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RESEARCH**

APPLICATION NUMBER:

208144Orig1s000

OTHER REVIEW(S)

Labeling Review for Brimonidine Tartrate Ophthalmic Solution 0.025%, Addendum 2 *Draft Labeling*

SUBMISSION DATES: December 20, 2017

NDA/SUBMISSION TYPE: NDA 208144

ACTIVE INGREDIENTS: Brimonidine Tartrate, 0.025%

DOSAGE FORMS: Solution

SPONSOR: Bausch+Lomb/Valeant Pharmaceuticals
Shaun A. Mbithi
Sr. Manager, Regulatory Affairs
Valeant Pharmaceuticals NA LLC
908-541-2166
shaun.mbithi@bausch.com

REVIEWER: Arlene Solbeck, M.S.

TEAM LEADER: Steven Adah, Ph.D.

PROJECT MANAGER Jung Lee, RPh

I. BACKGROUND

NDA 208144 is a proposed Rx to OTC switch for brimonidine tartrate ophthalmic solution 0.025% that was originally submitted on February 27, 2017. The purpose of this product is the reduction of eye redness. The sponsor submitted two container sizes with both commercial (trade) and sample labeling as shown in the below table.

The original labeling submitted in this NDA included the proposed name of Luminesse™. This name was withdrawn by Bausch+Lomb on November 14, 2017 after FDA expressed concerns about the similarity of the name to a marketed cosmetic product. In correspondence dated November 16, 2017, Bausch+Lomb submitted two new names for consideration, (b) (4) as the primary choice and Lumify™ as an alternate choice. Subsequently, on December 19th, the name (b) (4) was withdrawn and the name Lumify™ was proposed. On December 21, 2017 the

name Lumify™ was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

Initial labeling comments were submitted to the sponsor on December 5, 2017. On December 11, 2017 the sponsor responded to the comments provided on December 5 with revised draft labeling. On December 15, 2017 the sponsor was sent an information request (IR) regarding the labeling proposed on December 11. The December 15 IR requested that the sponsor remove the claim on the carton and container PDPs (b) (4) and on the right side of the outer carton (b) (4) because they are not supported by adequate data (see Labeling Review dated 12/19/17). The below labeling was submitted in response to the December 15, 2017 IR:

Labeling Submitted on December 20, 2017	Representative of Following SKUs
7.5 mL container label and carton	N/A
7.5 mL container label and carton - Sample	N/A
2.5 mL container label and carton	N/A
2.5 mL container label and carton - Sample	N/A

The proposed labeling was compared to the comments submitted to the sponsor in the December 15, 2017 IR.

II. REVIEWER'S COMMENTS

- A. The comments below are for the four outer cartons and corresponding four inner containers submitted in the sponsor's December 20, 2017 submission. The four carton/container combinations are the 7.5 mL and 2.5 mL trade (for marketing) cartons and containers and the 7.5 mL and 2.5 mL sample cartons and containers.

i. Outer Carton Label Outside Drug Facts

- a. In the December 15 IR to the sponsor, the sponsor was asked to remove (b) (4) from the PDPs of the cartons, and to remove (b) (4) from the right side panels of the cartons. As discussed in the Label Review dated 12/19/17, the phrase (b) (4) The labels submitted by the sponsor on December 20, 2017 had been revised and no longer included the statements about (b) (4).
- b. In addition, the sponsor revised the proposed proprietary name to Lumify™ in the December 20, 2017 submission.

Reviewer Comments: The sponsor made the requested changes. This labeling is acceptable.

Subsequent to the removal of the statements about (b) (4), the sponsor proposed by email that in place of (b) (4) an alternative could be (b) (4). This was discussed with the sponsor by telephone and both parties agreed, given the short timelines for approval, that the sponsor should propose additional statements in a labeling supplement

ii. Outer Carton Drug Facts Label (back panel; continuation on left side of the outer carton)

- a. In the December 15 IR to the sponsor, no changes were requested from the sponsor. This labeling is acceptable.

iii. Inner Container Labels

- a. In the December 15 IR to the sponsor, the sponsor was requested to remove the claim (b) (4) from the container label PDPs. The labels submitted by the sponsor on December 20, 2017 had been revised and no longer included the statement about (b) (4).
- b. In addition, the sponsor revised the proposed proprietary name to - Lumify™ in the December 20, 2017 submission.

Reviewer Comments: The sponsor made the change as requested. This labeling is acceptable.

B. Recommendations

The following comments can be conveyed to the sponsor:

Issue an APPROVAL letter to the sponsor for the product labeling submitted on December 20, 2017.

Submit final printed labeling for the 2.5 mL and 7.5 mL sample product cartons and outer containers – and the 2.5 mL and 7.5 mL Trade product cartons and outer containers, identical to the product labeling submitted on December 20, 2017, within 30 days after initial marketing of the product.

Remind the sponsor to remove the flag “New Product” from the principal display panel six months after introduction into the marketplace.

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted on December 20, 2017 and evaluated in this labeling review.

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/s/

ARLENE H SOLBECK
12/21/2017

STEVEN A ADAH
12/21/2017

Labeling Review for Brimonidine Tartrate Ophthalmic Solution 0.025%, Addendum 1 *Draft Labeling*

SUBMISSION DATES:	December 11, 2017
NDA/SUBMISSION TYPE:	NDA 208144
ACTIVE INGREDIENTS:	Brimonidine Tartrate, 0.025%
DOSAGE FORMS:	Solution
SPONSOR:	Bausch+Lomb/Valeant Pharmaceuticals Shaun A. Mbithi Sr. Manager, Regulatory Affairs Valeant Pharmaceuticals NA LLC 908-541-2166 shaun.mbithi@bausch.com
REVIEWER:	Arlene Solbeck, M.S.
TEAM LEADER:	Steven Adah, Ph.D.
PROJECT MANAGER	Jung Lee, RPh

I. BACKGROUND

NDA 208144 is a proposed Rx to OTC switch for brimonidine tartrate ophthalmic solution 0.025% that was originally submitted on February 27, 2017. The purpose of this product is the reduction of eye redness. The sponsor submitted two container sizes with both commercial (trade) and sample labeling as shown in the below table. The original labeling submitted in this NDA included the proposed name of Luminesse™. This name was withdrawn by Bausch+Lomb on November 14, 2017 after FDA expressed concerns about the similarity of the name to a marketed cosmetic product. In correspondence dated November 16, 2017, Bausch+Lomb submitted two new names for consideration, (b) (4) and Lumify. Review of these two names is pending as of this review.

Labeling comments were submitted to the sponsor on December 5, 2017. This review covers the sponsor's responses to the comments provided on December 5.

Submitted Labeling	Representative of Following SKUs
7.5 mL container label and carton	N/A
7.5 mL container label and carton - Sample	N/A
2.5 mL container label and carton	N/A
2.5 mL container label and carton - Sample	N/A

The proposed labeling was compared to the comments submitted to the sponsor on December 5, 2017.

II. REVIEWER'S COMMENTS

- A. Unless otherwise noted the comments below are for the four outer cartons submitted in the December 11, 2017 submission. The four cartons are the 7.5 mL and 2.5 mL trade (for marketing) cartons and the 7.5 mL and 2.5 mL sample cartons.

i. Outer Carton Label Outside Drug Facts

- a. The following recommendations/revisions to the principle display panel (PDP) were provided to Bausch+Lomb on December 5, 2017 by email.

1. The word *New* should be amended to read *New Product*
2. The statement of identity should be placed in 14 pt bold font and in all caps
3.  (b) (4)
4. 

The sponsor made the changes to items 1, 2, and 4 as requested. The sponsor changed  (b) (4)

Reviewer Comments: As noted in the original comments to the sponsor, this product  (b) (4). The statement  (b) (4) his statement is not acceptable.

- b. The following recommendations/revisions to the right side of the outer carton were provided to Bausch+Lomb on December 5, 2017 by email.

 (b) (4)

Reviewer Comments: The statement, as revised, is not acceptable. The phrase (b) (4)

[REDACTED]

- c. The following revisions/recommendations to the top panel of the outer carton were provided to Bausch + Lomb on December 5, 2017 by email.
1. The sponsor was asked to revise the tamper evident feature to more clearly identify how a consumer can tell if tampering has occurred. FDA recommended

“DO NOT USE IF NECKBAND IMPRINTED WITH THE YELLOW (mortar and pestle symbol) AND THE WORDS “PROTECTIVE SEAL” IS TORN OR BROKEN

The sponsor made these changes. This labeling is acceptable

- d. The following revisions/recommendations to the bottom panel of the carton were provided to Bausch + Lomb on December 5, 2017 by email.
1. Identify the expiry date format you intend to use. We recommend a format like either MMMYYYY or MMMDDYYYY.

The sponsor responded by identifying the format as MMYYY.

Reviewer Comments: The expiry date is not printed on the label but is believed to be punched in with the packaging of each lot. The punch format is MMYYY. The recommendations of MMMYYYY or MMMDDYYYY come from the DMEPA guidance “*Guidance for Industry – Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*”. While we agree the DMEPA proposals for expiration dating provides the consumer with better understanding of a products expiration date, the proposed MMYYY meets the regulations as spelled out in 21 CFR 211.137 and 201.17. This is acceptable.

ii. Outer Carton Drug Facts Label (back panel; continuation on left side of the outer carton

- a. The following recommendations/revisions were provided to the sponsor on December 5, 2017 in the form of a template:

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Reviewer Comment: All changes were made as requested. These panels are acceptable. This reviewer previously listed some other potential recommendations for the label (Label Review dated 11/28/17) as follows:

1. We consider the opaqueness of the inner container an issue if the sponsor advises not to use the product if the solution changes color or becomes cloudy (***Do not use***). However, the removal of the statement eliminates important information the consumer needs to safely use this product. Therefore, the statement is being retained.
2. We recommend that the sponsor add a bullet for the tamper evident feature in ***Other information***. The sponsor chose not to make this change and that is acceptable. There is no regulation that states that it should appear in that section – plus the sponsor has it on the carton and on the immediate container. This is acceptable.
3. Previous correspondence (8/26/15 and 9/30/15) with the sponsor suggested that the sponsor include a statement to discard the product 120 days after opening in their labeling. However, we believe that this statement (b) (4)

not necessary based on information from the clinical pharmacology reviewers (reviews dated 10/31/17) and/or inconsistent from similar products in this class on the OTC market.

4. Chemistry reviewers (review of 11/6/17) recommended strengthening the storage statement (*Other information*) by addition of a maximum storage temperature ("discard the product if stored at any temperature above 30°C (86°F)"). In a review by DTOP (Division of Transplant and Ophthalmology Products dated 11/27/17) DTOP advised that this statement is "not warranted from a clinical prospective since changes in pH and osmolality do not reach levels that are likely to affect the safety or efficacy of the drug product". After further discussion with the Chemistry and DTOP reviewers, DNDP decided the statement was not necessary.

iii. Immediate Container Label

The following recommendations/revisions were provided to the sponsor on December 5, 2017:

1. Remove the claim (b) (4) from the container label PDP.
2. Revise the tamper evident feature to be identical to the carton labeling.

The sponsor made the change as requested in item 2. However, the sponsor changed (b) (4). As discussed above for the PDP, this claim is not acceptable and must be removed from the inner container labels.

B. Recommendations

The following comments can be conveyed to the sponsor.

1. The claims on the carton PDP (b) (4) and on the right side of the carton (b) (4) are not supported by adequate data. We request that you provide sufficient data to support the claims or remove them from the labeling.
2. The claim on the inner container PDP (b) (4) should also be removed from the labeling if not supported by adequate data.

III. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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/s/

ARLENE H SOLBECK
12/19/2017

STEVEN A ADAH
12/19/2017

Labeling Review for Luminesse™ Ophthalmic Solution

SUBMISSION DATES:	February 27, 2017 November 17, 2017
NDA/SUBMISSION TYPE:	NDA 208144
ACTIVE INGREDIENTS:	0.025% brimonidine tartrate ophthalmic solution
DOSAGE FORMS:	Ophthalmic Solution
SPONSOR:	Bausch & Lomb, subsidiary of Valent Pharmaceuticals North America LLC 400 Somerset Corporate Blvd, Bridgewater NY 08807
REVIEWER:	Arlene Solbeck, MS, IDS
SECONDARY REVIEWER:	Steve Adah, Ph.D., IDS Team Leader

I. BACKGROUND

On February 27, 2017 Bausch & Lomb (B&L), a wholly-owned subsidiary of Valeant Pharmaceuticals International Inc. (VPII), and an affiliate of Valeant Pharmaceuticals North America LLC (VPNA), submitted an original NDA resubmission – 208144 - for Luminesse™ (Brimonidine tartrate ophthalmic solution, 0.025%) pursuant to Section 505(b)(2) of the FD&C Act. NDA 208144 was originally submitted on March 31, 2015 and received a Refusal to File (RTF) letter from FDA on May 29, 2015. B&L stated that this current NDA submission was updated in accordance with feedback from FDA. LUMINESSE™ is a topical vasoconstrictor OTC formulation to relieve redness of the eye due to minor eye irritations.

II. SUBMITTED LABELING

The sponsor stated that they used the following sections of the CFR for guidance for their labeling:

- §201.66 – Drug Facts
- §203.38 – Labeling for samples
- §211.132 – Tamper Evident Packaging and Labeling

- \$349.50 – Labeling of Ophthalmic Products
- \$349.75 – Labeling of Ophthalmic Products

The sponsor also stated that this application relies in part on the Agency's prior findings of nonclinical safety for the approved Rx listed product, Alphagan 0.2% (NDA 020613). The ALPHAGAN label was used as a reference when reviewing the sponsor's proposed labeling.

The sponsor submitted the following proposed carton and container labeling:

SKU	Container (Sponsor ID#)	Carton (Sponsor ID#)
2.5 mL trade	3812100	1715
2.5 mL sample	3811900	1714
7.5 mL trade	3812300	1716
7.5 mL sample	3820000	1713

Samples represent product that are NOT FOR SALE.

III. REVIEWER'S COMMENTS

A. Luminesse - Trade SKUs and Sample SKUs

The labeling comments below apply to all SKUs. The differences between the 2.5mL sample SKU and the 2.5 trade SKU or the 7.5 sample SKU and the 7.5 trade SKU are few and discussed below, in section B, after the major labeling comments.

i. Outer Carton Label Outside Drug Facts

Principal Display Panel (PDP)

IDS Comments: We have the following issues with the PDP labeling:

- The proprietary name "Luminesse™" was questioned by the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Nonprescription Drug Products (DNDP) clinical reviewers because there is another product on the market with a very similar name: "Luminess" cosmetic. Both groups of reviewers provided their concerns regarding potential confusion between the two products in their October 31, 2017 reviews. The sponsor was notified on November 7, 2017. The sponsor withdrew the name "Luminesse™" on November 14, 2017 and submitted labeling with proposed a new name (b) (4) and a secondary proposed name "Lumify" on November 17, 2017. These names are currently under review.
- The statement of identity (SOI) should be revised to be entirely in bold type, all capital letters, and enlarged to be 50% the size of the proprietary name (i.e. font size 14). The Division of Medication Error Prevention and Analysis (DMEPA) (Labeling Review of November 8, 2017) recommended increasing the prominence of the established name in accordance with Rx labeling (21 CFR 201.10(g)(2) and DNDP agrees.

- The claim on the PDP (b) (4) is not supported by data and is misleading and inaccurate according to the DTOP clinical reviewer (Martin Nevitt MD Review of October 31, 2017) and supported by DNDP (Clinical Reviewer Jenny Kelty MD in her review dated 10/31/17). According to these reviewers, (b) (4) the product temporarily relieves redness of the eye. This claim overstates the efficacy of the product.
- The claim (b) (4) is not supported by data. It is unclear what (b) (4) means and the rest of the claim also overstates the safety of the proposed product (b) (4). This claim must be removed from the PDP. This is supported by the DNDP Clinical Reviewer (Jenny Kelty MD in her review dated 10/31/17).
- DNDP recommends revising the “NEW” flag to read “NEW PRODUCT” in accordance with current policy, so that consumers know what it is that is “new” about the product. In addition, the flag “NEW PRODUCT” should be removed after 6 months of marketing.

Top Panel

IDS Comments: The regulations at 21 CFR 211.132 state that a tamper- evident package should have “one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred” and the feature must be described in the labeling. DNDP recommends some revisions for the tamper evident feature to make it clearer how consumers can judge that tampering has occurred. We recommend “DO NOT USE IF NECKBAND IMPRINTED WITH THE YELLOW (mortar and pestle symbol) AND THE WORDS “PROTECTIVE SEAL” IS TORN OR BROKEN”.

Side Panel (Right of the PDP)

IDS Comments: The labeling on the side of the carton should be revised or removed. It currently reads: “Luminesse™ eye drops, from the eye experts at Bausch & Lomb, (b) (4) (b) (4). Just one drop works within a minute and lasts up to 8 hours. (b) (4)” The claim about (b) (4) is not supported by data as discussed above in the PDP section above, and the claim about (b) (4) is not supported by data (see above in PDP section).

DMEPA in their review (November 8, 2017) suggested that the sponsor should identify the expiry date format they intend to use and recommend using a format like either MMMYYYY or MMMDDYYYY to minimize confusion and reduce the risk for deteriorated drug medication errors. The regulations for expiration dating at 211.137 to not specify the format. We agree with DMEPA’ recommendation and recommend either format.

IDS Comment: Other than what is discussed above, the labeling on the outer carton (not including the Drug Facts Label) is acceptable.

ii. Outer Carton Drug Facts Label

a. Active ingredient/Purpose

The sponsor proposes the following labeling for Active ingredient/Purpose:

Active ingredient

Brimonidine tartrate (0.025%).....

Purpose

Redness reliever

IDS comment: This labeling is acceptable.

b. Use

The sponsor proposes the following labeling for under the Use subheading:

Use

- relieves redness of the eye due to minor eye irritations

IDS comment: The labeling is acceptable.

c. Warnings

The sponsor proposes the following warnings:

Do not use

- if solution changes color or becomes cloudy (b) (4)

IDS comments: We consider the opaqueness of the inner container an issue if the sponsor advises not to use the product if the solution changes color or becomes cloudy (first bulleted statement). The sponsor should remove this statement or provide justification for it. (b) (4)

(b) (4)

- remove contact lenses before use
- wait at least 10 minutes before re-inserting contact lenses after use
- do not touch tip of container to any surface to avoid contamination
- replace cap after use

IDS comment: The statements that the sponsor included under (b) (4) appear to belong more under "Directions." Thus, we recommend moving these bulleted statements to under the "Directions" subheading and delete this section.

Stop use and ask a doctor if

- you experience eye pain, changes in vision, continued redness or irritation of the eye
- condition worsens or persists for more than (b) (4)

IDS comment: This labeling is acceptable at this time. Changes to this language may occur later.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away

IDS comment: This labeling is acceptable.

Additional IDS Comments: DNDP IDS and Clinical reviewers discussed with clinical reviewers from DTOP about the inclusion of other warnings from the ALPHAGAN Rx label for 0.2% brimonidine tartrate (NDA 20614) or under 21 CFR 349.75 (regulations for labeling OTC ophthalmic vasoconstrictors) such as:

- (1) a warning for drug interactions between brimonidine tartrate and antihypertensives, CNS depressants, tricyclic antidepressants or monoamine oxide inhibitors and antidepressant drugs (ALPHAGAN label);*
- (2) to include under the subheading “when using this product” that pupils may become enlarged temporarily (§349.75);*
- (3) “increased redness of the eye may result from over use of this product” (§349.75); and*
- (4) to include under the subheading “Ask a doctor before use if you have” a history of narrow angle glaucoma or increased pressure inside the eye (§349.75).*

DTOP advised that these warnings were not necessary because these problems were found in much higher concentrations of brimonidine and that the clinical trials presented in the NDA did not support a rebound redness warning. The exclusion of these statements from the Drug Facts label is supported by the DNDP clinical review dated October 31, 2017 (Jenny Kelty MD) and by DTOP (W. Boyd in email dated 10/2/17).

d. Directions

The sponsor proposes the following statements under the subheading “Directions”:

- **Adults and children 5 years of age and** (b) (4) instill 1 drop in the affected eye(s) every 6-8 hours, (b) (4) more than four times daily.
- **Children under 5 years:** consult a doctor

IDS Comments: The sponsor should make the following revisions to the “Directions” statements:

- In the first bulleted statement, “**Adults and children 5 years and** (b) (4):” should not be bolded; “Adults” should begin with a lower case “a” and the word (b) (4) should be changed to “over” to be consistent with other OTC products.
- We recommend the first bulleted statement be broken down into two bulleted statements as follows:

- instill 1 drop in the affected eye(s) every 6-8 hours
- do not use more than 4 times daily

(There is no period after the word “daily”).

- Move the statements from (b) (4) under the first two bulleted statements above as follows:
 - instill 1 drop in the affected eye(s) every 6-8 hours
 - do not use more than 4 times daily
 - remove contact lenses before use
 - wait at least 10 minutes before re-inserting contact lenses after use
 - do not touch tip of container to any surface to avoid contamination
 - replace cap after each use
- Then add a concomitant drug warning statement “if using other ophthalmic products while using this product, wait at least 5 minutes between each product” as follows: (from the Rx ALPHAGAN label)
 - instill 1 drop in the affected eye(s) every 6-8 hours
 - do not use more than 4 times daily
 - remove contact lenses before use
 - wait at least 10 minutes before re-inserting contact lenses after use
 - if using other ophthalmic products while using this product, wait at least 5 minutes between each product
 - do not touch tip of container to any surface to avoid contamination
 - replace cap after use
- In the last bulleted statement “**Children under 5 years:** consult a doctor”, unbold the first part of the statement “**Children under 5 years**” and revise the upper case “C” in “Children” to lower case.

e. Other Sections/Issues

Other Information

The sponsor proposes the following labeling:

(b) (4)

IDS Comments:

- *Add a bullet to describe the tamper-evident feature. This is discussed above in the outer carton labeling section. The same tamper statement should be repeated under this section. The tamper-evident feature statement is preceded by “This product contains a tamper-evident feature”.*
- *Chemistry (Review of 11/6/17) recommends strengthening the storage statement to include a warning to discard product if it has been stored at any temperature exceeding 30°C (86°F) based on stability testing. In a review dated 11/27/17) Dr. Wiley Chambers stated that this is not warranted from a clinical perspective. This has not been resolved yet.*

- Chemistry (Review of 11/6/17) states that the carton discard statement of 120 days for both fill configurations is supported by in-use and stability data up to 120 days. However, DTOP recommends removing the discard statement because it is not supported by submitted data (review of 10/31/17) (b) (4). DTOP argues that consumers would have to also remember when the bottle was opened to be able to recognize when 120 days occurred. Furthermore, DMEPA (review of 11/8/17) recommends keeping the discard statement and moving it to the PDP.

Previous correspondence with the sponsor suggests that the Agency recommended that the sponsor have a discard statement in their labeling. On 8/26/15 in correspondence to the sponsor it was stated “Provide in-use stability data for the different presentations of drug product that will cover the intended period of use. Accordingly, update label indicating “don’t use the product --- days after opening the bottle”. Then on 9/30/15 in a correspondence letter regarding the Agency’s request that the labeling be updated to indicate “don’t use the product --- days after opening the bottle” the sponsor asked if this is a new requirement to have the discard date indicated on the labeling of OTC products - and we responded “We are aware that the statement “don’t use the product --- days after opening the bottle” is not a regulatory requirement; however, because you will be performing the “in-use-stability study for the drug product” we recommend including this information in the labeling”.

In a review dated 11/27/2017, Dr. Wiley Chambers states that the necessity of discarding the product after 120 days after opening is not supported. There is no justification to shorten the allowable use to a period shorter than the established shelf life of the product (as supported by the standard stability studies). This issue hasn’t been resolved yet.

Questions or comments

IDS Comment: This labeling is acceptable.

Drug Facts Specifications

The Drug Facts specifications (e.g., font size, barlines, hairlines, etc.) are acceptable.

iii. Immediate Container Label

IDS Comment: The labeling is acceptable with the following exceptions:

- The claim (b) (4) should be removed from the container label PDP. This is discussed above in the outer carton labeling section comments (III.A.i).
- The Tamper-Evident Feature Labeling to the left of the container label PDP should be revised to be identical to the carton and Drugs Facts labeling (see above III.A. (top Panel) and III.A.ii(e)).

The rest of the immediate container label is acceptable.

B. Luminesse™ - Sample SKU Labeling vs. Trade SKU Labeling

The only difference between the 2.5 ml and 7.5 ml trade SKUs and the 2.5 ml and 7.5 sample SKUs is:

- The sample SKUs contain the words SAMPLE-NOT FOR SALE at the bottom of the PDP and on the container label to the right of the proprietary name.

The only difference between the 2.5 mL SKUs and the 7.5 mL SKUs is:

- The 2.5 mL SKUs are in a smaller carton. For the smaller cartons, the sponsor used an alternative bullet format in Drug Facts where more than one bullet can be on the same line. It is an alternative FDA allows for smaller package sizes.
- The products also differ in fill weight and fill line on the figure on the outer carton side panel.

IDS Comment: These labeling differences are acceptable.

IV. RECOMMENDATIONS

Reviewer Notes

- Proprietary name: Sponsor submitted a request to withdraw the name “Luminesse™” on November 14, 2017 and submitted a request for a new name (b) (4) or “Lumify” on November 17, 2017. These names are currently being reviewed by the review team for acceptability. It will become an IR to the sponsor if the name is not deemed acceptable.
- Under “Do not use” (b) (4)
- Under “Other information” the decision as to whether to strengthen the storage statement is unresolved. The decision as to whether to delete the discard statement is not resolved. These may become IRs to the sponsor if the storage statement should be strengthened and/or the discard statement should be deleted.

The Sponsor should revise their labeling as follows:

Carton Principal Display Panel (PDP)

- Enlarge the Statement of Identity to be 50% the size of the proprietary name (i.e. use font size 14), all capital letters, and bolded – making it more prominent.
- Remove the claim (b) (4). It is not supported by data and overstates the efficacy of the product.

- Remove the claim (b) (4). It is not supported by data. It overstates the efficacy of the product (b) (4).
- The word “NEW” (to the left of the figure of the eye) should be revised to “NEW PRODUCT” and should be removed after 6 months of marketing.
- Identify the format you intend to use for expiration date labeling. We recommend you use a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).

Carton Top Panel

- Revise Tamper Evident Feature labeling to make it clearer how consumers can judge that tampering has occurred. We recommend “DO NOT USE IF NECKBAND IMPRINTED WITH YELLOW (mortar and pestle symbol) AND THE WORDS “PROTECTIVE SEAL” IS TORN OR BROKEN”.

Carton Side Panel (Right of the PDP)

- Revise or delete labeling on the side of the carton above the figure of the inner container that currently reads: (b) (4) TM “eye drops, from the eye experts at Bausch & Lomb, (b) (4). Just one drop works within a minute and lasts up to 8 hours. (b) (4). The claim about (b) (4) is not supported by data and is misleading and inaccurate. (b) (4) the product temporarily relieves redness of the eye. The claim (b) (4) is not supported by data. Both statements overstate the effectiveness of the product (b) (4).

Carton Outer Carton Drug Facts Label

- Warnings: Under “Do not use”, since the bottle is opaque, justify or delete the bulleted statement that says not to use the product if the solution has changed color or becomes cloudy.
- Warnings: Moved the bulleted statements under (b) (4) to the “Directions” subheading (see Directions below) and delete (b) (4).
- Directions: Revise this section as follows:
 - In the first bulleted statement, unbold “**Adults and children 5 years and (b) (4)**” and use lowercase “A” for “adults”. Also, revise the word (b) (4) to “over”.
 - Revise first bulleted statement to make two bulleted statements, i.e.,
 - instill 1 drop in the affected eye(s) every 6-8 hours
 - do not use more than 4 times daily
 - In the first bulleted statement, there is no period after the word “daily”.

o Add the statements from (b) (4) under the first two bulleted statements above so that the section reads as follows:

- instill 1 drop in the affected eye(s) every 6-8 hours
- do not use more than 4 times daily
- remove contact lenses before use
- wait at least 10 minutes before re-inserting contact lenses after use
- do not touch tip of container to any surface to avoid contamination
- replace cap after each use

o Then, add the statement “if using other ophthalmic products while using this product, wait at least 5 minutes between each product”, after the bulleted statement “wait at least 10 minutes before re-inserting contact lenses after use”. It becomes bulleted statement 5 in this section, i.e.,

- instill 1 drop in the affected eye(s) every 6-8 hours
- do not use more than 4 times daily
- remove contact lenses before use
- wait at least 10 minutes before re-inserting contact lenses after use
- if using other ophthalmic products while using this product, wait at least 5 minutes between each product
- do not touch tip of container to any surface to avoid contamination
- replace cap after each use

o In the last bulleted statement “**Children under 5 years:** consult a doctor”, unbold “Children under 5 years”, and revise the upper case “C” in “Children” to lower case.

- Other Information:
 - Add a bullet to describe the tamper-evident feature. The tamper-evident feature that is described on the carton and inner container can also be part of “Other information”. The statement “This product contains a tamper-evident feature” can appear before description of the tamper-evident feature. The wording of the tamper-evident feature under this subheading should be the same as the wording on the carton and inner container, as discussed above.
 - Begin the discard statement with a lower case “D” in the word “Discard”.

Immediate Container Label

- Remove the claim (b) (4) from the container label PDP as discussed above for PDP recommen
- Revise the Tamper-Evident Feature Labeling to the left of the container label PDP to be consistent with what is on the carton and in Drug Facts as discussed above.

V. SUBMITTED LABELING

The sponsor submitted the following labeling:

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/s/

ARLENE H SOLBECK
11/28/2017

STEVEN A ADAH
11/28/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 8, 2017
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 208144
Product Name and Strength:	Luminesse (Brimonidine Tartrate) Ophthalmic Solution, 0.025%
Product Type:	Single-ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	Bausch & Lomb
Submission Date:	February 27, 2017
OSE RCM #:	2017-429
DMEPA Primary Reviewer:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of NDA 208144 submission, this review evaluates the proposed Luminesse container labels and carton labeling to identify areas of vulnerability that could lead to medication errors.

The application received a Refusal to File (RFT) letter on May 29, 2015. The Applicant then resubmitted their application on February 27, 2017.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed container labels and carton labeling, which contain a graphical representation of a star for the dot in the letter “i” in the proposed proprietary name, Luminesse. This graphical star image does not appear to interrupt the presentation of the proposed proprietary name. Additionally, the proposed Luminesse carton labeling contains a graphical image of an eye and eyebrow appearing above the proposed proprietary name. Furthermore, the graphical eye/eyebrow image also does not appear to interrupt the presentation of the proposed proprietary name, however, we defer to DNDP regarding the appropriateness of the graphical eye/eyebrow image on the proposed carton labeling.

Our review of the carton labeling identified the statement, “Discard remaining product 120 days after opening,” which appears in the *Other Information* section of the Drug Facts Label (DFL). According to the Office of Pharmaceutical Quality (OPQ) review for NDA 208144, once the bottle is opened, it should be discarded after 120 days, which is based on the Applicant’s

submitted in-use stability data.^a Therefore, because this statement will remain on the DFL, we recommend that this statement is repeated on the Principal Display Panel (PDP) throughout the carton labeling and on the container labels to mitigate the potential risk of medication error.

In addition, below the proposed proprietary name, the established name lacks prominence commensurate with the proposed proprietary name such that the letters are not at least half as large as the letters for the proposed proprietary name. The container labels and carton labeling can be improved to enhance the readability and prominence of the established name, which can facilitate identification of the proposed product.

4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed Luminesse container labels and carton labeling may be improved to ensure safe use of the proposed product and to minimize potential medication errors.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Container Labels and Carton Labeling

1. Revise and increase the prominence of the established name to at least half the size of the proposed proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). As currently presented in the proposed container labels and carton labeling, the established name is the least prominent text.
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).
3. Add the statement, "Discard remaining product 120 days after opening," to the principal display panel.

^a See Panorama under NDA 208144 Integrated Quality Assessment, Executive Summary, dated November 6, 2017.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Luminesse that Bausch & Lomb submitted on February 27, 2017.

Table 2. Relevant Product Information for Luminesse	
Initial Approval Date	N/A
Active Ingredient	Brimonidine tartrate
Indication	Relieves redness of the eye due to minor eye irritations
Route of Administration	Ophthalmic
Dosage Form	Solution
Strength	0.025%
Dose and Frequency	Adults and children 5 years and older: • instill 1 drop in the affected eye(s) every 6-8 hours, no more than four times daily Children under 5 years: • consult a doctor
How Supplied	Sample size bottles: • 2.5 mL fill in 10 mL bottle • 7.5 mL fill in 10 mL bottle Trade bottles: • 2.5 mL fill in 10 mL bottle • 7.5 mL fill in 10 mL bottle
Storage	Store at 15°-25°C (59°-77°F)

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/s/

GRACE JONES
11/08/2017

CHI-MING TU
11/08/2017

FDA Social Science Review: Label Comprehension Study

Division of Nonprescription Drug Development

Date: November 1, 2017
From: Amanda Pike-McCradden, MAA, Social Scientist, DNDP
Through: Steven Osborne, MD, Clinical Team Leader, DNDP

To: Karen Mahoney, MD, Deputy Director, DNDP

Subject: A Label Interpretation Study For Bausch and Lomb Eye Drops (Brimonidine Tartrate Ophthalmic Solution, 0.025%) Redness Reliever Eye Drops

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/s/

AMANDA H PIKE-MCCRUDDEN
11/02/2017

STEVEN F OSBORNE
11/02/2017

Clinical Inspection Summary

Date	August 15, 2017
From	Sharon Gershon, Pharm.D, Susan Thompson, M.D., Team Leader, Kassa Ayalew, M.D., M.P.H., Branch Chief, DCCE/GCPAB/OSI
To	Jenny Kelty, M.D., Division of Nonprescription Drug Products (DNDP) Steven Osborne, M.D., Team Leader, DNDP Jung Lee, Regulatory Health Project Manager, DNDP
NDA #	NDA 208144
Applicant	Bausch & Lomb
Drug	Luminesse® (brimonidine tartrate .025%) Ophthalmic Solution
NME	No
Therapeutic Classification	Priority
Proposed Indication	relief of redness of the eye due to minor eye irritations
Consultation Request Date	May 10, 2017
Summary Goal Date	September 18, 2017
Action Goal Date	December 27, 2017
PDUFA Date	December 27, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The inspection for NDA 208144 was conducted at one domestic site. The clinical investigator, Dr. Gail Torkildsen (Site #0001) conducted two of the three efficacy studies to support approval of this NDA.

No regulatory violations were found during the inspection of Dr. Torkildsen, and no Form FDA-483 was issued. The inspection was classified No Action Indicated (NAI). OSI recommends the data at this site be considered acceptable to support approval.

II. BACKGROUND

The sponsor seeks approval of Luminesse™ (brimonidine tartrate ophthalmic solution .025%) to be used Over-the-Counter (OTC) to relieve ocular redness due to minor eye irritations. This NDA was originally submitted on March 31, 2015. A Refuse to File (RTF) letter was issued from the Agency on May 29, 2015. The primary reason stated in the RTF was that the application failed to provide post-marketing data critical for an adequate safety review of this product for its proposed use in an OTC consumer population.

The following two studies were conducted in support of efficacy under this NDA:

1. Protocol No. 10-100-0008: A Single-Center, Randomized, Double-Masked, Placebo and Active Controlled, Dose-Ranging Evaluation of the Duration of Action of Brimonidine.

This study evaluated the safety, efficacy, and dose response of brimonidine tartrate 0.01% and 0.025% ophthalmic solution as compared to placebo in the prevention of allergen-induced conjunctival redness using a conjunctival allergen challenge (CAC) model. In addition, oxymetazoline hydrochloride 0.025% ophthalmic solution was used as an active control in the study.

The study was performed at a single site using one investigator who screened a total of 111 subjects at Visit 1. There were 43 screen failures. The remaining 68 subjects were enrolled at Visit 3a, randomized, and received an in-office dose of the assigned study medication. Enrolled subjects were randomized in a 1:1:1:1 ratio into one of the following treatment groups:

- Brimonidine tartrate 0.01% ophthalmic solution
- Brimonidine tartrate 0.025% ophthalmic solution
- Oxymetazoline hydrochloride 0.025% ophthalmic solution
- Vehicle of brimonidine tartrate ophthalmic solution (placebo)

Primary Efficacy Measurement: **Conjunctival redness** evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 unit scale, allowing half unit increments) at Visits 3, 4, 5, and 6. See Protocol Section 9.5.1.1. for descriptions of Conjunctival Redness Assessment Grades.

Secondary Efficacy Measurements:

- **Ocular itching** evaluated by the subject at 3, 5, and 7 minutes post-challenge (0-4 unit scale, allowing half unit increments) at Visits 3, 4, 5, and 6
 - **Ciliary and episcleral redness** evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3, 4, 5, and 6
 - **Chemosis** evaluated by the investigator at 7, 15, and 20 minutes post-challenge (0-4 scale, allowing half unit increments) at Visits 3, 4, 5, and 6
 - **Lid swelling** evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-3 scale, not allowing half unit increments) at Visits 3, 4, 5, and 6
 - **Tearing/watery eyes** evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-4 scale, not allowing half unit increments) at Visits 3, 4, 5, and 6
 - **Rhinorrhea, nasal pruritus, ear or palate pruritus, and nasal congestion** evaluated by the subject at 7, 15, and 20 minutes post-challenge (0-4 scale, not allowing half-unit increments) at Visits 3, 4, 5, and 6
 - A composite score of **presence or absence of at least one nasal symptom** evaluated by the subject at 7, 15, and 20 minutes post-challenge at Visits 3, 4, 5, and 6
- 2. Protocol No. 11-100-0015** A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of Brimonidine Tartrate 0.025% Ophthalmic Solution Used Four Times Daily in a Population of Adult and Geriatric Subjects

This was a single center, double-masked, randomized, vehicle-controlled, parallel-group, safety and efficacy study which comprised four visits over approximately five weeks.

Adult (≥ 40 years old) and geriatric (≥ 65 years old) subjects were screened with a planned enrollment of up to 60 healthy subjects (actual enrollment was 57 subjects) with normal ocular health. Subjects were not stratified by age group when assigned to investigational product. Subjects were randomized at a ratio of 2:1 (active: vehicle) at Visit 1 to receive one of the following treatments bilaterally:

- Brimonidine tartrate 0.025% ophthalmic solution (N=40)
- Vehicle ophthalmic solution (N=20)

Reasons for Site Selection: Dr. Torkildsen enrolled a large number of subjects for both studies. Two of the three efficacy studies for this NDA were conducted at this site.

III. RESULTS (by site):

Name of CI, Address	Protocol # , Site #, and # of Subjects	Inspection Dates	Final Classification
Gail Torkildsen, MD Andover, MA 01810	Site #0001 10-100-0008 68 subjects 11-100-0015 57 subjects	June 14 – 20, 2017	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Gail Torkildsen, M.D.
300 Brickstone Square,
3rd Floor
Andover, MA 01810

The inspection of Dr. Torkildsen covered Protocols 10-100-0008 and 11-100-0015. Dr. Torkildsen has 39 IND studies in the CDER clinical investigator database. Prior inspections of Dr. Torkildsen were conducted in October 2014 and September 2016. Both inspections were

classified NAI.

For each study, the following records were reviewed: subject inpatient and outpatient medical records; correspondence between the Clinical Investigator (CI) and the sponsor; correspondence between the CI and the Institutional Review Board (IRB); the sponsor monitoring log, all informed consent documents and revisions; source records were selectively compared to the case report forms (CRFs) submitted to the sponsor; serious adverse event (SAE) records; and accountability for the study drug.

For Protocol 10-100-0008, a total of 68 subjects were enrolled. The field investigator reviewed the inclusion and exclusion criteria for 25% of the charts (17 subjects). All subjects met the inclusion and exclusion criteria. The field investigator reviewed protocol deviations and adverse events for all subjects. No discrepancies were observed, and there was no under-reporting of adverse events.

The primary efficacy endpoint for this study was conjunctival redness evaluated 7, 15, and 20 minutes post conjunctival allergen challenge (CAC) on a scale of 0-4, with zero being no conjunctival redness. The field investigators noted that the primary endpoint data was recorded on a scale table in the patient chart, and that conjunctival redness was assessed and documented by designated study personnel. The field investigators compared endpoint results in the data listings with those in source records for 25% of subjects (17 subjects). All data points matched.

The field investigators conducted a spot check of two subject charts for secondary efficacy variables: chemosis evaluated by the investigator at 7, 15, and 20 minutes post-challenge on a 0-4 scale at visits 3, 4, 5, and 6; and ciliary and episcleral redness evaluated by the investigator at 7, 15, and 20 minutes post-challenge on a 0-4 scale at Visits 3, 4, 5, and 6. All data points matched.

With respect to monitoring, the sponsor completed monitoring visits monthly. A follow-up email was sent to the clinical investigator after each visit with a review of items looked at and any follow-up needed. Monitoring appeared adequate.

For Protocol 11-100-0015, a total of 57 subjects were enrolled. A total of 14 subjects were discontinued from this study. Eight of the subjects were discontinued for administrative reasons, such as not showing up for follow-up appointments. Four were discontinued due to adverse events and two were discontinued for protocol violations.

Protocol deviations and adverse events were compared between source documents and data listings for all subjects. There were no discrepancies. There was no under-reporting of adverse events.

The two primary efficacy endpoints for the study were: 1) ocular redness evaluated by the investigator prior to study medication instillation and at 5, 15, 30, 60, 90, 120, 180, and 240 minutes post study medication instillation (0-4 unit scale) at Visit 1; and 2) ocular redness evaluated by the subject as captured in the subject's dosing diary throughout the treatment period (0-4 unit scale). Conjunctival redness was assessed and documented by designated

study personnel for Visit 1.

For the first primary endpoint, the field investigators compared results in the data listings with those in source records for 25% of subjects. All data was verifiable. For the second primary endpoint, the field investigators selected five subjects and randomly chose three separate dates from their diaries, which equated to 24 data entry points per subject, and corroborated the data with the data listings. All data was verifiable.

For this study, the sponsor completed monitoring visits several times a month. A follow-up email was sent to the clinical investigator after each visit with a review of items looked at and any follow-up needed. Monitoring appeared adequate.

For both studies, documents were organized and complete, and paper copies legible. A delegation log was reviewed, and key personnel involved in collecting and analyzing data was identified.

There were no serious violations and no FDA-483 was issued.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D., Team Leader for
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. NDA #208144
DNNDP/Medical Officer/Jenny Kelty
DNNDP/Team Leader/Steven Osborne
DNNDP/Regulatory Project Manager/Jung Lee
OSI/Office Director /David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Sharon Gershon
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SHARON K GERSHON
08/15/2017

SUSAN D THOMPSON
08/15/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 208144	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Lumify Established/Proper Name: brimonidine tartrate Dosage Form: ophthalmic soln Strengths: 0.025%		
Applicant: Bausch + Lomb		
Date of Receipt: February 27, 2017		
PDUFA Goal Date: December 27, 2017		Action Goal Date (if different): December 22, 2017
RPM: Jung Lee		
Proposed Indication(s): Relief of redness of the eye due to minor eye irritations		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Nonclinical safety
NDA 020613 (Alphagan 0.2%)	FDA's previous finding of safety (nonclinical)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The relied upon listed drug and products described in the published literature contain higher strengths and are used at higher doses of brimonidine. The applicant conducted a PK study (13-100-0007) evaluating the pharmacokinetics of the proposed OTC drug product. The PK study showed that exposure to the proposed OTC brimonidine tartrate 0.025% was below the lower limit of quantification (LLOQ). This information in addition to the lower concentration of the proposed OTC drug product (0.025%) as compared to the relied upon listed drug (Alphagan 0.2%) provides justification that it is reasonable to rely upon the listed drug for purposes of nonclinical safety. Published literature was also relied upon to establish that the proposed drug product specification of the (b) (4) leachable of (b) (4) %. Per internal review, it was determined that the proposed spec was acceptable as it is below the threshold of NMT 0.01% for a non-genotoxic impurity.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

If "NO," proceed to question #5.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Alphagan 0.2%	020613	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing: Alphagan 0.2%

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a lower strength (0.025%) and a new indication (relief of redness of the eye due to minor eye irritations).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO ☒

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “**N/A**”

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer “**N/A**”

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
--

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- ☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUNG E LEE
12/22/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208144	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Luminesse Established/Proper Name: brimonidine tartrate Dosage Form: solution Strengths: 0.025% Route(s) of Administration: ophthalmic		
Applicant: Bausch + Lomb Agent for Applicant (if applicable):		
Date of Application: February 27, 2017 Date of Receipt: February 27, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA Goal Date: Wednesday, December 27, 2017		Action Goal Date (if different):
Filing Date: Friday, April 28, 2017		Date of Filing Meeting:
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Relief of redness of the eye due to minor eye irritations		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		☐ 351(a) ☐ 351(k)

Review Classification: <i>The application will be a priority review if:</i> - A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) - The product is a Qualified Infectious Disease Product (QIDP) - A Tropical Disease Priority Review Voucher was submitted - A Pediatric Rare Disease Priority Review Voucher was submitted		☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☒		
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☒ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)			
☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☒ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): Division of Transplants and Ophthalmology Products (DTOP)				
List referenced IND Number(s): IND 108524				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	☒	☐		The proprietary name “Luminesse” was found conditionally acceptable under IND 108524 on February 12, 2015.

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☒ Paid (on 2/27/17) ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☐ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	☒	☐		NDA 020613 Alphagan (brimonidine tartrate ophthalmic soln, 0.2%)
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☒																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☒		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If no, include template language in the 74-day letter. Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)] Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; <u>and</u> (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.	☐	☐		n/a																

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	☐	☒		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 3 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☒	☐	☐	This NDA contains new clinical investigation reports conducted by the applicant that are essential to the approval of the application. Therefore, pursuant to 21 CFR 314.108(b)(4), Bausch & Lomb, a division of Valeant Pharmaceuticals North America LLC requests three (3) years of marketing exclusivity for brimonidine tartrate ophthalmic solution, 0.025%.
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐	☐	☒	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> <i>Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	8 establishments

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☒	☐		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒	☐		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒	☐		PeRC Mtg: Wed, November 29, 2017
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	Submitted to NDA 5/8/15
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	☐	☒		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	PNR submitted 2/28/2017 (and on 4/23/15 to IND 108524; found conditionally acceptable on 2/15/15)
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☐	☒	
Prescription Labeling	☒ Not applicable			
Check all types of labeling submitted.	☐ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☐	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☐	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐ ☐	☐ ☐	☒ ☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in</i>	☐	☐	☒	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

PLLR format before the filing date.				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☐	☐	☒	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☒	
OTC Labeling	☐ Not Applicable			
Check all types of labeling submitted.	☒ Outer carton label ☒ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☒ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☒	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☒	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	DMEPA consult sent on 3/1/17
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	OSI Clinical Study Site Inspection Needed; consult sent 4/7/17
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 5/15/2013 (Type B EOP2 Mtg): Mtg minutes provided to Sponsor on 6/10/2013	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11/15/2011 (Type C Pre-NDA Mtg): Mtg minutes provided to Sponsor on 12/12/2011 10/24/2014 (Type B Pre-NDA Mtg): Mtg minutes provided to Sponsor on 11/10/2014	☒	☐		

Any Special Protocol Assessments (SPAs)? Date(s):	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 5, 2017

NDA 208144

PROPRIETARY NAME: Luminesse

ESTABLISHED NAME: brimonidine tartrate

DOSAGE FORM/STRENGTH: ophthalmic solution, 0.025%

APPLICANT: Bausch + Lomb

PROPOSED INDICATION: Relief of redness of the eye due to minor eye irritations

BACKGROUND: The Applicant submitted a 505(b)(2) application for a direct to nonprescription (Direct-to-OTC) switch for NDA 208144, Luminesse (brimonidine tartrate ophthalmic solution, 0.025%), a topical alpha 2-adrenergic agonist vasoconstrictor in the imidazoline class. The proposed OTC indication is for the relief of redness of the eye due to minor eye irritations.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jung Lee	Y
	CPMS/TL:	Dan Brum	Y
Cross-Discipline Team Leader (CDTL)	Steven Osborne		Y
Division Director/Deputy	Karen Mahoney		Y
Office Director/Deputy	Charles Ganley/Leslie Furlong		N
Clinical	Reviewer:	Jenny Kelty (DNBP) Martin Nevitt (DTOP)	Y
	TL:	Steven Osborne (DNBP) William Boyd (DTOP)	Y Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	Amanda Pike-McCrudden	Y
	TL:	Steven Osborne	Y
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	Arlene Solbeck	Y
	TL:	Steve Adah	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	

	TL:	N/A	
Clinical Pharmacology	Reviewer:	Eric (Yongheng) Zhang	Y
	TL:	Philip Colangelo	N
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Wonyul Lee (DTOP)	Y
		Joo-Yeon Lee (OTC)	Y
	TL:	Yan Wang (DTOP) Rima Izem (OTC)	Y Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Charlie Thompson	Y
	TL:	Jane Sohn	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Swapan De (DP) Donna Christner (DS)	Y N
	RBPM:	Thao Vu	N
• Drug Substance	Reviewer:	Martin Haber	Y
• Drug Product	Reviewer:	Anne Marie Russell	N
• Process	Reviewer:	Tarun Mehta Haitao Li (TL)	Y N
• Microbiology	Reviewer:	Elizabeth Berr Erica Pfeiler (TL)	N N
• Facility	Reviewer:	Donald Lech	N
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Danae Christodoulou		N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Grace Jones	Y
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:	Sharon Gershon (OSI)/Roy Blay Lopa Thambi (OSE/DPV)	N/Y Y
	TL:	Susan Thompson (OSI TL) Lynda McCulley (OSE/DPV TL)	N N
Other attendees	Jagjit Grewal (ODE IV ADRA)		N
	Betsy Scroggs (DNDP ADL)		Y
	Wiley Chambers (DTOP DD)		N
	Renata Albrecht (DTOP Director)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO In order to bridge known systemic exposure information on Alphagan® and Alphagan® P to the low dose brimonidine tartrate ophthalmic solution, 0.025% being investigated following ocular instillation, the sponsor conducted a separate pharmacokinetic (PK) study to determine PK parameters for absorbed brimonidine from the low dose brimonidine formulation that can be related to those for the known ophthalmic drugs containing brimonidine tartrate (study 13-100-0007).
Per reviewers, are all parts in English or English	☒ YES

translation? If no, explain:	☐ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments: Clinical pharmacology study site(s) inspections(s) needed?	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
BIOSTATISTICS Comments: IR sent via email to applicant on 4/13/17	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: IR sent via email to applicant on 4/13/17	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments: IR sent via email to applicant on 4/13/17	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
<u>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</u> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Karen Mahoney, MD, Deputy Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA's completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUNG E LEE
05/04/2017