '4844 further states that the SGLT-2 inhibitors may be used in conjunction with other substances, particularly for the treatment and/or prevention of diseases and conditions including metabolic disorders or conditions such as type-1 and type-2 diabetes mellitus and complications of diabetes and obesity [see IN '4844, internal page 47 and granted claim 9]. The therapeutic agents listed include DPPIV inhibitors; of these, LAF237, i.e. *vildagliptin*, and MK-431, i.e. *sitagliptin*, are specifically mentioned [see IN '4844, internal pages 47 to 48].
68. IN '4844 discloses a pharmaceutical composition comprising the claimed SGLT2-inhibitors and the second active substance, including DPPIV inhibitors to treat or prevent diseases or conditions which can be affected by inhibiting SGLT, particularly metabolic diseases such as diabetes or diabetes complications [see IN '4844, internal page 49]. It claims *empagliflozin* as and when

used in preparation of a pharmaceutical composition [*see* IN '4844, claim 6] together with at least one anti-diabetic agent including DPPIV inhibitors [*see* IN '4844, granted claims 7 and 8].

69. IN '4844 also discloses that the use of the claimed SGLT2 inhibitor in combination with the other active substance, including DPPIV inhibitors, could take place simultaneously or at staggered times [*see* IN '4844, internal page 49]. The two substances could be present together in one formulation, for example a tablet [*see* IN '4844, internal page 49].
70. It further discloses pharmaceutical composition of such a combination optionally with one or more inert carriers or diluents [*see* IN '4844, internal page 49].
71. Thus, IN '4844 discloses a pharmaceutical composition comprising *empagliflozin* and DPPIV inhibitors. As of the priority date, *linagliptin* was already known as a DPPIV inhibitor. It formed part of the common general knowledge relating to DPPIV inhibitors of the person skilled in the art.
72. Therefore, as of the priority date, IN '4844 disclosed a pharmaceutical composition of *empagliflozin*, *linagliptin* and other inert carriers known to persons skilled in the art. Such a pharmaceutical composition would also necessarily include all possible particle sizes and particle size distribution ranges of the active ingredients.
73. Therefore, Claim 1 (pharmaceutical composition) and dependent Claims 2 and 3 (particle size limitation), dependent Claims 4 to 6 (pharmaceutical composition with excipients), Claim 7 (percentage

by weight) and Claims 8 to 10 (pharmaceutical dosage form) of the present Application are anticipated by the disclosures of IN '4844.

74. Additionally, IN '4844 discloses that the dosage of the compounds of formula I, including *empagliflozin* may be from 1 to 100 mg [*see* IN '4844, internal page 47]. Therefore, Claim 12 of the present Application is anticipated by the disclosures of IN '4844.
75. Because Claim 1 and Claims 9, 10 and 12 are anticipated, Claims 13 and 14 which describe their properties in terms of dissolution test results and disintegration test results respectively are inherently anticipated.
76. With respect to the diseases or conditions that may be treated, IN '4844 discloses several diseases and conditions that can be treated or prevented by the claimed SGLT2 inhibitors (including *empagliflozin*) and a combination of the SGLT2 inhibitors with other compounds, (including DPPIV inhibitors) which could treat and / or prevent the same listed diseases and conditions [*see* IN '4844, internal pages 46 to 48]. This is similar to the list of diseases and conditions that can be treated and / or prevented by the present Application. Therefore, Claim 16 of the present Application (pharmaceutical composition for manufacture of medicament to treatment to treat various conditions that are listed therein and to achieve certain outcomes in a patient) is anticipated by the disclosures of IN '4844.
77. For the aforementioned reasons, the disclosures of IN '4844 anticipate Claims 1 to 10, 12 to 14 and 16 by prior publication.

Claims 1 to 10, 12 to 14 and 16 are not new and are anticipated by the disclosures of WO '610

78. The Claims of the present Application are also anticipated by the disclosures of WO 2007/093610.
79. WO 2007/093610 (hereinafter referred to as “WO '610”) titled “Glucopyranosyl-substituted benzonitrile derivatives, pharmaceutical compositions containing such compounds, their use and process for their manufacture”, which was published on 23 August 2007, too similarly anticipates the Claims of the present Application. WO '610 are hereto annexed and marked as “**Exhibit F**”.
80. WO '610 discloses glucopyranosyl-substituted benzene compounds, including *empagliflozin* [see WO '610, internal pages 1 and 37, Example XIV(2)]. It describes the derivatives as being useful for the treatment and/or prevention of diseases and conditions including those that can be influenced by inhibiting SGLT2, metabolic disorders and preventing degeneration of pancreatic beta cells and / or for improving and / or restoring the functionality of pancreatic beta cells [see WO '610, internal pages 3 to 4].
81. WO '610 further states that the SGLT2 inhibitors may be used in conjunction with other substances, particularly for the treatment and/or prevention of diseases and conditions including metabolic disorders or conditions such as type-1 and type-2 diabetes mellitus and complications of diabetes and obesity [see WO '610, internal pages 23 to 27]. The therapeutic agents listed include DPPIV inhibitors; of these, LAF237, i.e. *vildagliptin*, and MK-431, i.e.

sitagliptin are specifically mentioned [see WO '610, internal page 26].

82. WO '610 discloses a pharmaceutical composition comprising the claimed SGLT2-inhibitors and the second active substance, including DPPIV inhibitors, to treat or prevent diseases or conditions, particularly metabolic diseases such as diabetes or diabetes complications [see WO '610, internal pages 25 to 26].
83. WO '610 also discloses that the use of the claimed SGLT2 inhibitor in combination with the other active substance, including DPPIV inhibitors, could take place simultaneously or at staggered times [see WO '610, internal page 27]. The two substances would be present together in one formulation, for example a tablet [see WO '610, internal page 27]. It further discloses pharmaceutical composition of such a combination optionally with one or more inert carriers or diluents [see WO '610, internal page 27].
84. Thus, WO '610 discloses a pharmaceutical composition comprising *empagliflozin* and DPPIV inhibitors. As of the priority date, *linagliptin* was already known as a DPPIV inhibitor. It formed part of the common general knowledge relating to DPPIV inhibitors of the person skilled in the art.
85. Therefore, as of the priority date, WO '610 disclosed a pharmaceutical composition of *empagliflozin*, *linagliptin* and other inert carriers known to persons skilled in the art. Such a pharmaceutical composition would also necessarily include all possible particle sizes and particle size distribution ranges of the active ingredients.

86. Therefore, Claim 1 (pharmaceutical composition) and dependent Claims 2 and 3 (particle size limitation), dependent Claims 4 to 6 (pharmaceutical composition with excipients), Claim 7 (percentage by weight) and Claims 8 to 10 (pharmaceutical dosage form) of the present Application are anticipated by the disclosures of WO '610.
87. Additionally, WO '610 discloses that the dosage of the compounds of formula I, including *empagliflozin* may be from 1 to 100 mg [*see* WO '610, internal page 25]. Therefore, Claim 12 of the present Application is anticipated by the disclosures of WO '610.
88. Because Claim 1 and Claims 9, 10 and 12 are anticipated, Claims 13 and 14 which describe their properties in terms of dissolution test results and disintegration test results respectively are inherently anticipated.
89. With respect to the diseases or conditions that may be treated, WO '610 discloses several diseases and conditions that can be treated or prevented by the claimed SGLT2 inhibitors (including *empagliflozin*) and a combination of the SGLT2 inhibitors with other compounds, (including DPPIV inhibitors) which could treat and / or prevent the same listed diseases and conditions [*see* WO '610, internal pages 24 to 25]. This is similar to the list of diseases and conditions that can be treated and / or prevented by the present Application. Therefore, Claim 16 of the present Application (pharmaceutical composition for manufacture of medicament to treatment to treat various conditions that are listed therein and to achieve certain outcomes in a patient) is anticipated by the disclosures of WO '610.

90. For the aforementioned reasons, the disclosures of WO '610 anticipate Claims 1 to 10, 12 to 14 and 16 by prior publication.

Conclusion

91. As set out above, Claims 1 to 10, 12 to 14 and 16 of the present Application are anticipated by prior publication by the disclosures of either IN '4844 or WO '610 and ought to be rejected under section 2(1)(j) read with section 25(1)(b) of the Patents Act.

VI.C. SECTION 25(1)(e): LACK OF INVENTIVE STEP

92. Section 25(1)(e) provides a ground of opposition on the ground that the invention so far is claimed in a claim of complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published, *inter alia*, in India or elsewhere in any other document.
93. Section 2(1)(ja) defines inventive step thus: “‘inventive step’ means a feature of an invention that involves technical advance as compared to existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art” (emphasis supplied).
94. Thus, to possess inventive step, the invention must have a feature that (i) involves technical advance as compared to existing knowledge and (ii) is not obvious to a person skilled in the art. It is an established position of law that both these elements set out in the definition of “inventive step” have to be satisfied.

95. As shown below, the Claims of the present Application are obvious to a person skilled in the art. Further, they do not involve any technical advance.

Linagliptin and its pharmaceutical composition were known

96. It is an admitted position that *linagliptin*, methods of manufacture thereof [see Complete Specification, internal page 18], its preferred crystalline forms [see Complete Specification, internal pages 18 and 34] and its pharmaceutical compositions [see Complete Specification, internal page 2] were known.
97. In WO 2007/128724 (hereinafter referred to as WO '724"), titled "DPP IV inhibitor formulations" and published on 15 November 2007, a copy of which is hereto annexed and marked as "**Exhibit G**", the Patent Applicant sets out the alleged problem of incompatibilities and degradation faced by DPPIV inhibitors with primary or secondary amino groups, including *linagliptin* [see WO '724, internal page 1]. WO '724 discloses the choice of excipients—a first and second diluent, a binder, a disintegrant and further second disintegrant, a lubricant and an optional glidant—and sets out preferred excipients to solve this alleged problem [see WO '724, internal pages 1 to 3 and 10 to 17 (examples 1 to 6)]. The examples also set out the dosage of active ingredient 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg [see WO '724, internal pages 10 to 17 (examples 1 to 6)] and provide an example of a high dose formulation too [see WO '724, internal page 17 (example 6.3)].
98. Thus, as of the priority date, *linagliptin* and its pharmaceutical composition comprising preferred excipients to overcome the alleged problems of degradation and incompatibilities were known.

Empagliflozin was known

99. It is an admitted position that *empagliflozin* and its preferred crystalline forms were known [see Complete Specification, internal pages 2 and 18 to 20].
100. As stated earlier, WO '877 and its Indian equivalent IN '4844 disclose *empagliflozin* [see IN '4844 (Exhibit E above), internal pages 1 to 8, 29 (compound 3) and granted claim 5]. IN '4844 discloses (i) the SGLT2 inhibiting effect of the compounds claimed, including *empagliflozin* [see IN '4844, internal page 7] and (ii) the use of the claimed compounds for treatment and / or prevention of diseases or conditions which could be influenced by inhibiting the sodium-dependent cotransporter SGLT, particularly SGLT2, and for treatment of metabolic disorders [see IN '4844, internal pages 7 and 46].

Combination of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, was known

101. As shown below, combinations of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, were known in the art as of the priority date.
102. Patent documents such as WO 2005/085246 titled "8-[3-amino-piperidin-1-yl]-xanthine, the production thereof and the use in the form of a DPP inhibitor" (published on 15 September 2005) and US Publication No. 2006/0079541 titled "3-methyl-7-butyryl-xanthines, the preparation thereof and their use as pharmaceutical compositions" (published on 13 April 2006) (equivalent of WO 2006/029769 published on 23 March 2006) disclose DPPIV inhibitors and their combination with SGLT2 inhibitors.

103. WO 2006/078593 (hereinafter referred to as “WO ’593”), titled “Direct compression formulation and process” published on 27 July 2006, is hereto annexed and marked as “**Exhibit H**”, discloses an oral tablet formulation of vildagliptin in the form of a tablet. It also discloses a combination of DPPIV inhibitors with other therapeutic agents [*see* WO ’593, internal pages 49 to 50] as well as excipients such as diluents, disintegrants, lubricants, diluents, fillers, binders [*see* WO ’593, internal pages 16 to 18].
104. The rationale for combining different drugs was well-known. For example, WO 2007/033350 (hereinafter referred to as “WO ’350”), titled “Dipeptidyl peptidase inhibitors for treating diabetes” and published on 22 March 2007, is hereto annexed and marked as “**Exhibit I**” discloses some such reasons. WO ’350 disclosed pharmaceutical compositions comprising a DPPIV inhibitor (referred to as “Compound I”) and other anti-diabetic compounds [*see* WO ’350, internal pages 4 to 8]. It stated that the combinations provide excellent effects such as (i) enhancement in therapeutic effects of either of Compound I and / or the anti-diabetic compounds, (ii) reduction in side-effects of Compound I and / or the anti-diabetic compounds and (iii) reduction in dose of Compound I and / or the anti-diabetic compounds [*see* WO ’350, internal page 4]. These reflect the benefits that were expected to arise out of a combination of different active ingredients.
105. Thus, the combination of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, and the rationale for such combination was known in the art.

Combination of linagliptin with other anti-diabetic drugs, including SGLT2 inhibitors, was known

106. More specifically, the combination of *linagliptin* with other anti-diabetic drugs, including SGLT-2 inhibitors, was also known in the art.
107. For example, WO 2002/068420, titled “Xanthine derivative, production and use thereof as a medicament” and published on 6 September 2002, discloses xanthine compounds as DPP-IV inhibitors and their combinations. Because this patent document is in German, reference is being made to its Indian national phase equivalent, i.e. 01092/DELNP/2003 (hereinafter referred to as “IN ’1092”) titled “Xanthine derivatives, the preparation thereof and their use as pharmaceutical compositions” which was published on 12 January 2007. The bibliographic page and relevant extracts of the complete specification and claims of IN ’1092, as retrieved from the website of the Indian Patent Office, are hereto annexed and marked are hereto annexed and marked as “**Exhibit J**”. IN ’1092 discloses xanthine compounds as DPP-IV inhibitors [*see* IN ’1092, internal page 1] and also discloses a combination of DPP-IV inhibitors with other antidiabetic drugs [*see* IN ’1092, internal pages 101 to 102]. It discloses a dosage of DPP-IV inhibitors of 1 to 100 mg [*see* IN ’1092, internal page 102] and also examples of compositions of DPP-IV inhibitors in different dosage forms [*see* IN ’1092, internal pages 282 to 287].
108. WO 2004/018468, titled “8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments” and published on 4 March 2004, discloses xanthine compounds as

DPPIV inhibitors, including *linagliptin*, and also its combination with other anti-diabetic drugs. Because this patent document is in German, reference is being made to its Indian national phase equivalent, i.e. 567/DELNP/2005 (hereinafter referred to as “IN ’567”), titled 8-[3-amino-piperidin-1-yl]-xanthine compounds” which was published on 23 January 2009. The bibliographic page and relevant extracts of the complete specification and claims of IN ’567, as retrieved from the website of the Indian Patent Office, are hereto annexed and marked as hereto annexed and marked as **“Exhibit K”**. Its divisional application, i.e. IN 6108/DELNP/2007, makes similar disclosures and is not included herein for the sake of brevity. IN ’567 discloses (i) xanthine compounds having valuable pharmacological properties—particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase—including *linagliptin* and their compositions, (ii) the combination of DPPIV inhibitors with other anti-diabetic drugs and (iii) their use in various disorders [see IN ’567, internal pages 1, 26 (compound 13), 37 to 38, page 161 (example 2(142) and claims]. It also discloses the dosage range of 1 to 100 mg for oral administration [see IN ’567, internal page 38] and examples of compositions of DPPIV inhibitors in different dosage forms [see IN ’567, internal pages 189 to 193]. Thus, IN ’567 discloses a combination of *linagliptin* with other antidiabetic drugs.

109. US Publication No. 2004/097510 titled “8-[3-amino-piperidin-1-yl]-xanthines, the preparation thereof and their use as pharmaceutical compositions” (hereinafter referred to as “US ’510”) and published on 20 May 2004, makes disclosures similar to that of IN ’567.

110. US Publication No. 2007/0281940 (hereinafter referred to as “US ’940”), titled “Use of DPP-IV inhibitors” and published on 6 December 2007, a copy of which is hereto annexed and marked as “**Exhibit L**”, describes the use of selected DPP IV inhibitors, including *linagliptin* which is identified as a preferred compound, for the treatment of physiological functional disorders including diabetes and obesity and for reducing the risk of the occurrence of such functional disorders in at-risk patient groups [*see* US ’940, title page and internal pages 2 to 3]. It describes the use of the DPP-IV inhibitors in combination with other active substances, including SGLT1 and SGLT2 inhibitors, for treating various disease conditions by means of which improved treatment outcomes can be achieved [*see* US ’940, internal page 5, para 0060 and 0061 and internal page 12, example 15]. More particularly, example 15 discloses the dosage ranges of both the DPP-IV inhibitor and SGLT-2 inhibitor and exemplifies how the appropriateness and effectiveness of a combination of DPP-IV inhibitor with an SGLT-2 inhibitor can be determined [*see* US ’940, internal page 12]. US ’940 also discloses excipients for the manufacture of compositions of DPP-IV inhibitors as well as methods for manufacture of dosage forms [*see* US ’940, internal pages 4 to 5]. Thus, a person skilled in the art would only have to engage in routine tests and experimentation to determine a preferred combination of DPP-IV inhibitor and SGLT-2 inhibitor.
111. Katsuno, *et al.* discusses the benefits of SGLT-2 inhibitors [*see* Katsuno, *et al.*, “Sergliflozin, a Novel Selective Inhibitor of Low-Affinity Sodium Glucose Cotransporter (SGLT2), Validates the Critical Role of SGLT2 in Renal Glucose Reabsorption and

Modulates Plasma Glucose Level” (2007) *The Journal of Pharmacology and Experimental Therapeutics* 320:323–30, a copy of which is hereto annexed and marked as “**Exhibit M**”]. They noted that sergliflozin, an SGLT2 inhibitor, had glucose-lowering effects by increasing urinary glucose excretion, without inducing hypoglycaemia or excessive insulin secretion. They also noted that these properties enabled SGLT-2 inhibitors to meet the suitable (*sic*) for blood glucose control with body weight control and preservation of insulin secretion. Katsuno, *et al.*, concluded that SGLT2 inhibitors offered advantages over existing anti-diabetic drugs and were a useful new category for treatment of diabetes:

“In this sense, SGLT2 inhibitors offers some advantages as antidiabetic drugs over existing antidiabetic drugs such as sulfonylureas, α -glucosidase inhibitors, thiazolidinediones, and biguanides. Our results with sergliflozin, a novel selective SGLT2 inhibitor developed by us, demonstrate that SGLT2 plays a major role in renal glucose reabsorption. We propose this SGLT2 inhibitor as a representative of a useful new category of drug for the treatment of diabetes mellitus.”
(emphasis supplied)

112. Thus, US '940 (Exhibit L) discloses a combination of DPP-IV inhibitors, including *linagliptin* as a preferred compound, and SGLT2 inhibitors. As shown below, *linagliptin* had already emerged as a preferred DPP-IV inhibitor. Katsuno, *et al.* (Exhibit M) too provides support for the choice of an SGLT2 inhibitor for a combination drug.

113. A person skilled in the art would only have to engage in routine tests and experimentation to determine an appropriate combination. The determination of an appropriate combination of preferred ingredients is thus obvious to a person skilled in the art. It also does not involve a technical advance.
114. Therefore, in light of the disclosures contained in IN '1092 (Exhibit J), IN '567 (Exhibit K) and / or US '940 (Exhibit L), supported by Katsuno, *et al.* (Exhibit M), the combination of *linagliptin* with other SGLT-2 inhibitors is obvious to a person skilled in the art and does not involve a technical advance.

Combination of empagliflozin with other anti-diabetic drugs, including DPPIV inhibitors, was known

115. As shown below, the combination of empagliflozin with other anti-diabetic drugs, including DPP-IV inhibitors, was also known as of the priority date.
116. WO 2008/055940 (hereinafter referred to as “WO '940”), titled “Combination therapy with SGLT-2 inhibitors and their pharmaceutical compositions” and published on 15 May 2008, relevant extracts of which are hereto annexed and marked as “**Exhibit N**”, discloses pharmaceutical compositions comprising one or more SGLT2 inhibitors, including *empagliflozin*, in combination with one or more therapeutic agents and the conditions that could be treated [*see* WO '940, internal pages 1, 5 to 7, 17 and 19]. It sets out that anti-diabetic drugs that have different mechanisms of action are suitable for combination treatment [*see* WO '940, internal page 2]. It discloses that the combination can be administered individually or as a single

pharmaceutical composition, such as a single dosage form [see WO '940, internal page 5]. WO '940 notes that the administration of the combination can have an additive or over additive effect [see WO '940, internal page 8]. It also discloses a dosage range of 1 to 100 mg for the SGLT-2 inhibitor [see WO '940, internal page 26].

117. As adverted to earlier, IN '4844 (Exhibit E) discloses that the SGLT-2 inhibitor compounds, including *empagliflozin*, can be used in conjunction with other active substances, including DPPIV inhibitors, particularly for treatment and / or prevention of diseases or conditions including metabolic disorders or conditions such as type-1 and type-2 diabetes mellitus and complications of diabetes and obesity [see IN '4844, internal pages 47 to 49 and granted claim 9]. It provides the rationale for such combination, i.e. a combination with active substances which can potentiate the therapeutic effect of the claimed SGLT inhibitor and / or which will allow its dosage to be reduced [see IN '4844, internal page 47]. Amongst the DPPIV inhibitors specifically listed are LAF 237, i.e. *vildagliptin*, and MK-431, i.e. *sitagliptin* [see IN '4844, internal pages 47 to 48].
118. IN '4844 discloses a pharmaceutical composition comprising the claimed SGLT-2 inhibitors and a second active substance, including DPPIV inhibitors, to treat or prevent diseases or conditions which could be affected by inhibiting SGLT, particularly metabolic diseases such as diabetes or diabetes complications [see IN '4844, internal page 49]. It also claims *empagliflozin* as and when used in preparation of a pharmaceutical composition [see IN '4844, granted claim 6] together with at least one anti-diabetic agent including DPPIV inhibitors [see IN '4844,

granted claims 7 and 8]. It discloses a composition optionally together with one or more inert “conventional” carriers and / or diluents [see IN '4844, internal pages 7, 8 and 47] as well as pharmaceutical composition of such a combination optionally with one or more inert carriers or diluents [see IN '4844, internal page 49].

119. IN '4844 also discloses that the use of the claimed SGLT-2 inhibitor in combination with the other active substance, including DPPIV inhibitors, could take place simultaneously or at staggered times [see IN '4844, internal page 49]. When used simultaneously, the two substances would be present together in one formulation, for example a tablet [see IN '4844, internal page 49].
120. Thus, IN '4844 discloses a pharmaceutical composition comprising *empagliflozin*, DPPIV inhibitors and other inert carriers known to persons skilled in the art. As of the priority date, *linagliptin* was already known as a DPPIV inhibitor.
121. As adverted to in the “Background” above, DPPIV inhibitors were a known class of promising drugs that allowed glycaemic control without the risk of hypoglycaemia or weight gain and were known to possess advantages over other anti-diabetic agents.
122. In 2007, Heise, *et al.*, reported the safety, pharmacokinetic and pharmacodynamic properties of BI-1356, i.e. *linagliptin* and conclude that it had the potential to be a best in class DPP-IV inhibitor [see Tim Heise, *et al.*, “Treatment with BI 1356, a Novel and Potent DPP-IV Inhibitor, Significantly Reduces Glucose Excursions after an oGTT in Patients with Type 2 Diabetes”, (2007) *Diabetes* Jun 2007 Supplement 1, 56: A156 (abstract) ::

American Diabetes Association 67th Scientific Sessions (2007) Abstract No. 0588-P, copies of which are hereto annexed and marked as “**Exhibit O-1**” and “**Exhibit O-2**” respectively].

123. In 2008, Thomas, *et al.* (hereinafter referred to as “Thomas, *et al.* (2008)”) provided data to show that BI 1356, i.e. *linagliptin*, inhibited DPPIV more effectively than *vildagliptin*, *sitagliptin*, *saxagliptin* and *alogliptin* and concluded that it had the potential to become a once-a-day DPPIV inhibitor for treatment of type 2 diabetes [see Thomas, *et al.*, “(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a Novel Xanthine-Based Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors” (2008) *The Journal of Pharmacology and Experimental Therapeutics* 325:175–82, a copy of which is hereto annexed and marked as “**Exhibit P**”).
124. Again, in early February 2009, Thomas, *et al.* (hereinafter referred to as “Thomas, *et al.* (2009)”) concluded that the effects on HbA1c and GLP-1 were superior to the short-acting DPP-4 inhibitor vildagliptin, demonstrating the potential of BI 1356 as a once daily treatment for type 2 diabetes at low therapeutic doses [see Thomas *et al.*, “Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor BI 1356 [(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione] Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models” (2009) *The Journal of Pharmacology and Experimental Therapeutics* 328:556–63

(published on 1 February 2009), a copy of which is hereto annexed and marked as “**Exhibit Q**”].

125. Thus, Heise, *et al.* (Exhibit O-1 and O-2), Thomas, *et al.* (2008) (Exhibit P) and / or Thomas, *et al.* (2009) (Exhibit Q) provide the incentive to choose *linagliptin* as the ideal and most preferred candidate for combination with *empagliflozin*.
126. A combination of *empagliflozin* and *linagliptin* would therefore have been obvious to a person skilled in the art reading WO '940 (Exhibit N) or IN '4844 (Exhibit E) together with Heise, *et al.* (Exhibit O), Thomas, *et al.* (2008) (Exhibit P) and / or Thomas, *et al.* (2009) (Exhibit Q).
127. In light of the above, Claim 1 is obvious to a person skilled in the art. It does not involve any technical advance. It therefore lacks inventive step.

Pharmaceutical composition and pharmaceutical dosage form

128. Claims 4 to 6 are dependent on Claim 1 and relate to a pharmaceutical composition as claimed in Claims 1, 2 or 3, wherein the excipients comprise (i) one or more diluents, (ii) one or more diluents and binders and (iii) one or more diluents, binders and disintegrants respectively. In the Complete Specification accompanying the present Application, the Patent Applicant sets out an alleged problem of providing a composition of *linagliptin* because of the problems of degradation and incompatibility with excipients. This is merely a paper tiger.
129. First, stability of drugs in a formulation is a *sine qua non* for drug formulation. It is routine to test for incompatibilities of an active

ingredient with excipients. Preformulation is a standard step in the drug development stage, where the reactivity of an active (drug) is ascertained by reacting it with various possible excipients to weed out incompatible excipients and select only the most stable excipients for further development of the formulation. During “Preformulation Stage”, all the possible physical and chemical interactions between the active(s) and the constituents (excipients) are determined through standard routine experiments. For instance, Fiese and Hagen, “Preformulation”, in Lachman and Lieberman (eds), *The Theory and Practice of Industrial Pharmacy* (3rd edition 1987), a copy of which is hereto annexed and marked as “**Exhibit R**”, note that once bulk drug stability is established, compatibility with excipients ought to be established and describe how such compatibility could be tested [*see* Fiese and Hagen, internal pages 171 to 196, *at* internal pages 173, 176 and 194]. They also note that, in addition to drug-excipient compatibility testing, hypothetical tablet formulations should be prepared and tested in the same stability protocol to check for incompatibilities in a multi-component formulation [*see* Fiese and Hagen, *at* internal page 194].

130. Second, in WO '724 (Exhibit G) the Patent Applicant sets out the same alleged problem faced by DPPIV inhibitors containing primary or secondary amino groups, including *linagliptin*, and discloses the choice of excipients to solve this alleged problem [*see* WO '724, internal pages 1 to 3]. The following preferred excipients are amongst those disclosed: mannitol and pregelatinized starch (preferred first diluent), pre-gelatinized starch and low-substituted hydroxypropylcellulose (preferred second

diluent and having additional binder properties), magnesium stearate (preferred lubricant), copovidone and pregelatinized starch (preferred binders), corn starch (preferred disintegrant) and colloidal silicon dioxide (optional glidant) [*see* WO '724, internal page 2]. In fact, the weight of the various excipients in the pharmaceutical composition of example 4 of WO '724 is similar to the examples set out in the Complete Specification accompanying the present Application.

131. The excipients and methods used for the manufacture of the claimed composition are all known in the art.
132. In light of (i) the routine experimentation involved in testing for incompatibilities while developing a drug, and more particularly its formulation or combination, (ii) the known excipients, and (iii) the disclosures contained in WO '724, Claims 4 to 6 (pharmaceutical composition with excipients) of the present Application are obvious to a person skilled in the art. Further, these claims do not involve a technical advance.
133. Claim 7 (percentage by weight) as well as Claims 8 to 10 (pharmaceutical dosage form) too are obvious to a person skilled in the art and do not involve a technical advance.
134. As Claim 1 and Claims 9 to 10 are obvious to a person skilled in the art, dependent Claims 13 and 14 which only describe their properties in terms of dissolution test results and disintegration test results too are obvious to a person skilled in the art. They do not involve any technical advance.

135. Therefore, Claims 4 to 10 and 13 and 14 are obvious to a person skilled in the art, do not involve a technical advance and lack inventive step.

Dosage of linagliptin

136. Claim 11 relates to the quantity of *linagliptin* or its pharmaceutically acceptable salt (0.1 to 30 mg) in the pharmaceutical dosage forms claimed in the previously recited claims.
137. WO '724 (Exhibit G) discloses the preferred dosage range for the claimed DPPIV inhibitors, including *linagliptin*, of 0.1 to 100 mg, with dosages of 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg being preferred [*see* WO '724, internal page 3 and examples 1 to 6].
138. Therefore, Claim 11 of the present Application is obvious to a person skilled in the art. Further, it does not involve a technical advance. Therefore, it lacks inventive step.

Dosage of empagliflozin

139. Claim 12 relates to the quantity of *empagliflozin* (0.5 to 100 mg) in the pharmaceutical dosage forms claimed in the previously recited claims.
140. IN '4844 (Exhibit E) discloses a dosage of the claimed compounds of (i) from 1 to 100 mg, preferably 1 to 30 mg, by intravenous route and (ii) from 1 to 1000 mg, preferably 1 to 100 mg, by oral route [*see* IN '4844, internal page 47].
141. WO 2006/117359 (hereinafter referred to as "WO '359"), titled "Crystalline form of 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-

tetrahydrofuran-3-yloxy)-benzyl]-benzene, a method for its preparation and the use thereof for preparing medicaments” and published on 9 November 2006, a copy of which is hereto annexed and marked as “**Exhibit S**”, discloses and claims allegedly advantageous crystalline forms of *empagliflozin* and discloses that the dosage may be from 1 to 100 mg [*see* WO ’359, internal page 12].

142. Therefore, Claim 12 of the present Application is obvious to a person skilled in the art. Further, it does not involve a technical advance. Therefore, it lacks inventive step.

Particle size

143. Reduced particle size of the components is known in the art of pharmaceutical formulation for improving dissolution profiles and achieving high content uniformity.
144. Such reduced particle size was also known for *vildagliptin*, another DPPIV inhibitor. WO ’593 (Exhibit H) discloses direct compression tablets of DPPIV inhibitors, more particularly vildagliptin. It discloses a preferred particle size distribution of less than 250 μm , more preferably between 10 to 250 μm or 50 to 150 μm [*see* WO ’593, internal pages 25 to 27].
145. WO ’359 (Exhibit S), which discloses and claims allegedly advantageous crystalline forms of *empagliflozin*, also note that uniform distribution of the medicament is important and that particle size can be reduced to ensure this [*see* WO ’359, internal page 2].

146. Thus, dependent Claims 2 and 3 relating to particle size and particle size distribution of *linagliptin* and *empagliflozin* are obvious to a person skilled in the art. They do not involve any technical advance. Therefore, they lack inventive step.

Diseases and conditions

147. With respect to the diseases or conditions that may be treated, IN '4844 (Exhibit E) discloses several diseases and conditions that can be treated or prevented by the claimed SGLT2 inhibitors (including *empagliflozin*) and a combination of the SGLT2 inhibitors with other compounds, (including DPPIV inhibitors) which could treat and / or prevent the same listed diseases and conditions [*see* IN '4844, internal pages 46 to 48]. This is similar to the list of diseases and conditions that can be treated and / or prevented by the present Application. Therefore, Claim 16, which relates to a pharmaceutical composition claimed in Claims 1 to 8 for manufacture of a medicament to treat various conditions that are listed therein and to achieve certain outcomes in a patient is obvious to a person skilled in the art in light of the disclosures of IN '4844.

148. WO '359 (Exhibit S) which discloses and claims allegedly advantageous crystalline forms of *empagliflozin* states that the compounds described in WO 2005/092877 have a valuable inhibitory effect on sodium-glucose cotransporter SGLT, particularly SGLT2 [*see* WO '359, internal page 1]. It lists the disease conditions that can be treated [*see* WO '359, internal pages 11 to 12]. This list is identical to the ones listed in the Complete Specification accompanying the present Application.

149. Thus, Claim 16 is obvious to a person skilled in the art. It does not involve a technical advance. Therefore, it lacks inventive step.

Conclusion

150. Thus, Claims 1 to 16 of the present Application lack inventive step because they are obvious to a person skilled in the art and do not involve a technical advance. They, therefore, ought to be rejected under section 2(1)(ja) read with section 25(1)(e) of the Patents Act.

VI.D. SECTION 25(1)(f): FAILURE TO MEET SECTION 3(d)

151. Section 25(1)(f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.

152. Section 3(d) provides that new forms of known substances are not patentable unless they exhibit an enhanced efficacy. The explanation to section 3(d) provides that this includes combinations of known substances.

153. It is an established position of law that “efficacy” in section 3(d) means therapeutic efficacy [(i) *Novartis AG v. Union of India and Others*, (2007) 4 MLJ 1153, at para 13; (ii) *Novartis AG v. Union of India and Others*, IPAB order dated 26 June 2009, at pages 154–58 and 187–88 and (iii) *Novartis AG v. Union of India and Others*, [2013] 13 SCR 148, at para 180]

154. It is also an established position of law that the burden of proof of showing enhanced efficacy, i.e. enhanced therapeutic efficacy, for

the claimed compound is on the patent applicant and that the proof of enhanced efficacy is to be part of the complete specification [*Novartis AG v. Union of India and Others*, (2007) 4 MLJ 1153, at para 13].

155. Admittedly, as of the priority date, both active ingredients—*linagliptin* and *empagliflozin*—as well as the excipients were known.
156. The efficacy of both *linagliptin* and *empagliflozin* were also known.
157. In 2007, Heise, *et al.* (Exhibit O-1 and O-2) reported the safety, pharmacokinetic and pharmacodynamic properties of *linagliptin*. They reported (i) an absence of cases of hypoglycaemia, (ii) reduced plasma DPP-IV activity that was well correlated with plasma concentrations of *linagliptin*, (iii) reduced DPP activity by 80% two hours after administration of 2.5 mg of *linagliptin* which remained at that level at steady state, (iv) more than two-fold increased levels of GLP-1 and (v) reduced area under the plasma glucose excursions on day 13. They concluded that, 24 hours after the last dose, DPP-IV inhibition was greater than 70 percent after administration of 1 mg of BI 1356.
158. The abstract of Wang, Y., *et al.*, “BI-1356”, *Drugs of the Future*, 2008, 33(6): 473, a copy of which is hereto annexed and marked as “**Exhibit T**”, disclosed that treatment with BI-1356 (i) demonstrated long-lasting DPP-IV inhibition, (ii) increased concentrations of GLP-1 and reduced concentrations of glucose in patients with type 2 diabetes and (iii) significantly reduced Hb1Ac in diabetic patients.

159. Thomas, *et al.* (2008) (Exhibit P) also provided data to show that BI 1356, i.e. *linagliptin*, inhibited DPPIV more effectively than *vildagliptin*, *sitagliptin*, *saxagliptin* and *alogliptin* and had the potential to become a once-a-day DPPIV inhibitor for treatment of type 2 diabetes.
160. Additionally, Thomas, *et al.* (2009) (Exhibit Q) reported results in two different animal models and found that multiple dosing of *linagliptin* led to sustained increase in basal levels of active GLP-1 in the systemic circulation and also lowered HbA1c.
161. Thus, the DPPIV inhibiting activity of *linagliptin*, its effect of increasing active GLP-1 levels as well as its effect of lowering HbA1c were known.
162. Further, the efficacy of *empagliflozin* was known.
163. WO '359 (Exhibit S) disclosed glucopyranosyl-substituted benzene derivatives and allegedly advantageous crystalline forms of *empagliflozin*. It stated that the compounds described in WO 2005/092877 have a valuable inhibitory effect on sodium-glucose cotransporter SGLT, particularly SGLT2 [*see* WO '359, internal page 1]. It admitted that the compound A, i.e. *empagliflozin*, has pharmaceutical efficacy and proceeded to provide an allegedly advantageous crystalline form [WO '359, internal page 4, lines 5 to 7]. Thus, *empagliflozin* is a known substance with known efficacy. More particularly, this efficacy has been admitted to by the Patent Applicant itself in a publication as early as November 2006.
164. The Complete Specification accompanying the present Application does not allege an enhanced efficacy for the composition comprising *linagliptin* and *empagliflozin* over the known efficacy

of DPP-IV-inhibiting activity of *linagliptin* or SGLT2 inhibiting activity of *empagliflozin*.

165. Indeed, the Complete Specification admits that the two active ingredients may be administered together or alternately with the same result. It states:

“A monotherapy using a DPP IV inhibitor is not independent from the insulin secretory capacity or the insulin sensitivity of a patient. On the other hand, a treatment with the administration of a SGLT2 inhibitor does not depend on the insulin secretory capacity or the insulin sensitivity of the patient. Therefore, any patient independent of the prevailing insulin levels or insulin resistance and/or hyperinsulinemia may benefit from a therapy using a pharmaceutical composition and a pharmaceutical dosage combination according to this invention. *Independent of their prevailing insulin levels or their insulin resistance or hyperinsulinemia these patients can still be treated with a pharmaceutical composition and a pharmaceutical dosage because of the combined or alternate administration of the SGLT2 inhibitor.*” (emphasis supplied) [see Complete Specification, internal page 48]

166. This is also borne out by the Patent Applicant’s averment that a pharmaceutical dosage form according to the first embodiment of the invention comprises only *linagliptin* [see Complete Specification, internal page 37].

167. The Complete Specification states that “[t]he pharmaceutical composition and pharmaceutical dosage form according to this invention exhibit a very good efficacy with regard to glycaemic control, in particular in view of a reduction of fasting plasma glucose, postprandial plasma glucose and/or glycosylated hemoglobin (HbA1c)” [see Complete Specification, internal page 49].
168. Even if this is to be taken into account, at most, the Complete Specification provides data for only one pharmacological example to show an alleged glucose excursion effect for the combination against a control, *linagliptin* alone and *empagliflozin* alone [see Complete Specification, internal pages 54 to 55].
169. The Patent Applicant has not shown significantly enhanced efficacy for *linagliptin* or *empagliflozin* or the claimed combination. Further, the Patent Applicant has not shown significantly enhanced efficacy for the combination over simultaneous or sequential administration of the known active ingredients. Therefore, the Patent Applicant has failed to discharge the burden of showing enhanced therapeutic efficacy for the claimed composition.
170. The Patent Applicant has also not shown any enhanced therapeutic efficacy for the any of the claim limitations claimed in Claims 2 to 14 or 16 to 20.
171. Therefore, Claim 1 and all dependent claims, i.e. Claims 1 to 14 and 16 to 20, fail the test of section 3(d) and ought to be rejected under section 3(d) read with section 25(1)(f) of the Patents Act.

VI.E. SECTION 25(1)(f): FAILURE TO MEET SECTION 3(e)

172. Section 25(1)(f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.
173. Section 3(e) provides that a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance are not inventions within the meaning of the Patents Act.
174. All the ingredients of the claimed pharmaceutical composition are admittedly known substances.
175. Claim 1 relates to a mere admixture of known substances resulting only in the aggregation of the properties of the components thereof.
176. Indeed, the Patent Applicant itself admits that because of the independence of the SGLT2 inhibitor from the insulin levels or insulin resistance of patients, patients can “*still be treated with a pharmaceutical composition and a pharmaceutical dosage because of the combined or alternate administration of the SGLT2 inhibitor*” [see Complete Specification, internal page 48].
177. Indeed, in various previous patent applications, the Patent Applicant itself has referred to the combined, simultaneous and sequential or staggered use of the combination of a DPP-IV inhibitor and an SGLT2 inhibitor.
178. For instance, in IN '4844 (Exhibit E) the Patent Applicant discloses that (i) the SGLT2 inhibitors disclosed therein may be used with other active substances including anti diabetic agents, such as DPPIV inhibitors [see IN '4844, internal pages 47 to 48], (ii) that

the administration of the combination may take place simultaneously or at staggered times [*see* IN '4844, page 49] and (iii) that the compound and the additional active substance may be present together in one formulation [*see* IN '4844, page 49].

179. In another admission, the Patent Applicant in IN '1006 (Exhibit A) states that the glucopyranosyl-substituted benzene derivative, i.e. *empagliflozin*, and the DPPIV inhibitor can be administered in combination, i.e. simultaneously, or in alteration [*see* IN '1006, internal pages 38, 42 and 43]. It further states that with regard to administration, both active ingredients may be present either in a single dosage form or a separate dosage form [*see* IN '1006, internal pages 42 to 43]. Pertinently, it also states that “[*t*]he effects mentioned above are observed both, when the glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor are administered in combination, for example simultaneously, and when they are administered in alternation, for example successively in separate formulations” [*see* IN '1006, internal page 38].
180. While IN '1006 was published after the priority date of the present Application, it is nonetheless indicative of the Patent Applicant's own admission with respect to the various ways in which the two drugs can be administered as a combination and as to the effect of the alternate and simultaneous administration of the two drugs.
181. Given the disclosures in IN '4844, the combination of the two active ingredients—*linagliptin* and *empagliflozin*—is known and their administration for combined use, simultaneous use and sequential use is known.

182. The pharmaceutical composition claimed in the present Application is a single composition, more particularly an oral dosage form, combining both the active ingredients. In the Complete Specification, there is no comparative data to show that this claimed composition provides improved results than when the two active ingredients are administered simultaneously or sequentially.
183. Example I only provides data to show an alleged increase in glucose excursion for a combination against a control, *linagliptin* alone and *empagliflozin* alone. The comparison in the data is to the individual compounds administered alone. There is no comparison with the simultaneous or sequential administration of the two active ingredients.
184. Apart from this data relating to glucose excursion, the Complete Specification does not provide any other data to claim any other effect.
185. With respect to the data relating to glucose excursion, there is only an additive effect for the claimed composition which is a mere admixture resulting only in the aggregation of the properties of the components thereof.
186. Therefore, the Patent Applicant has failed to show synergistic effect for the claimed composition. As Claim 1 relates to a mere admixture of two or more substances that results only in the aggregation of the properties of the components thereof, it fails the test of section 3(e).

187. Further, the Patent Applicant has not shown any synergistic effect for any of the claim limitations claimed in Claims 2 to 14 or 16 to 20.
188. Claim 15 relates to a process for producing a pharmaceutical composition that is a mere admixture. Therefore, it too fails the test of section 3(e).
189. Summarily, Claims 1 to 20 fail the test of section 3(e) and therefore ought to be rejected under section 3(e) read with section 25(1)(f) of the Patents Act.

VI.F. SECTION 25(1)(f): METHOD OF TREATMENT CLAIMS DISALLOWED BY SECTION 3(i)

190. Section 25(1)(f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.
191. Section 3(i) prohibits patenting of a process, *inter alia*, for medicinal, curative, prophylactic, therapeutic or other treatment of human beings to render them free of disease.
192. Claim 16 is directed to a pharmaceutical composition as claimed in Claims 1 to 8 for manufacture of a medicament to treat various conditions that are listed therein and to achieve certain outcomes in a patient for treatment. As the pharmaceutical composition is already claimed in Claims 1 to 8, Claim 16 is essentially a claim directed to a process of treating the conditions listed therein.

193. Therefore, Claim 16 is hit by section 3(i) and ought to be rejected under section 3(i) read with section 25(1)(f) of the Patents Act.

VI.G. SECTION 25(1)(f): OPPOSED TO MORALITY AND DISALLOWED UNDER SECTION 3(b)

194. Section 25(1)(f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.
195. Section 3(b) prohibits the patenting of an invention the primary or intended use or commercial exploitation of which would be contrary to morality.
196. Claims 17 to 20 are dependent on Claim 16 and are directed to human patients with certain conditions to be treated. Because the pharmaceutical compositions are already claimed in Claims 1 to 8 of the present Application, Claims 17 to 20 of the present Application essentially claim human patients with certain conditions and, as such, are contrary to morality.
197. Therefore, Claims 17 to 20 are hit by section 3(b) and ought to be rejected under section 3(b) read with section 25(1)(f) of the Patents Act.

VI.H. SECTION 25(1)(f): NOT CAPABLE OF INDUSTRIAL APPLICATION AS REQUIRED UNDER SECTION 2(1)(ac)

198. Section 25(1)(f) provides a ground of opposition on the ground that the subject of any claim is not an invention within the meaning of the Patents Act or is not patentable under the Patents Act.
199. Section 2(1)(j) defines an invention as “a new product or process involving an inventive step and capable of industrial application”. Section 2(1)(ac) defines “capable of industrial application” as meaning that “the invention is capable of being made or used in an industry”.
200. Claims 17 to 20 relate to pharmaceutical compositions already claimed in Claims 1 to 8 and are directed to human patients with certain conditions.
201. As such, the aspects of the claims which pertain to human patients are not capable of industrial application.
202. Therefore, Claims 17 to 20 ought to be rejected under section 2(1)(j) and section 2(1)(ac) read with section 25(1)(f) of the Patents Act.

VI.I. SECTION 25(1)(g): INSUFFICIENCY OF DESCRIPTION

203. Section 25(1)(g) provides a ground of opposition on the ground that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
204. Claims 16 to 20 are not supported by the Complete Specification accompanying the present Application.

205. Claim 16 relates to a pharmaceutical composition claimed in Claims 1 to 8 of the present Application for manufacture of a medicament to treat various conditions that are listed therein and to achieve certain outcomes in a patient for treatment
206. However, apart from Example I of the pharmacological examples, there is no test result or data that supports the claim to treat the diseases or conditions and the treatment outcomes listed in Claim 16.
207. Dependent Claims 17 to 20 fail for the same reason.
208. Because the Complete Specification does not sufficiently and clearly describe the invention, Claims 16 to 20 ought to be rejected under section 25(1)(g) of the Patents Act.
209. Thus, for all the reasons stated above, the present Application ought to be rejected in its entirety.
210. As permitted under section 25(1) of the Patents Act read with Rule 55 of the Rules, the Opponent requests that the Patent Office immediately furnish the Opponent a copy of any reply and evidence, if any, filed by the Patent Applicant to this representation by way of opposition and amendment to the Complete Specification and / or claims, if any, and also permit it to file response / rejoinder to the same. The Opponent also craves leave to that it be permitted to amend the pleadings and / or grounds in its representation by way of opposition and submit further documents and evidence, as and when necessary and especially in reply to the Patent Applicant's reply and / or in response to any

amendments that the Patent Applicant may make to the Complete Specification or claims.

211. The Opponent also requests a hearing in the present matter.
212. The Opponent also craves leave to refer to and rely upon the full text of documents, both patent and non-patent literature, referred to in the representation by way of opposition
213. The Opponent reiterates that the fundamental right to health has paramount importance and states that a patent application that does not meet the patentability standards set out in the Indian patent law ought to be rejected.
214. The Opponent states that grant of patents to the Patent Applicant in other jurisdictions cannot be tantamount to a grant of a patent in India. The Indian patent law is different from the patent laws of other jurisdictions. Indian Parliament has deliberately set higher standards to disallow patents for pharmaceutical products that are not new, are not genuinely inventive, that are obvious to a person skilled in the art or that do not involve a technical advance. The Indian patent law also specifically prohibits grant of patents for new forms of known substances and mere admixtures of known substances. These higher standards have been set to prevent abuse of the patenting mechanism and to prevent undeserving patents from being granted.
215. The Opponent submits that the present Application is directed at pharmaceutical composition, and more particularly, a pharmaceutical dosage form, of two known drugs and is clearly an attempt to evergreen by extending the period of monopoly already

available to the Patent Applicant on account of other patents held by it over these drugs.

216. The Opponent states that the present Application ought to be rejected as various publications that predate the priority date of the Applicant anticipate the claims of the present Application. Novelty or “new”ness is destroyed when the essential elements are disclosed in a prior art document and also when the claimed invention is inherently anticipated. The prior documents cited in part VI.B. above show that Claims 1 to 14 and 16 of the present Application are not new, lack novelty and are anticipated by prior publication. Additionally, these claims are also anticipated by prior claiming. Therefore, these claims ought to be rejected under section 2(1)(j) read with section 25(1)(b) and section 25(1)(c) of the Patents Act.
217. Further, the invention so far as claimed in Claims 1 to 16 is obvious to a person skilled in the art. The prior art documents cited in Part VI.C. above show that Claims 1 to 16 of the present Application are obvious to a person skilled in the art. They do not involve any technical advance. The claimed invention thus lacks inventive step. Therefore, Claims 1 to 16 ought to be rejected under section 2(1)(j) and section 2(1)(ja) read with section 25(1)(e) of the Patents Act.
218. Further, Claims 1 to 14 of the present Application relate to a pharmaceutical composition and dosage form of two known drugs and known excipients for which the Patent Applicant has not shown significant enhancement of therapeutic efficacy or synergistic effects. As such, they are not patentable under section

3(d) and section 3(e). Claim 15 too is not patentable under section 3(e). Additionally, Claims 17 to 20 are method of treatment claims, are opposed to morality and are also not capable of industrial application. Therefore, these claims ought to be rejected under section 2(1)(j), section 2(1)(ac) and sub-sections (b), (d), (e) and (i) of section 3, as the case may be, read with section 25(1)(f) of the Patents Act.

219. Claims 16 to 20 are also not supported by description and ought to be rejected under section 25(1)(g) of the Patents Act.

Having established non-patentability of the impugned invention and having adduced supporting evidence for each of the above grounds of Opposition, the Opponent prays for the following reliefs:—

- (a) That Patent Application bearing No. 6148/DELNP/2011 titled “Pharmaceutical composition comprising *linagliptin* and optionally a SGLT2 inhibitor, and uses thereof” be rejected *in toto* and the grant of patent to the said Application be refused;
- (b) That copy of the reply of the Patent Applicant and evidence, if any, and / or amendment to the Complete Specification or claims, if any, be forwarded forthwith to the Opponent;
- (c) That the Opponent be allowed to file response / rejoinder to the reply and evidence, if any, filed by the Patent Applicant;
- (d) That the Opponent be allowed to amend the pleadings and / or grounds in its representation by way of opposition and submit further documents and evidence, as and when necessary and especially in reply to the Patent Applicant’s reply and / or in


response to any amendments that the Patent Applicant may make to the Complete Specification or claims;

- (e) That the Opponent be granted a hearing under section 25(1) read with Rule 55;
- (f) That the Opponent be granted leave to refer to and rely upon the full text of documents, both patent and non-patent literature, referred to in the representation by way of opposition;
- (g) For costs;
- (h) For such other and further reliefs that the Learned Controller may deem necessary in the facts and circumstances of this case.

All communications relating to these proceedings may be sent to the following address in India:

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Dated this 10th day of February 2017



Dr. GOPAKUMAR G. NAIR
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To,
The Controller of Patents
The Patent Office, Delhi.