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December 19, 2013

Via FedEx® Priority Overnight Service

Bausch & Lomb, Inc.
50 Technology Drive
Irvine, CA 92618

Valeant Pharmaceuticals International, Inc.
2150 St. Elzéar Blvd. West
Laval, Quebec H7L 4A8
Canada

HIGHLY CONFIDENTIAL[1]

Senju Pharmaceutical Co., Ltd.
5-8 Hiranomachi 2-Chome, Chuo-Ku
Osaka-Shi, Osaka 541-0046 Japan

Re: Notification of Certification of Invalidity, Unenforceability, and/or Noninfringement for U.S. Patent No. 8,129,431 Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act

Dear Madam or Sir:

Pursuant to § 505(j)(2)(B)(ii) and (iv) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95, we hereby provide notice on behalf of Lupin Ltd. ("Lupin") of the following information to Bausch & Lomb, Inc. ("Bausch & Lomb"), as the purported holder of approved New Drug Application ("NDA") No. 203168 for Prolensa® Bromfenac Ophthalmic Solution 0.07%, according to the records of the U.S. Food and Drug Administration ("FDA"). In addition, Lupin provides notice to Senju Pharmaceutical Co., Ltd. ("Senju") as the purported assignee of U.S. Patent No. 8,129,431, according to the electronic records of the United States Patent and Trademark Offices ("PTO").

As a courtesy, Lupin also provides a copy of this Notice Letter and detailed statement to Valeant Pharmaceuticals International, Inc., which reportedly acquired Bausch & Lomb in 2013.

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[1] You are not authorized to attach this Notice Letter and detailed statement to any court pleading (unless filed under seal) or to attach this Notice Letter and detailed statement to any other document that is publicly disclosed.

Pursuant to 21 C.F.R. § 314.95(e), permission from FDA to send this Notice Letter by means other than registered or certified mail was requested and received. Specifically, permission to send this notice by FedEx® was requested. FDA granted this request prior to this notice being sent. Consequently, the operative date for determining the start of the 45-day clock under 21 U.S.C. § 355(j)(5)(B)(iii) begins from the receipt of this Notice Letter sent via FedEx®.

I. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. § 314.95(c)(1), Lupin advises that FDA has received an Abbreviated New Drug Application ("ANDA") from Lupin for Bromfenac Ophthalmic Solution 0.07%. The ANDA contains the required bioavailability and/or bioequivalence data and/or bioequivalence waiver. The ANDA was submitted under 21 U.S.C. §§ 355(j)(1) and (2)(A), and contains a Paragraph IV certification to obtain approval to engage in the commercial manufacture, use or sale of Bromfenac Ophthalmic Solution 0.07%, before the expiration of U.S. Patent No. 8,129,431, which is listed in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly known as "the Orange Book").

II. Pursuant to 21 C.F.R. § 314.95(c)(2), we advise you that the ANDA submitted by Lupin is assigned the number 206027 by FDA.

III. Pursuant to 21 C.F.R. § 314.95(c)(3), Lupin advises that the established name of the drug product that is the subject of Lupin's ANDA is Bromfenac Ophthalmic Solution 0.07%.

IV. Pursuant to 21 C.F.R. § 314.95(c)(4), Lupin advises that the active ingredient in the proposed drug product is bromfenac sodium; the strength of the proposed drug product is a 0.07% solution; and the dosage form of the proposed drug product is an ophthalmic solution.

V. Pursuant to 21 C.F.R. § 314.95(c)(5), Lupin advises that the patent alleged to be invalid, unenforceable and/or not infringed in the Paragraph IV certification is Senju's U.S. Patent No. 8,129,431, which is now listed in the Orange Book in connection with Bausch & Lomb's approved NDA No. 203168 for Prolensa® (Bromfenac Ophthalmic Solution 0.07%).

According to information submitted for listing in the Orange Book, U.S. Patent No. 8,129,431 will purportedly expire on or about September 11, 2025.

VI. Lupin alleges, and has certified to FDA, that in Lupin's opinion and to the best of its knowledge, U.S. Patent No. 8,129,431 is invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the drug products described in Lupin's ANDA. Therefore, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6), Lupin's detailed statement of the legal and factual basis for the Paragraph IV certification set forth in Lupin's ANDA is attached hereto and made part hereof. Lupin reserves the right to demonstrate additional grounds, reasons and authorities that the claims of the '431 patent are invalid, unenforceable, and/or not infringed.

VII. Pursuant to 21 C.F.R. § 314.95(c)(7), the name and address of an agent in the United States authorized to accept service of process for Lupin, limited to commencement of a patent infringement suit based on this notification of certification, is:

Elizabeth J. Holland
KENYON & KENYON LLP
One Broadway
New York, NY 10004-1007
eholland@kenyon.com

VIII. Pursuant to 21 U.S.C. § 355(j)(5)(C), this Notice Letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i)(III), Lupin offers to provide confidential access to certain information from its ANDA No. 206027 for the sole and exclusive purpose of determining whether an infringement action referred to in §355(j)(5)(B)(iii) for a patent listed in the Orange Book for NDA No. 203168 can be brought.

Section 355(j)(5)(C)(i)(III) allows Lupin to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants Lupin the right to redact its ANDA in response to a request for Confidential Access under this offer.

As permitted by statute, Lupin imposes the following terms and restrictions on its Offer of Confidential Access:

(1) Lupin will permit confidential access to certain information from its proprietary ANDA No. 206027 to attorneys from one outside law firm representing Bausch & Lomb and/or Senju; provided, however, that such attorneys do not engage, formally or informally, in any patent prosecution for Bausch & Lomb or Senju, or any FDA counseling, litigation or other work before or involving FDA. Such information (hereinafter, "Confidential Lupin Information") shall be marked with the legend "CONFIDENTIAL."

(2) The attorneys from the designated outside law firm representing Bausch & Lomb and/or Senju shall not disclose any Confidential Lupin Information to any other person or entity, including Bausch & Lomb or Senju employees, outside scientific consultants, and/or other outside counsel retained by Bausch & Lomb or Senju, without the prior written consent of Lupin.

(3) As provided by § 355(j)(5)(C)(i)(III), the designated outside law firm representing Bausch & Lomb and/or Senju shall make use of the Confidential Lupin Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought and for no other purpose. By way of example only, the Confidential Lupin Information shall not be used to prepare or prosecute any future or pending patent applications by Bausch & Lomb or Senju, or in connection with any filing to, or communication with, FDA or the United States Pharmacopeia or any similar or related organization relating to Lupin's ANDA No. 206027. The outside law firm for Bausch & Lomb

and/or Senju agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential Lupin Information, and that all Confidential Lupin Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Lupin Information disclosed is, and remains, the property of Lupin. By providing the Confidential Lupin Information, Lupin does not grant Bausch & Lomb, Senju and/or their outside law firm any interest in or license for the Confidential Lupin Information.

(5) The designated outside law firm representing Bausch & Lomb and/or Senju shall, within thirty-five (35) days from the date that it first receives the Confidential Lupin Information, return to Lupin all Confidential Lupin Information and any copies thereof. The outside law firm of Bausch & Lomb and/or Senju shall return all Confidential Lupin Information to Lupin before any infringement suit is filed by Bausch & Lomb and/or Senju, if suit is commenced before this 35-day period expires. In the event that Bausch & Lomb and/or Senju opts to file suit, none of the information contained in or obtained from any Confidential Lupin Information that Lupin provides shall be included in any publicly-available complaint or other pleading.

(6) Nothing in this Offer of Confidential Access shall be construed as an admission by Lupin regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Lupin with respect to the competency, relevance, or materiality of any such Confidential Lupin Information, document, or thing. The fact that Lupin provides Confidential Lupin Information upon request of Bausch & Lomb and/or Senju shall not be construed as an admission by Lupin that such Confidential Lupin Information is relevant to the disposition of any issue relating to any alleged infringement of U.S. Patent No. 8,129,431, or to the validity or enforceability of that patent.

(7) The attorneys from the designated outside law firm representing Bausch & Lomb and/or Senju shall acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Lupin Information. Such written acknowledgement shall be provided to Lupin.

(8) If Confidential Lupin Information is disclosed by the designated outside law firm representing Bausch & Lomb and/or Senju to any person not authorized to receive such Confidential Lupin Information pursuant to this Offer of Confidential Access, then the designated outside law firm representing Bausch & Lomb and/or Senju must immediately bring all pertinent facts relating to such disclosure to the attention of Lupin and, without prejudice to other rights and remedies of Lupin, make every effort to prevent further disclosure by it or by the person who was the recipient of such Confidential Lupin Information.

Section 355(j)(5)(C)(i)(III) provides that any request for access that Bausch & Lomb and/or Senju makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that Bausch & Lomb and/or Senju requests access to Confidential Lupin Information, they necessarily accept the terms and restrictions outlined above. Written notice requesting access under this Offer of Confidential Access should be made to:

Elizabeth J. Holland
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By providing this Offer of Confidential Access, Lupin maintains the right and ability to bring and maintain a Declaratory Judgment action under 28 U.S.C. §§ 2201 *et seq.*, pursuant to 21 U.S.C. § 355(j)(5)(C).

Very truly yours,

Elizabeth J. Holland
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Counsel for Lupin Ltd.

Enclosure: Lupin Ltd.'s Detailed Factual and Legal Bases for Its Opinion That U.S. Patent No. 8,129,431 Is Invalid, Unenforceable and/or Not Infringed by the Manufacture, Use or Sale of Lupin Ltd.'s Proposed Bromfenac Ophthalmic Solution 0.07%

Lupin Ltd.'s Detailed Statement of the Factual and Legal Bases for Its Opinion That U.S. Patent No. 8,129,431 Is Invalid, Unenforceable and/or Not Infringed by the Manufacture, Use or Sale of Lupin Ltd.'s Proposed Bromfenac Ophthalmic Solution 0.07%

Pursuant to Section 505(j)(2)(B)(ii) of the Food, Drug and Cosmetic Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii)), and 21 C.F.R. § 314.95(c), this is the detailed statement of Lupin Ltd. ("Lupin") of the factual and legal bases for its opinion that U.S. Patent No. 8,129,431 ("the '431 patent") is invalid, unenforceable, and/or not infringed by the manufacture, use or sale of Lupin's proposed bromfenac ophthalmic solution 0.07% described in ANDA No. 206027 ("Lupin's proposed product"). The bases for Lupin's opinion follow.

I. U.S. PATENT 8,129,431

The '431 patent, entitled "AQUEOUS LIQUID PREPARATION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL)PHENYLACETIC ACID," issued on March 6, 2012 from U.S. Application Serial No. 10/525,006, which was filed on March 28, 2005 as a U.S. national phase application of PCT Application No. PCT/JP2004/000350, which was filed on January 16, 2004, and claims the benefit of Japanese Application No. 2003-12427, which was filed on January 21, 2003. The '431 patent lists Shirou Sawa and Shuhei Fujita as inventors, and is assigned on its face to Senju Pharmaceutical Co., Ltd. The '431 patent has a patent term adjustment of 604 days. According to the Orange Book listing for Prolensa, the '431 patent will expire on September 11, 2025.

A. Claims of the '431 Patent

The '431 patent issued with 22 claims, which are reproduced below:

1. An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylaceticacid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate and the second component is tyloxapol, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a

quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.

2. The aqueous liquid preparation according to claim 1, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

3. The aqueous liquid preparation according to claim 1, wherein the second component is tyloxapol and the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt , wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v %.

4. The aqueous liquid preparation according to claim 3, wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.3 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

5. The aqueous liquid preparation according to claim 4, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

6. The aqueous liquid preparation according to claim 4, wherein the concentration of the tyloxapol is about 0.02 w/v %.

7. The aqueous liquid preparation according to claim 1, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

8. The aqueous liquid preparation according to claim 7, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

9. The aqueous liquid preparation according to claim 8, wherein the pH is from about 7 to about 9.

10. The aqueous liquid preparation according to claim 8, wherein the pH is from about 7.5 to about 8.5.

11. The aqueous liquid preparation according to claim 4, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

12. The aqueous liquid preparation according to claim 4, wherein the concentration of the tyloxapol is about 0.3 w/v %.

13. The aqueous liquid preparation according to claim 12, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

14. The aqueous liquid preparation according to claim 13, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

15. The aqueous liquid preparation according to claim 11, wherein the concentration of the tyloxapol is about 0.02 w/v %.

16. The aqueous liquid preparation according to claim 15, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

17. The aqueous liquid preparation according to claim 16, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

18. An aqueous liquid preparation consisting essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate, (b) tyloxapol, (c) boric acid, (d) sodium tetraborate, (e) EDTA sodium salt, (f) benzalkonium chloride, (g) polyvinylpyrrolidone, (h) sodium sulfite, wherein said liquid preparation is formulated for ophthalmic administration, and wherein benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation.

19. The aqueous liquid preparation of claim 18, wherein (a) is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

20. The aqueous liquid preparation of claim 19, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v %.

21. The aqueous liquid preparation of claim 20, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.01 w/v %.

22. The aqueous liquid preparation of claim 20, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

B. Specification of the '431 Patent

The specification of the '431 patent acknowledges that ophthalmic solutions containing bromfenac were described in the prior art. ('431 patent, col. 1, ll. 24-47.) The specification

quotes a prior art reference (Japanese Patent No. 2,954,356, corresponding to U.S. Patent Nos. 5,603,929 and 5,653,972) for the teaching that benzalkonium chloride (BAC) (a widely used preservative in ophthalmic solutions) and other quaternary ammonium compounds "are generally considered to be incompatible" with non-steroidal anti-inflammatory drugs (NSAIDs) with acidic groups (a –COOH group) because "[t]hese preservatives lose their ability to function as they form complexes with the charged drug compounds." ('431 patent, col. 1, l. 62 – col. 2, l. 3.) Bromfenac is an NSAID with a –COOH group. Thus, the specification presents the problem to be overcome as producing an ophthalmic solution containing an NSAID with a –COOH group and BAC wherein the NSAID and the BAC do not form a complex (*i.e.*, with improved stability).

The specification indicates that this problem has been overcome by including an alkyl aryl polyether alcohol type polymer such as tyloxapol or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate in the ophthalmic solution. ('431 patent, col. 2, ll. 34-49.) The specification describes an experiment (Experimental Example 1) in which formulations containing bromfenac, BAC and three different surfactants (polysorbate 80, polyoxyl 40 stearate, and tyloxapol) were prepared and tested for stability. ('431 patent, col. 7, l. 8 – col. 8, l. 2.) Two formulations containing tyloxapol were the most stable, followed by a formulation containing polyoxyl 40 stearate, followed by a formulation containing polysorbate 80. The polysorbate 80 formulation was not considered to be part of the invention, as indicated by the fact that it was referred to as "Comparison Example 1."

C. Prosecution History of the '431 Patent

During prosecution, the PTO Examiner cited prior art describing ophthalmic solutions containing bromfenac, BAC and polysorbate 80 as a surfactant, as well as prior art showing that

tyloxapol and polysorbate 80 were both known as surfactants in ophthalmic solutions, and rejected the claims on the basis that it would have been obvious to substitute tyloxapol for polysorbate 80. (May 6, 2011 Office Action at 2-3 ["It would have been obvious to one of ordinary skill in the art at the time of the invention to interchange polysorbate 80 and tyloxapol. The motivation comes from the teaching of Guy et al. that both compounds are non-ionic surfactant surface active agents. Hence, a skilled artisan would have had a reasonable expectation of successfully producing a composition with similar efficacy and results.") In response, applicants repeatedly argued that they had discovered that substituting tyloxapol for polysorbate 80 produced unexpected results (*i.e.*, improved stability) and pointed to Experimental Example 1 from the specification to support this assertion. (*See, e.g.*, September 6, 2011 Amendment at 7-8 ["The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80. Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification."].) The PTO Examiner eventually accepted this argument, and allowed the claims of the '431 patent on the basis of the alleged unexpected results. (December 23, 2011 Notice of Allowability at 3-4 ["The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80. Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification."].)

II. NON-INFRINGEMENT ANALYSIS

A. Relevant Law

1. Claim Construction

To ascertain the meaning of claims, the claims, the specification and the prosecution history must be considered. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996); *see also Boss Control, Inc. v. Bombardier, Inc.*, 410 F.3d 1372, 1376 (Fed. Cir. 2005). In interpreting a claim, one looks first to the intrinsic evidence of record, *i.e.*, the patent itself, including the claims, the specification and the prosecution history. *See Markman*, 52 F.3d at 979; *see also, Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). "Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language." *Bell Atlantic Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1267 (Fed. Cir. 2001) (citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Where construction of claim terms would add clarity to this detailed statement, it has been provided below.

2. Law of Infringement

A patent claim is literally infringed if every limitation found in a properly interpreted claim is present in the accused product or process. *See, e.g., Hutchins v. Zoll Medical Corp.*, 492 F.3d 1377, 1380 (Fed. Cir. 2007); *Bowers v. Bayside Techs., Inc.*, 320 F.3d 1317, 1334 (Fed. Cir. 2003). Thus, literal infringement requires the presence of each and every claim element. *See Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F. 3d 1343, 1351 (Fed. Cir. 2001); *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

B. At Least Claims 5 and 8-22 of the '431 Patent Would Not Be Infringed by Lupin's Proposed Product

1. Claims 5, 11, 15-17 and 21-22

At least claims 5, 11, 15-17 and 21-22 of the '431 patent would not be infringed either literally or under the doctrine of equivalents by Lupin's proposed product because the concentration of bromfenac sodium salt in Lupin's proposed product (which is equivalent to 0.07 w/v % bromfenac free acid) is substantially different from the concentration of bromfenac sodium salt required by those claims. Specifically, claims 5 and 22 require a concentration of bromfenac sodium salt of "about 0.1 w/v %," claims 11 and 15-17 require a concentration of "about 0.2 w/v %," and claim 21 requires a concentration of "about 0.01%."

2. Claims 12-14

Claims 12-14 of the '431 patent would not be infringed either literally or under the doctrine of equivalents by Lupin's proposed product because each of those claims requires a concentration of tyloxapol that is different from the concentration of tyloxapol in Lupin's proposed product. Specifically, claims 12-14 require a concentration of tyloxapol of "about 0.3 w/v %," while the concentration of tyloxapol in Lupin's proposed product is substantially different.

3. Claims 8-10, 14 and 17-22

Claims 8, 14 and 17-22 of the '431 patent would not be infringed by Lupin's proposed product because each of those claims requires the inclusion of tetrasodium edetate, but neither tetrasodium edetate nor an equivalent thereof is contained in Lupin's proposed product.

Specifically, claims 8, 14 and 17 require the inclusion of "sodium edetate," which refers to tetrasodium edetate according to the Handbook of Pharmaceutical Excipients (2000 edition).

Claims 18-22 require the inclusion of "EDTA sodium salt," a term that is not used in the specification of the '431 patent. However, during the prosecution of the application that issued as the '431 patent, when the term "EDTA sodium salt" was first included in the claims, applicants indicated that "EDTA sodium salt is also known as sodium edetate." (March 24, 2010 Amendment at 7.) In this way, applicants indicated that "EDTA sodium salt" referred to tetrasodium edetate. Since tetrasodium edetate is not contained in Lupin's proposed product, that product would not literally infringe claims 8, 14 and 17-22.

Nor would Lupin's proposed product infringe under the doctrine of equivalents since the doctrine of equivalents cannot be employed in a manner that wholly vitiates a claim limitation. *See Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 29-30 (1997); *Asyst Techs., Inc. v. Emtrak, Inc.*, 402 F.3d 1188, 1195 (Fed. Cir. 2005). Moreover, other ingredients in Lupin's proposed product (*i.e.*, ingredients other than tetrasodium edetate) cannot be considered insubstantially different from tetrasodium edetate given that, for formulations intended for ophthalmic use, FDA generally requires generic versions to contain the same inactive ingredients and in the same concentration as the brand name drug product. *See* 21 C.F.R. § 314.94(a)(9)(iv) ("Generally, a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant...").

III. INVALIDITY ANALYSIS

A. Relevant Law

A claim is invalid if the differences between the claimed subject matter and the prior art are such that the claimed subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the pertinent art. 35 U.S.C. § 103(a). This determination is a question of law based on factual inquiries:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 663 (Fed. Cir. 2000) ("Our precedent clearly establishes that the district court must make *Graham* findings before invalidating a patent for obviousness."); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007) ("[T]he [*Graham*] factors . . . define the inquiry that controls. If a court, or patent examiner, conducts [the *Graham*] analysis and concludes the claimed subject was obvious, the claim is invalid under § 103."). Thus, *Graham* sets out a four-part inquiry including the three elements of the primary consideration of obviousness (the level of ordinary skill in the pertinent art, the scope and content of the prior art, and the differences between the prior art and the claims at issue), and secondary considerations of nonobviousness. *Ruiz*, 234 F.3d at 662–63; *see also KSR*, 550 U.S. at 406.

B. Prior Art

1. U.S. Patent No. 4,910,225

U.S. Patent No. 4,910,225 ("the '225 patent") issued on March 20, 1990 and thus is prior art to the '431 patent under 35 U.S.C. § 102(b). The '225 patent describes formulations for ophthalmic solutions containing bromfenac sodium monohydrate (referred to in the '225 patent

as "sodium 3-(4-bromobenzoyl)-2-aminophenylacetate monohydrate") as the active ingredient. One such formulation is Example 6, which reads as follows:

EXAMPLE 6

Ophthalmic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate	0.1 g
Boric acid	1.25 g
Borax	1.0 g
Disodium edetate	0.02 g
Benzalkonium chloride	0.005 g
Polysorbate 80	0.15 g
Polyvinyl pyrrolidone	2.0 g
Sodium sulfite	0.2 g
Sterile purified water pH 8	To make 100 ml

Example 6 of the '225 patent includes each of the elements of independent claim 1 of the '431 patent except for tyloxapol, and includes each of the elements of independent claim 18 of the '431 patent except for tyloxapol and "EDTA sodium salt." Specifically, the formulation described in Example 6 of the '225 patent differs from claim 18 in that Example 6 utilizes (i) polysorbate 80 instead of tyloxapol and (ii) disodium edetate instead of "EDTA sodium salt."

The formulation described in Example 6 of the '225 patent is very similar to the formulation that was marketed in Japan beginning in 2000 under the brand name Bronuck® and marketed in the United States beginning in 2005 under the brand name Xibrom®.

2. EP 0 306 984 A1

European patent application 88114804.3 was published as EP 0 306 984 A1 ("EP '984") on March 15, 1989, and thus is prior art to the '431 patent under 35 U.S.C. § 102(b). EP '984 describes improved formulations for ophthalmic solutions containing non-steroidal anti-inflammatory drugs ("NSAIDs") that have a –COOH group (*i.e.*, that are acidic). EP '984 indicates that benzalkonium chloride ("BAC") "has been widely used in ophthalmic solutions, and is considered to be the preservative of choice." (EP '984, p. 2, ll. 31-33.) EP '984 further reports that BAC has proven to be incompatible with NSAIDs that contain a –COOH group because a complex forms between BAC and the –COOH group, thereby reducing the activity of both BAC and the NSAID. (EP '984, p. 2, ll. 40-44.) When an ophthalmic solution was made with ketorolac (an NSAID with a –COOH group), BAC and polysorbate 80 as a surfactant, the solution became cloudy or turbid after a short period of time, indicating that a complex had formed between BAC and the NSAID. (EP '984, p. 2, ll. 46-49.)

EP '984 solves this problem by including "a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant." (EP '984, p. 3, ll. 1-3.) The specific examples of ethoxylated octylphenols given by EP '984 are Octoxynol 9, Octoxynol 12, Octoxynol 13 and Octoxynol 40. (EP '984, p. 5, ll. 23-28.)

EP '984 describes an experiment (Example 5) in which three formulations containing an NSAID having a –COOH group (ketorolac), BAC and a surfactant were tested for their stability. (EP '984, p. 9, ll. 1-39.) One formulation included an ethoxylated octylphenol (Octoxynol 40) as the surfactant, while the other formulations did not include an ethoxylated octylphenol as the surfactant but rather included Polysorbate 80 or Myrj 52. The formulation including the ethoxylated octylphenol as the surfactant remained clear (and thus were stable), while the other

two formulations became turbid (and thus were not stable). The text of Example 5 of EP '984 reads as follows:

EXAMPLE 5

Physical stability of the formulations of the present invention is measured by preparing clear formulations, in the concentrations shown in the table below, sealing them in sterilized containers, and observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

The formulations of the present invention have proven to be stable when tested in accordance with the above procedure. Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable.

Three surfactants were evaluated for their ability to dissolve the ketorolac - benzalkonium chloride complex and maintain a physically clear solution over an extended period of time. The three surfactants tested were: Octoxynol 40; Polysorbate 80 (Tween 80); and Myrj 52. Two concentrations of each surfactant were incorporated into the ophthalmic formulation, and these were placed at various temperatures for future visual observations.

	Octoxynol 40		Tween 80		Myrj 52	
	0.004%	0.02%	0.0035%	0.01%	0.0015%	0.01%
1 month						
60° C	clear	clear	clear	clear	clear	clear
40° C	clear	clear	very turbid	very turbid	turbid	turbid
RT	clear	clear	turbid	turbid	clear	clear
4-40° C	clear	clear	turbid	turbid	clear	clear
5 month						
60° C	clear	clear	clear	clear	clear	clear
40° C	clear	clear	turbid	turbid	turbid	turbid
RT	clear	clear	turbid	turbid	turbid	turbid

At the 5 month time period it was apparent that the Octoxynol 40 surfactant was superior to the other two surfactants. At 5 months, Tween 80 and Myrj 52 displayed turbidity when stored at RT. The presence of turbidity suggested the inability to solubilize a precipitate formation between the Ketorolac moiety and benzalkonium chloride.

A further study has shown a 2 year shelf life for the ophthalmic formulation. Precipitate formation and turbidity are not a problem with this formulation. Preservative efficacy is maintained throughout the 2 year shelf life.

In this way, for ophthalmic solutions that contain an NSAID with a –COOH group and BAC, EP '984 suggests using an ethoxylated octylphenol as the surfactant instead of polysorbate 80.

An ophthalmic solution marketed in the United States beginning in 1992 under the brand name Acular® contains ketorolac as the active ingredient, BAC as a preservative and an ethoxylated octylphenol (Octoxynol 40) as a surfactant. One of the patents listed in the Orange Book for the Acular® drug product was U.S. Patent No. 5,110,493, which claims priority from the same U.S. application (Serial No. 07/096,173, filed September 11, 1987) from which EP '984 claims priority.

EP '984 was not before the Patent and Trademark Office (PTO) during the prosecution of the '431 patent. Although U.S. Patent No. 5,110,493 and Canadian Patent 2,013,188 – both of which are related to EP '984 – were before the PTO during the prosecution of the '431 patent, neither contains Example 5, which teaches that ophthalmic solutions containing an NSAID with a –COOH group, BAC and an ethoxylated octylphenol as a surfactant are more stable than ophthalmic solutions containing an NSAID with a –COOH group, BAC and polysorbate 80 as a surfactant.

3. Schott Article

An article entitled "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of its Oligomer, Tyloxapol (Triton WR-1339)" and authored by Hans Schott ("the Schott article") was published in 1998 (Journal of Colloid and Interface Science, 205, 496-502 (1998)). Thus, the Schott article is prior art to the '431 patent under 35 U.S.C. § 102(b). The Schott article indicates that tyloxapol is a heptamer of Octoxynol 9 (Schott article at 496-97), which was one of the four specific ethoxylated octylphenols referred to in EP '984. The Schott article goes on to compare some of the properties of tyloxapol and Octoxynol 9, and concludes that tyloxapol has certain advantages. The Schott article was not before the PTO during the prosecution of the '431 patent.

4. U.S. Patent No. 6,274,609

U.S. Patent No. 6,274,609 ("the '609 patent") issued on August 14, 2001, and thus constitutes prior art to the '431 patent under 35 U.S.C. § 102(b). The '609 patent is assigned to Ono Pharmaceutical Co., Ltd. and Senju Pharmaceutical Co., Ltd. (the assignee of the '431 patent). The '609 patent describes ophthalmic formulations containing the active ingredient pranlukast (manufactured by Ono), BAC and a surfactant (Preparation Examples 1-4). The '609 patent describes using both tyloxapol and polysorbate 80 as surfactants. ('609 patent, col. 2, ll. 49-63.) However, the '609 patent indicates that solutions containing tyloxapol are more stable than solutions made containing polysorbate 80. Experiment 4 from the '609 patent describes an experiment in which the stability of solutions containing tyloxapol was compared with the stability of solutions containing polysorbate 80. ('609 patent, col. 6, l. 47 – col. 7, l. 45.) The solutions containing tyloxapol were found to be more stable in that there was more pranlukast

remaining in the tyloxapol solutions after two weeks. Experiment 4 from the '609 patent reads as follows:

> Experiment 4
>
> Test for stability of aqueous solution of pranlukast
>
> Method
>
> According to the formulations in Table 4, solutions A to F were prepared. Each solution was filled in a 5 ml-glass ampoule and stored at 60° C. for 2 weeks. After 2 weeks, pranlukast in the solution was determined by HPLC and its residual rate was calculated.

TABLE 4

	Formulation					
Component	A	B	C	D	E	F
pranlukasut	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
polysorbate 80	—	—	—	4.0 g	4.0 g	4.0 g
Tyloxapol	4.0 g	4.0 g	—	—	—	—
HCO-60*	—	—	4.0 g	—	—	—
boric acid	—	1.9 g	—	—	—	—
BHT**	—	—	—	—	0.01 g	—

TABLE 4-continued

Component	Formulation A	B	C	D	E	F
sodium edetate	—	—	—	—	—	0.01 g
sodium dihydrogen phosphate	0.1 g	—	0.1 g	0.1 g	0.1 g	0.1 g
benzalkonium chloride	0.005 g	—	—	—	—	—
0.1 N sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
sterilized purified water	up to total 100 ml	up to total 100 ml	up to total 100 ml	up to total 100 ml	upt to total 100 ml	up to total 100 ml
pH	7.0	7.0	7.0	7.0	7.0	7.0

*polyoxyethylene hydrogenated castor oil 60
**butylated hydroxytoluene

Results

The residual rate of pranlukast is shown in Table 5.

TABLE 5

	Residual rate (%) A	B	C	D	E	F
Immediately after preparation	100.0	100.0	100.0	100.0	100.0	100.0
After two weeks	99.6	99.4	98.9	85.0	97.5	95.1

As seen from Table 5, when Tyloxapol and polyoxyethylene hydrogenated castor oil 60 were used as the solubilizing agents (formulations A, B and C), the residual rate of pranlukast was more than 98% and was stable. When polysorbate 80 was used as the solubilizing agent (formulation D), although stability of pranlukast was somewhat lowered in comparison with the other surfactants, stability of more than 95% was obtained by adding the stabilizer, BHT or sodium edetate (formulations E and F).

In each solution, no deposit of any insoluble material was observed.

The '609 patent was not before the PTO during the prosecution of the '431 patent.

C. Level of Ordinary Skill in the Art

The subject matter of the '431 patent falls within the field of pharmaceutical sciences. The level of skill in the art would be high. The person of ordinary skill to whom the '431 patent is directed would generally be a pharmaceutical scientist involved in the research and development of pharmaceuticals, and would have a Ph.D. and several years of experience in the field. The amount of post-graduate level experience would depend upon the level of formal education and particular experience in the field. A person of ordinary skill in the art relevant to the '431 patent would easily have understood the prior art references referred to herein and would have the capacity to draw inferences from them.

D. Claims 1-22 of the '431 Patent Would Have Been Obvious from the Prior Art

Claim 1 of the '431 patent requires an aqueous liquid preparation formulated for ophthalmic administration "consisting essentially of" bromfenac (or a salt or hydrate thereof) and tyloxapol. The transitional phrase "consisting essentially of" permits the inclusion of ingredients besides bromfenac and tyloxapol if those additional ingredients "do not materially affect the basic and novel characteristics" of the claimed invention. *See In re Herz,* 537 F.2d 549, 551-552 (C.C.P.A. 1976). Claim 1 itself indicates that benzalkonium chloride may be included within the liquid preparation claimed in claim 1 (as long as it is the only quaternary ammonium compound in the preparation). However, benzalkonium chloride is not a required element of claim 1 since conditional or permissive elements in a claim do not narrow the claim. *See In re Johnston*, 435 F. 3d 1381 (Fed. Cir. 2006). The claims dependent on claim 1 (*e.g.*, claims 7 and 8) indicate that a preservative, buffer, thickener, stabilizer, chelating agent and pH controlling agent may be included in the liquid preparation claimed in claim 1. Accordingly, claim 1 requires an aqueous

liquid preparation formulated for ophthalmic administration containing bromfenac and tyloxapol, and may contain other ingredients as long as they do not materially affect the basic and novel elements of the claim.

Example 6 of the '225 patent describes an ophthalmic solution that includes the elements of claim 1 except for tyloxapol. The ophthalmic solution described in Example 6 includes bromfenac, which is an NSAID containing a –COOH group, BAC as a preservative and polysorbate 80 as a surfactant. EP '984 teaches that such solutions are unstable because the –COOH group of the NSAID will form a complex with BAC and precipitate out of solution. (EP '984, p. 2, ll. 40-45.) EP '984 teaches that this problem may be solved by using an ethoxylated octylphenol as a surfactant instead of polysorbate 80. (EP '984, p. 2, ll. 46-49 and Example 5.) EP '984 identifies Octoxynol 9 as one of just four specific examples of ethoxylated octylphenols that are preferred for use the invention described in EP '984. The Schott article teaches that tyloxapol is a heptamer of Octoxynol 9. Based on these teachings, it would have been obvious to substitute tyloxapol for polysorbate 80 in the ophthalmic solution described in Example 6 of the '225 patent so as to produce a more stable formulation and avoid the problem of the –COOH group of bromfenac forming a complex with the BAC and precipitating out of solution (and thereby making the solution turbid. This motivation would have been reinforced by the teaching of the '609 patent that tyloxapol provided more stable ophthalmic solutions than polysorbate 80. The resulting formulation (with tyloxapol being substituted for polysorbate 80 in the formulation of Example 6 of the '225 patent) would have included all of the elements of claim 1 of the '431 patent. Accordingly, claim 1 of the '431 patent would have been obvious from the prior art.

Claim 2 of the '431 patent is dependent on claim 1 and further requires that the bromfenac be in the form of a sodium salt. The bromfenac in the ophthalmic solution described

in Example 6 of the '225 patent is in the form of a sodium salt. Thus, claim 2 would have been obvious from the prior art for the reasons given above with respect to claim 1.

Claim 3 of the '431 patent is dependent on claim 1 and further requires that the bromfenac concentration be between about 0.01 w/v % and about 0.5 w/v %, and that the concentration of tyloxapol be between about 0.01 w/v % and 0.5 w/v %. The concentration of bromfenac in the ophthalmic solution described in Example 6 of the '225 patent falls within the range required by claim 3. And EP '984 teaches using a concentration of an ethoxylated octylphenol compound that falls within the range required by claim 3. (*See, e.g.*, EP '984, p. 4, ll. 8-18 and Examples 1, 2, 4 and 5.) Other prior art taught ophthalmic solutions containing an NSAID with a –COOH group, BAC and tyloxapol in the range required by claim 3. (See, *e.g.*, U.S. Patent No. 5,891,913 at Examples, 2 and 15 [0.1 w/v %]; U.S. Patent No. 6,342,524 at Example 2 [0.1 w/v %]; U.S. Patent No. 6,638,976 at Example 1, Formulation 3 [0.01 w/v %].) Thus, claim 3 would have been obvious from the prior art as well.

Claim 4 of the '431 patent is dependent on claim 3 and further requires that the bromfenac concentration be between about 0.05 w/v % and about 0.2 w/v %, and that the concentration of tyloxapol be between about 0.01 w/v % and 0.3 w/v %. The concentration of bromfenac in the ophthalmic solution described in Example 6 of the '225 patent falls within the range required by claim 4. And EP '984 teaches using a concentration of an ethoxylated octylphenol compound that falls within the range required by claim 4. (*See, e.g.*, EP '984, p. 4, ll. 8-18 and Examples 1, 2, 4 and 5.) Thus, claim 4 would have been obvious from the prior art.

Claim 5 of the '431 patent is dependent on claim 4 and further requires that the bromfenac concentration be about 0.1 w/v %. The concentration of bromfenac in the ophthalmic

solution described in Example 6 of the '225 patent is about 0.1 w/v %. Thus, claim 5 would have been obvious from the prior art.

Claim 6 of the '431 patent is dependent on claim 4 and further requires that the concentration of tyloxapol be about 0.02 w/v %. EP '984 teaches using this concentration of an ethoxylated octylphenol compound. (*See, e.g.*, EP '984, p. 4, ll. 8-18 and Examples 2 and 5.) Thus, claim 6 would have been obvious from the prior art.

Claim 7 of the '431 patent is dependent on claim 1 and further requires the inclusion of one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. The ophthalmic solution described in Example 6 of the '225 patent includes one or more such additives. Thus, claim 7 would have been obvious from the prior art.

Claim 8 of the '431 patent is dependent on claim 7 and further requires that (i) the preservative be benzalkonium chloride, (ii) the buffer be boric acid and/or sodium borate, (iii) the thickener be polyvinylpyrrolidone, (iv) the stabilizer be sodium sulfite, (v) the chelating agent be sodium edetate, and (vi) the pH controlling agent be sodium hydroxide. The ophthalmic solution described in Example 6 of the '225 patent includes benzalkonium chloride as a preservative, boric acid as a buffer, polyvinylpyrrolidone as a thickener, and sodium sulfite as a stabilizer. Although the chelating agent in Example 6 is disodium edetate, the '225 patent teaches the use of sodium edetate (*i.e.*, tetrasodium edetate) as a chelating agent, and thus it would have been obvious to use sodium edetate. ('225 patent, col. 4, ll. 33-39 and Examples 2 and 7.) And the '225 patent also teaches the use of sodium hydroxide as a pH controlling agent. ('225 patent, col. 3, ll. 62-67.) Thus, claim 8 would have been obvious from the prior art.

Claim 9 of the '431 patent is dependent on claim 8 and further requires that the pH be "from about 7 to about 9." The pH of the ophthalmic solution described in Example 6 of the '225 patent is 8, which falls within the range required by claim 9. Thus, claim 9 would have been obvious from the prior art.

Claim 10 of the '431 patent is dependent on claim 8 and further requires that the pH be "from about 7.5 to about 8.5." The pH of the ophthalmic solution described in Example 6 of the '225 patent is 8, which falls within the range required by claim 10. Thus, claim 10 would have been obvious from the prior art.

Claim 11 of the '431 patent is dependent on claim 4 and further requires that the concentration of the bromfenac be "about 0.2 w/v %." The '225 patent teaches using this concentration of bromfenac. ('225 patent, col. 4, ll. 40-46.) Thus, claim 11 would have been obvious from the prior art.

Claim 12 of the '431 patent is dependent on claim 4 and further requires that the concentration of tyloxapol be "about 0.3 w/v %." EP '984 teaches using this concentration of an ethoxylated octylphenol compound. (*See, e.g.*, EP '984, p. 4, ll. 8-18.) Thus, claim 12 would have been obvious from the prior art.

Claim 13 of the '431 patent is dependent on claim 12 and further requires the inclusion of one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. The ophthalmic solution described in Example 6 of the '225 patent includes one or more such additives. Thus, claim 13 would have been obvious from the prior art.

Claim 14 of the '431 patent is dependent on claim 13 and further requires that (i) the preservative be benzalkonium chloride, (ii) the buffer be boric acid and/or sodium borate, (iii)

the thickener be polyvinylpyrrolidone, (iv) the stabilizer be sodium sulfite, (v) the chelating agent be sodium edetate, and (vi) the pH controlling agent be sodium hydroxide. The ophthalmic solution described in Example 6 of the '225 patent includes benzalkonium chloride as a preservative, boric acid as a buffer, polyvinylpyrrolidone as a thickener, and sodium sulfite as a stabilizer. Although the chelating agent in Example 6 is disodium edetate, the '225 patent teaches the use of sodium edetate (*i.e.*, tetrasodium edetate) as a chelating agent, and thus it would have been obvious to use sodium edetate. ('225 patent, col. 4, ll. 33-39 and Examples 2 and 7.) And the '225 patent also teaches the use of sodium hydroxide as a pH controlling agent. ('225 patent, col. 3, ll. 62-67.) Thus, claim 14 would have been obvious from the prior art.

Claim 15 of the '431 patent is dependent on claim 11 and further requires that the concentration of tyloxapol be about 0.02 w/v %. EP '984 teaches using this concentration of an ethoxylated octylphenol compound. (*See, e.g.*, EP '984, p. 4, ll. 8-18 and Examples 2 and 5.) Thus, claim 15 would have been obvious from the prior art.

Claim 16 of the '431 patent is dependent on claim 15 and further requires the inclusion of one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. The ophthalmic solution described in Example 6 of the '225 patent includes one or more such additives. Thus, claim 16 would have been obvious from the prior art.

Claim 17 of the '431 patent is dependent on claim 16 and further requires that (i) the preservative be benzalkonium chloride, (ii) the buffer be boric acid and/or sodium borate, (iii) the thickener be polyvinylpyrrolidone, (iv) the chelating agent be sodium edetate, and (v) the pH controlling agent be sodium hydroxide. The ophthalmic solution described in Example 6 of the '225 patent includes benzalkonium chloride as a preservative, boric acid as a buffer, and

polyvinylpyrrolidone as a thickener. Although the chelating agent in Example 6 is disodium edetate, the '225 patent teaches the use of sodium edetate (*i.e.*, tetrasodium edetate) as a chelating agent, and thus it would have been obvious to use sodium edetate. ('225 patent, col. 4, ll. 33-39 and Examples 2 and 7.) And the '225 patent also teaches the use of sodium hydroxide as a pH controlling agent. ('225 patent, col. 3, ll. 62-67.) Thus, claim 17 would have been obvious from the prior art.

Claim 18 of the '431 patent is an independent claim that requires an aqueous liquid preparation formulated for ophthalmic administration "consisting essentially of" (i) bromfenac (or a salt or 1/2, 1 or 3/2 hydrate thereof), (ii) tyloxapol, (iii) boric acid, (iv) sodium tetraborate, (v) EDTA sodium salt, (vi) benzalkonium chloride, (vii) polyvinylpyrrolidone, and (viii) sodium sulfite. Claim 18 further requires that benzalkonium chloride be the only quaternary ammonium compound in the aqueous liquid preparation. As explained above with respect to claim 1, based on the prior art (and, in particular, the teachings of EP '984), it would have been obvious to substitute tyloxapol for polysorbate 80 in the ophthalmic solution described in Example 6 of the '225 patent. The resulting ophthalmic solution would have contained bromfenac sodium monohydrate (which is bromfenac or a salt or 1/2, 1 or 3/2 hydrate thereof), tyloxapol, boric acid, borax (*i.e.*, sodium tetraborate[1]), benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite. And benzalkonium chloride would have been the only quaternary ammonium compound in the resulting formulation. Although the resulting formulation would have contained disodium edetate as a chelating agent, the '225 patent teaches the use of sodium edetate (*i.e.*, tetrasodium edetate) as a chelating agent, and thus it would have been obvious to use sodium edetate. ('225

[1] During prosecution, applicants indicated that "sodium tetraborate is also known as borax." (March 24, 2010 Amendment at 7.)

patent, col. 4, ll. 33-39 and Examples 2 and 7.) Thus, claim 18 would have been obvious from the prior art.

Claim 19 of the '431 patent is dependent on claim 18 and further requires that the bromfenac be in the form of a sodium salt. The bromfenac in the ophthalmic solution described in Example 6 of the '225 patent is in the form of a sodium salt. Thus, claim 19 would have been obvious from the prior art for the reasons given above with respect to claim 18.

Claim 20 of the '431 patent is dependent on claim 19 and further requires that the bromfenac concentration be between about 0.01 w/v % and about 0.5 w/v %, and that the concentration of tyloxapol be about 0.02 w/v %. The concentration of bromfenac in the ophthalmic solution described in Example 6 of the '225 patent falls within the range required by claim 20. And EP '984 teaches using a concentration of an ethoxylated octylphenol compound that is the same as the concentration required by claim 20. (*See, e.g.*, EP '984, p. 4, ll. 8-18 and Examples 2 and 5.) Thus, claim 20 would have been obvious from the prior art.

Claim 21 of the '431 patent is dependent on claim 20 and further requires that the concentration of bromfenac be "about 0.01 w/v %." The '225 patent teaches using this concentration of bromfenac. ('225 patent, col. 4, ll. 40-46.) Thus, claim 21 would have been obvious from the prior art.

Claim 22 of the '431 patent is dependent on claim 20 and further requires that the concentration of bromfenac be "about 0.1 w/v %." The concentration of bromfenac in the ophthalmic solution described in Example 6 of the '225 patent is about 0.1 w/v %. Thus, claim 22 would have been obvious from the prior art.

E. Secondary Considerations

In making a determination regarding obviousness, a court must examine any secondary considerations (also called objective indicia) of non-obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1079–80 (Fed. Cir. 2012). Courts look to such "objective indicia" to guard against a challenger relying on hindsight in attacking the validity of a patent. The secondary considerations that courts have looked to include, for example, unexpected results, commercial success of the invention, licensing of the invention, whether the invention solved a long-felt but unmet need, copying of the invention by others, expressions of disbelief by experts, and failure of others. *See Graham*, 383 U.S. at 17–18; *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000).

The patentee bears the burden of establishing that any alleged commercial success is due to the patented invention and not, for example, due to marketing activities. *See, e.g., Brown*, 229 F.3d at 1129–30; *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003). Here, the patentee must show that the commercial success is due to the allegedly innovative nature of the claimed formulations, as opposed to the properties of bromfenac itself, which is disclosed in the prior art. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1068 ("If commercial success is due to an element in the prior art, no nexus exists.") (citing *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011)). There is no evidence, that the commercial success of the Prolensa® drug product, if any, is due to the claimed features rather than the fact that the drug is, for example, supported by extensive marketing.

With respect to "unexpected results," the applicants, during prosecution of the '431 patent, argued that the claimed aqueous liquid preparations (containing tyloxapol as a surfactant)

had surprisingly improved stability in comparison with prior art formulations (containing polysorbate 80 as a surfactant). The increased stability of the claimed aqueous liquid preparations is not surprising, however, when viewed in light of the prior art. Specifically, EP '984 disclosed that substituting an ethoxylated octylphenol compound for polysorbate 80 as a surfactant would improve the stability of an ophthalmic solution containing an NSAID with a –COOH group and BAC. And the Schott article taught that tyloxapol was a heptamer of one of the four specific ethoxylated octylphenol compounds disclosed in EP '984.

Further, there is no evidence of copying by others even though an ANDA was filed. Courts have held that copying in the context of an ANDA is not compelling evidence of nonobviousness because "the ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001); *see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed. Appx. 978, 983 (Fed. Cir. 2010) ("we do not find compelling Purdue's evidence of copying in the ANDA context where a showing of bioequivalency is required for FDA approval"). In addition, there is no evidence that the '431 patent solved a long-felt but unmet need. Similarly, there is no evidence of expressions of disbelief by experts, or failure of others to make the claimed invention.

Here, where there is a strong and straight-forward case of obviousness, in which the art provides motivation to modify the closest prior art in order to make the claimed invention, the claims should be found invalid in spite of any evidence of secondary considerations. *Dow Chem. Co. v. Halliburton Oil Well Cementing Co.*, 324 U.S. 320, 330 (1945) ("[Secondary] considerations are relevant only in a close case where all other proof leaves the question of invention in doubt. Here the lack of invention is beyond doubt and cannot be outweighed by

such factors [as long felt need and commercial success].") (citations omitted); *see also Graham*, 383 U.S. at 36 (ruling that the secondary considerations of commercial success and long-felt need presented by the patentee did not overcome the clearly obvious nature of the claimed invention in view of the prior art); *Geo M. Martin Co.*, 618 F.3d at 1306 ("Balancing all of the secondary considerations, this court agrees with the district court that, in light of the strong evidence of obviousness based on the . . . prior art coupled with the near-simultaneous invention, . . . [the] objective evidence of non-obviousness, even if fully credited by a jury, would fail to make a difference in this case.").

IV. CONCLUSION

For the reasons stated above, it is Lupin's opinion that the claims of U.S. Patent No. 8,129,431 are invalid, unenforceable, and/or not infringed by the manufacture, use, or sale of Lupin's proposed product. Lupin reserves the right to demonstrate additional grounds, reasons and authorities that the claims of the '431 patent are invalid, unenforceable, and/or not infringed.