The Patents Act 1970
And
The Patents (Amendment) Act 2005
And
The Patents Rules 2003
And
The Patents (Amendment) Rules 2006
SECTION 15 & 25(1)

In the matter of the Application for Patent bearing number 202017050717
Titled

"GIP/GLP1 AGONIST COMPOSITIONS"

ELI LILLY AND COMPANY

..... *Applicant*

Represented by: K&S PARTNERS Intellectual Property Attorneys

Dr. C. Manivannan,

..... *Opponent*

Represented by: Khurana and Khurana Advocates and IP Attorneys

Hearing held on 23rd July 2024

Present on behalf of Applicant 1. Amrish Tiwari (IN/PA-1202),
2. Sachin Bindal (IN/PA-2560)

Present behalf of Opponent 1. SK Verma (IN/PA-3609)

1. History of the proceedings:

1. **ELI LILLY AND COMPANY ,**Lilly Corporate Center Indianapolis, Indiana 46285, U.S.A hereinafter referred as 'Applicant', have filed Pct national phase application for grant of patent for their invention titled "**GIP/GLP1 AGONIST COMPOSITIONS**" on 21st November 2020 through their agent called K&S PARTNERS,, hereinafter called as 'agent for the applicant' and it was numbered as 202017050717 .

2. The agent for the applicant filed a request for Examination of the application for a patent on 21st November 2020 and the application was published under section 11(A) of the Patents (Amendment) Act, 2005, hereinafter referred as 'Act' in the Patent Journal No. 07/2021 dated 12th February 2021.

3. The application was taken up for the examination and the First Examination Report (FER) was issued on 01st March 2021. The agent for the applicant filed a reply to the FER on 31st August 2021.

4. Dr. C. Manivannan, an Indian citizen, resident of 3A, Chinna Andaar Street, Kulithalai (TK),Karur (Dt), Tamil Nadu - 639104, India, through their agent called Khurana and Khurana Advocates and IP Attorneys, hereinafter referred to as the 'Opponent', has filed a representation on 23rd August 2023 in writing by way of opposition to the grant of the patent [along with FORM-7A dated 23/08/2023] in respect of application number 202017050717 Dated 21/11/2020 on the grounds of sections 25(e), 25(1) (f) and 25 (1) (g) of the Act and Rule 55 of The Patents Rules 2003(as amended).

5. On consideration of the representation, the Applicant was informed in respect of said representation by way of opposition under section 25(1) and Rule 55 through Pre-grant Opposition Notice vide letter dated 15th December 2023 as required by Rule 55(3) and also a copy sent to the Opponent. The Applicant has filed a reply statement and evidence 14/03/2024 as required by Rule 55(4) of the Patent Rules, 2003(as amended) within three months from the date of such Notice.

6. The hearing under Section 25(1) (pre-grant opposition) and Section 14 (examination-related issues) was initially scheduled for 03/06/2024 and a notice of this hearing was sent to both parties on 29/04/2024. The applicant filed for an adjournment under Rule 129A on 30/05/2024 and 19/06/2024. The hearing was rescheduled to 23/07/2024, considering the both adjournment requests and a revised notice of the rescheduled hearing was sent to both parties on 24/06/2024.

A Hearing was rescheduled to 23/07/2024 for (4h 30 mins) to appear before the Controller with reference to Pre-grant Opposition and Hearing Notice u/r 55(5) was issued with a vide letter dated 24th June 2024 to both the Applicant and Opponent. The said Hearing Notice also includes hearing u/s 14 for objections outstanding in the application after consideration of the reply to FER filed by the applicant to decide the application u/s 15 simultaneously. Both the Applicant's agent and Opponent's agent were present on date of hearing and submitted the written submissions on 07th August 2024 and 20th August 2024 respectively.

2. Subject matter of the invention:

2.1 The present invention discloses a pharmaceutical GIP/GLP1 co-agonist peptide composition for subcutaneous injection. The composition comprises tirzepatide, NaCl, and dibasic sodium phosphate. The composition provides commercially acceptable shelflife stability, in-use stability, and is associated with acceptable patient injection site experience. An alternative composition comprises tirzepatide, propylene glycol, and dibasic sodium phosphate that also provide acceptable shelf-life stability.

2.2 The Applicant submitted amended/revised set of claims 1-12 on 20th August 2024 along with written submissions in response to the hearing held on 23nd July 2024 as follows:

1. A pharmaceutical composition comprising tirzepatide, or a pharmaceutically acceptable salt thereof; NaCl at a concentration from 6.2 mg/mL to 9.5 mg/mL; and dibasic sodium phosphate at a concentration from 0.67 mg/mL to 2.68 mg/mL.

2. A pharmaceutical composition as claimed in Claim 1 wherein the tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is from 5 to 30 mg/mL.

3. A pharmaceutical composition as claimed in Claim 1 wherein the dibasic sodium phosphate concentration is 1.34 mg/mL.

4. A pharmaceutical composition as claimed in Claim 1 wherein the tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is selected from the group consisting of 5, 10, 15, 20, 25, and 30 mg/mL.

5. A pharmaceutical composition as claimed in Claim 4 wherein the tirzepatide, or pharmaceutically acceptable salt thereof, concentration is selected from the group consisting of 10, 20, and 30 mg/mL.

6. A pharmaceutical composition as claimed in Claim 1 wherein the concentration of NaCl is from 7.0 mg/mL to 9.0 mg/mL.

7. A pharmaceutical composition as claimed in Claim 6 wherein the NaCl concentration is 8.2 mg/mL.

8. A pharmaceutical composition as claimed in Claim 1 wherein tirzepatide, or pharmaceutically acceptable salt thereof, concentration is from 5 mg/mL to 30 mg/mL; dibasic sodium phosphate concentration is from 0.67 mg/mL to 2.68 mg/mL; and NaCl concentration is from 6.2 mg/mL to 9.5 mg/mL.

9. A pharmaceutical composition as claimed in Claim 8 wh erein tirzepatide, or pharmaceutically acceptable salt thereof, concentration is from 5 mg/mL to 30 mg/mL; dibasic sodium phosphate concentration is 1.34 mg/mL; and NaCl concentration is 8.2 mg/mL.

10. A pharmaceutical composition as claimed in Claim 9 wherein the composition is presented in an automatic injection apparatus.

11. A pharmaceutical composition as claimed in Claim 1 wherein the pH of the composition is from 6.5 to 7.5.

12. A pharmaceutical composition as claimed in Claim 11 wherein the pH is from 6.7 to 7.3.

3. Grounds of opposition:

3.1. The Opponent has relied upon the following grounds of opposition in the Pre-Grant Representation.

(i)Obviousness or Lack of Inventive Step U/S 25 (1) (e)
(ii) Non-Patentable subject matter U/S 25(1) (f)
(iii) Lack of sufficient disclosure U/S 25(1) (g)

3.2. The following documents relied upon by the Opponent in the opposition

D1: US 9474780 B2. Oct. 25, 2016

D2: WO 2003/002136 A2. Jan. 09, 2003

D3: US 8114833 B2. Feb. 14, 2012

D4: US 2006/0084605 A1. Apr. 20, 2006

D5: WO 1999/043341 A1. Sep. 02, 1999

D6: WO 2001/043762 A2. June 21, 2001

3.2 Obviousness/lack of inventive step U/S 25 (1) (e):

The Opponent states that claims 1-12 of the impugned application lack inventive step and are obvious based on prior art documents D1-D6.

D1 (US9474780B2) discloses dual incretin peptide mimetic compounds that act as GIP and GLP-1 receptor agonists for treating type 2 diabetes mellitus. It specifically claims tirzepatide (claim 15) and a pharmaceutical composition containing tirzepatide with a pharmaceutically acceptable carrier (claim 16). Additionally, D1 discloses a method for treating type 2 diabetes by administering a tirzepatide-containing composition (claim 17).

While D1 discloses a pharmaceutical composition comprising tirzepatide as active ingredient, D1 does not explicitly disclose a composition of tirzepatide comprising NaCl and dibasic sodium phosphate as recited in instant claim 1.

However, the use of NaCl and dibasic sodium phosphate in peptide-containing pharmaceutical formulations is commonly known, and also suggested for liquid parenteral formulations comprising glucagon-like peptides, see, e.g., documents D2 to D6. Documents D2 to D6 are concerned with the same field of aqueous parenteral pharmaceutical compositions (e.g., subcutaneous injections) comprising glucagon-like peptides. These documents provide formulations that are formulated in a way to improve the physical and chemical stability of the formulations.

The Opponent further states that the skilled person would learn from D2 (WO2003002136A2) that therapeutic proteins (peptides) are typically unstable and are susceptible to both chemical and physical degradation (see, D2, page 2, lines 12-24)and, would also learn from D2 that such peptide instability can be avoided by providing peptide compositions comprising an isotonic agent (e.g. sodium chloride) and a buffer (e.g. disodium hydrogen phosphate, also known as dibasic sodium phosphate) (see, D2, page 37, lines 12-21, “Example 1”; page 17, lines 27-33; and page 18, lines 33-35).

From D3 (US8114833B2) the skilled person would learn that shelf-stable formulation of therapeutic peptides is obtained by a pharmaceutical composition comprising a therapeutic peptide, propylene glycol (isotonic agent) and disodium phosphate 9 dihydrate buffer (dibasic sodium phosphate buffer) (see, column 1, lines 53-60, and claim 1 at column 22). Further, the opponent states that the skilled person would also learn from D3 that said isotonic agent can present in the formulation in a concentration of from about 1 mg/ml to about 100 mg/ml, and that the pH of the formulation can range from about 7.0 to about 10.0 (see, claims 1-3 at column 22). It is explained in document D2 that sodium

chloride is a known isotonic agent and is an equally suitable alternative to propylene glycol (see, D2, page 18, lines 33-35).

D4 (US20060084605A1) discloses stable pharmaceutical compositions for parenteral (e.g. subcutaneous) administration, comprising a glucagon-like peptide, human serum albumin or a variant thereof, a pharmaceutically acceptable buffer (e.g. sodium phosphate), a pharmaceutically acceptable preservative, and an isotonicity agent (e.g. sodium chloride) (see, D4, pages 13-14, claims 1, 3, 8, 48, 50, 51).

D5 (WO1999043341A1) discloses pharmaceutical compositions comprising a GLP-1 derivative with improved solubility and stability (see, abstract). Said composition comprises a GLP-1 derivative, sodium chloride as isotonic agent and sodium phosphate as buffer (see, D5, page 10, lines 19-27).

From D6 (WO2001043762A2) the skilled person would learn that in order to avoid injection-site pain upon injection of peptide drug formulations, a pharmaceutical composition of a therapeutic peptide additionally may comprise sodium chloride as an excipient (see, D6, page 1, lines 23-28).

Therefore , taking into account the disclosure of document D1 with respect to pharmaceutical composition of tirzepatide and given the teachings of D2 to D5 that shelf stable formulation of therapeutic peptides can be obtained by a pharmaceutical composition comprising therapeutic peptide, sodium chloride as isotonic agent and dibasic sodium phosphate as buffer – the provision of a composition of tirzepatide, comprising sodium chloride and dibasic sodium phosphate is not based on any inventive activity, and does not constitute an inventive contribution to the art. The skilled person would be motivated by the teaching of D2 to D6 to include sodium chloride and dibasic sodium phosphate into the pharmaceutical composition of tirzepatide as disclosed in D1 in order to obtain pharmaceutical compositions having prolonged stability during storage and providing acceptable patient injection site experience. In order to arrive at effective formulations, he would further adopt the concentrations of sodium chloride, dibasic sodium phosphate and the pH of formulation as suggested by D2 and D3 by routine experimentation, if at all required. By doing that, he would inevitably arrive at the claimed invention. Accordingly, the independent claim 1 lacks inventive step in view of D1 combined with the teaching of D2 to D6.

Further, the opponent States that the pharmaceutical composition comprising tirzepatide, sodium chloride and dibasic sodium phosphate is obvious and does not involve an inventive step in view of D1 combined with the teaching of D2 to D6. The Opponent states that the dependent claims 2 to 15 also do not involve an inventive step, because varying the amounts of excipients represents however a usual procedure for a skilled person and does not involve an inventive step. This applies in particular when these excipients are merely used in usual amounts well known to a skilled person and in absence of any surprising effects associated with such excipient variations: Isotonic agents, such as for example Sodium chloride, are known to be used in liquid parenteral formulations in the range between 1-50 mg/ml, e.g., from 8 mg/ml to 16 mg/ml (see, D2, page 18, lines 33-35, and page 19, lines 10-13), therapeutic peptides are known to be present in liquid parenteral formulations from 1 mg/ml to 80mg/ml, preferably from 1 mg/ml to 20mg/ml (see, D2, page 18, lines 1-6) – Peptide, containing parenteral

formulations are known to have pH in the range of 6.5 to 9.0 (see, D4, claim 2 at page 13). Thus, also the subject-matter of claims 2 to 12 of the impugned application lacks an inventive step in view of D1 combined with the teaching of D2 to D6.

For the reasons set forth above, it is therefore respectfully submitted that the subject matter of claims 1 to 12 of the impugned application is obvious and does not meet the requirements with regard to inventive step, and as such is not patentable under the provisions of Section 25(1)(e) read with Section 2(1)(ja) of the Patents Act.

Applicant submits that D1 discloses dual incretin peptide mimetic compounds that agonize receptors for both human glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) and may be useful for treating type 2 diabetes mellitus (T2D). The composition of D1 containing a GIP/GLP1 agonist, administered by parenteral routes. D1 does not disclose or suggest NaCl and dibasic sodium phosphate in pharmaceutical composition containing tirzepatide. The effect of this difference resides in composition with increased shelf life (table 4) and reduced pain at the site of injection (table 8).

D2 discloses a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1 (7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP- 1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10; provided that if an isotonic agent is present and pH is 7.4 then mannitol or NaCl is not the isotonic agent. Further, the composition of D2 consists of a stabilizer (claim 17) wherein said stabilizer is selected from the group consisting of L-histidine, imidazole and arginine (claim 18). Further the applicant states that D2 does not disclose tirzepatide, leave aside its composition as disclosed in the present invention that comprises tirzepatide, NaCl, and dibasic sodium phosphate.

D3 discloses a pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0. GLP-1 agonist of D3 is selected from the group consisting of GLP-1 (7-36)-amide, GLP-1 (7-37), a GLP1 (7-36)-amide analogue, a GLP-1 (7-37) analogue, or a derivative of any of these, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine (claims 10 and 11).

D3 does not disclose nor suggest the use of tirzepatide, leaving aside its composition as disclosed in the present invention that comprises tirzepatide, NaCl, and dibasic sodium phosphate.

D4 (US 2006/0084605 A1) discloses a pharmaceutical composition for parenteral administration, said composition comprising a glucagon-like peptide, human serum albumin or a variant thereof, a pharmaceutically acceptable buffer, a pharmaceutically acceptable preservative, and optionally an isotonicity agent and/or a stabilizer. Further, D4 discloses that it has unexpectedly found human serum albumin to be an excipient that can improve the stability of pharmaceutical compositions containing a

glucagon-like peptide (para 006). Thus, requirement of human serum albumin or a variant thereof in the composition is required to increase the stability of glucagon-like peptide.

D4 does not disclose nor suggest the use of tirzepatide, leaving aside its composition as disclosed in the present invention that comprises tirzepatide, NaCl, and dibasic sodium phosphate.

D5 discloses a pharmaceutical composition comprising a GLP-1 derivative which has a helix content as measured by CD at 222 nm in H2O at 22 + 2 °C exceeding 25%, preferably in the range of 25% to 50%, at a peptide concentration of about 10 µM. Further, D5 uses preservatives like phenol, m-cresol, methyl p-hydroxybenzoate, butyl p-hydroxybenzoate and benzyl alcohol which increases stability of the composition.

D5 does not disclose nor suggest the use of tirzepatide, leaving aside its composition as disclosed in the present invention that comprises tirzepatide, NaCl, and dibasic sodium phosphate.

D6 discloses an aqueous, parenteral pharmaceutical composition comprising a polypeptide and glycerin, wherein the glycerin is derived from a non-animal source. The polypeptide is produced biosynthetically (claim 10) in bacteria or yeast (claim 11) for example in E. coli (claim 12).

D6 does not disclose nor suggest the use of tirzepatide, leaving aside its composition as disclosed in the present invention that comprises tirzepatide, NaCl, and dibasic sodium phosphate.

None of the cited documents D1-D6 provide any suggestion or teaching whatsoever to develop a pharmaceutical composition of tirzepatide with NaCl and dibasic sodium phosphate. Any combination of alleged prior art elements to arrive at the pending claims constitutes nothing more than improper hindsight reconstruction. Further, the pharmaceutical composition of the present invention shows unexpected technical effects as it provides a stable and commercially useful formulation, and at the same time minimizing unpleasant injection administration experience.

The Applicant submits that tirzepatide exhibits superior stability when formulated with NaCl, unlike other GLP-1 agonists, as demonstrated in Table 4 of the specification. The unpredictability of peptide formulations is further supported by the affidavit of Dr. Ken Kangyi Qian (Exhibit C), which confirms that dulaglutide with NaCl shows significantly reduced stability, proving that incretin formulations are not interchangeable. Additionally, Table 8 provides evidence that the claimed composition results in reduced injection-site pain, enhancing patient comfort and compliance. Given these unexpected advantages, the claimed invention is non-obvious, and the objection regarding the lack of inventive step should be dismissed.

Based on the opponent’s submission and the applicant’s reply, it appears that the cited prior art documents D1-D6 do not disclose or suggest the specific formulation of tirzepatide with sodium chloride and dibasic sodium phosphate in the claimed concentrations. The applicant has demonstrated that this formulation provides unexpected technical effects, including enhanced stability and reduced injection-site pain, which are not taught or suggested by D1-D6. Additionally, the opponent has not provided

sufficient evidence to substantiate the alleged lack of inventive step. Therefore, the opponent has failed to establish the ground of opposition under Section 25(1) (e).

3.3 Non-Patentable subject matter U/S 25(1) (f):

The opponent argues that the claimed tirzepatide composition is not patentable under Section 3(e) of the Patents Act, as it lacks an unexpected or surprising effect. The composition, comprising tirzepatide, NaCl, and dibasic sodium phosphate, is obvious and lacks an inventive step. Prior art (D1-D5) already discloses similar pharmaceutical compositions, demonstrating that these components are well-known for stabilizing therapeutic peptides, making the claimed composition a predictable combination of known elements without any inventive advancement. Therefore, the claimed composition is merely an aggregation of known elements with expected properties, rendering it non-inventive.

The applicant contends that the claimed tirzepatide composition is novel and inventive, offering enhanced shelf-life, in-use stability, and improved patient injection experience. Experimental data (Tables 4 and 8) demonstrate that tirzepatide, when formulated with NaCl, exhibits superior stability compared to other in cretin compounds, which show reduced stability with NaCl. These unexpected interactions among the components indicate a synergistic effect rather than a mere admixture, thereby distinguishing the claimed composition from prior art and placing it outside the scope of Section 3(e) of the Patents Act.

Based on the Opponent’s submissions and the Applicant's response, it is observed that the pharmaceutical composition comprising tirzepatide, or a pharmaceutically acceptable salt thereof, as claimed in claims 1-12, demonstrates clear synergy and technical advancement. The experimental data (Tables 4 and 8) provided by the Applicant clearly establish that the claimed composition is not a mere admixture but exhibits a synergistic effect, resulting in significant improvements in stability and patient injection experience. The demonstrated technical advancement confirms that the composition meets the criteria for inventiveness and is not a simple combination of known elements with predictable properties. Furthermore, the claimed composition and its synergistic effects are not disclosed in any of the cited prior art documents (D1-D6). Consequently, the Opponent has failed to substantiate the ground of opposition under Section 25(1) (f) of the Patents Act.

3.3 Lack of sufficient disclosure [Section 25(1) (g)]:

The Opponent argues that Claim 1 is overly broad due to the absence of specified quantities for key components, raising concerns about its operability and compliance with Section 10(4) of the Patents Act, 1970.

Conversely, The Applicant submits that the claims of the invention sufficiently and clearly describe the subject matter of the present invention. In addition, the Applicant submits that a patent specification is addressed to a person of ordinary skill in the art. It is submitted that the claimed invention has been sufficiently disclosed in the specification in order for a person of ordinary skill in the art to work the invention to the fullest extent. In fact, various examples are provided in the present specification for claimed composition such as in Table 1, Table 2, Table 5 and Table 7. Thus, the complete specification fully and particularly describes the claimed invention to be performed by a person skilled in the art

without undue experimentation. Further, the Applicant asserts that the specification provides sufficient guidance for a skilled person to practice the invention without undue experimentation, making any restriction on component amounts unnecessary.

As the specification enables a skilled person to implement the invention, the absence of numerical limitations in Claim 1 does not imply insufficient disclosure. It appears that the disclosure made in the specification fulfills the requirement of sufficiency of the complete specification. Therefore, the opposition filed under Section 25(1) (g) is invalid.

Having carefully considered all the circumstances of this case, including the representations of the Opponents, the reply statement and evidence submitted by the Applicants, as well as the written submissions and oral arguments presented during the hearing, I have thoroughly examined and analyzed the matter. Based on my discussion and findings, as outlined above, I am of the considered opinion that the Opponent has failed to establish valid grounds for opposition under Section 25(1). Accordingly, the representation of the Opponent under Section 25(1) of The Act is hereby rejected.

Dated this 27th March 2025.

(G Nagendra)

Assistant Controller of Patents & Designs

Decision for under section 14 hearing:

The hearing was conducted on 23/07/2024, and the Applicant's agent submitted the written Submissions on 20/08/2024 along with claims 1-12. After considering the submissions made by the agent and the documents available on record, I am of the opinion that the applicant has complied with all the requirements as per the Patents Act, of 1970. Hence, the instant application is allowed to proceed for the grant of a patent right. Therefore, I hereby decide to proceed with the grant of a patent for application no. 202017050717 with amended claims 1-12 filed on 20/08/2024.

Dated this 27th March, 2025.

(G Nagendra)
Assistant Controller of Patents & Design