CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208144Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	November 29, 2017
From	Steven Osborne, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #, Supplement#	NDA 208144
Applicant	Bausch and Lomb, Inc., a subsidiary of Valeant Pharmaceuticals International, Inc.
Date of Submission	February 27, 2017
PDUFA Goal Date	December 27, 2017
Proprietary Name (Proposed)/ Non-Proprietary Name	"(b) (4) brimonidine tartrate ophthalmic solution 0.025%
Dosage form(s) / Strength(s)	Ophthalmic solution (eyedrop) containing: brimonidine tartrate 0.025%
Applicant Proposed Indication(s)/Population(s)	Eye Redness Reliever Adults and children **5** years of age and over
Recommendation on Regulatory Action	**Approval**
Recommended Indication(s)/Population(s)	Eye Redness Reliever Adults and children **5** years of age and over

1. Benefit-Risk Assessment

I recommend **approval** of brimonidine tartrate ophthalmic solution 0.025% for over-the-counter (OTC) use for the relief of red eye in consumers **5** years of age and older.

Highlights of the Submission and Approval Recommendation:

- The approval recommendation is for the indications and the intended populations the sponsor has requested. All discipline reviewers recommended **approval** or did not make a recommendation.

- This application is an original NDA resubmission (NDA 208144). This application relies in part on the Agency's prior findings of nonclinical safety for the approved listed drug product, Alphagan 0.2% (brimonidine tartrate 0.2%, NDA 020613) which was approved in 1996 for the treatment of glaucoma and increased intraocular pressure (IOP) in adults and children 5 years of age and over. Alphagan was approved for use in the pediatric population ≥2 years of age in 2001.

- The sponsor withdrew its original name request for Luminesse following a teleconference with FDA on November 7, 2017. An approved replacement name is pending at the time of this review, although the sponsor has proposed "(b) (4) as its first choice, with "Lumify" as a backup.

- The sponsor conducted 2 pivotal clinical efficacy trials, 1 safety trial, and a label interpretation study in support of this application. An additional study contributed safety information, yielding safety data from 4 clinical studies with 426 subjects on drug and 209 on placebo. This application relies in part on the safety and efficacy established for NDA 20613, as well as supportive studies from the published literature regarding the efficacy of the active ingredient.

- The sponsor's summary of clinical safety, which included literature and postmarket safety from the Bausch and Lomb internal database, FAERS and WHO through 2016, and DAWN (through 2011), did not raise safety concerns.

- Brimonidine tartrate ophthalmic solution 0.025% did not show tachyphylaxis or rebound congestion in clinical trials. The absence of tachyphylaxis or rebound congestion with an OTC ophthalmic vasoconstrictor to relieve redness of the eye is a potential advantage for the OTC consumer.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**Ocular Redness** • Ocular redness can be caused by an inflammation in the conjunctiva which may be due to exposure to allergens, environmental irritants, or a reaction to infectious agents (e.g., bacteria or virus). There are non-allergic and non-infectious causes of redness caused by minor eye irritations.	There can be a negative impact of eye redness, which may have eye irritation associated with it. Also, eye redness is noticeable to the individual and others and has a cosmetic importance.
Current Treatment Options	• OTC drug treatments used to relieve ocular redness are commonly topical vasoconstrictor agents. These vasoconstrictor agents are all α-adrenergic receptor (AR) agonists and induce contraction of smooth muscle. The α-ARs are further differentiated pharmacologically into α1-ARs and α2-ARs, both of which can induce vasoconstriction, but through different mechanisms. • There are 2 classes of vasoconstrictors: sympathomimetic amines and imidazolines. Sympathomimetic amines (e.g., ephedrine, pseudoephedrine, and phenylephrine) activate the sympathetic nerves by the pre-synaptic release of endogenous norepinephrine. • The active ingredients in current OTC ophthalmic solutions commonly used to relieve ocular redness are mixed alpha-adrenergic and vasoconstrictive imidazolines.	Pharmacotherapy has been the mainstay of treatment for conjunctival irritation and the fact that most sufferers self-treat for minor eye irritations, highlight the importance of OTC treatments for control of some of the symptoms.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Of note, prescription drug treatments are also available (e.g. olopatadine). It is unclear whether the Rx drug(s) are more effective than OTC drugs as redness relievers.	
Benefit	• Brimonidine tartrate is a relatively selective alpha-2 adrenergic receptor agonist that has a peak ocular hypotensive effect that occurs two hours post-installation in the eye. Fluorophotometric studies in animals and humans indicate that brimonidine tartrate may have a mechanism of action of reducing aqueous humor production and increasing uveoscleral outflow. At the proposed over-the-count (OTC) concentration of 0.025% (one-eighth the common prescription strength of 0.20%), the drug has a vasoconstrictive effect that can relieve redness of the eye • The sponsor is relying on preclinical and toxicology data and clinical studies for prior NDA submissions to support safety. For additional clinical support for the OTC indication, the sponsor performed 4 studies to evaluate effectiveness of brimonidine 0.025% ophthalmic solution (1 Phase 1 with 14 subjects, 2 Phase 2 with 57 subjects and 2 Phase 3 with 60 subjects and 507 subjects respectively). The clinical studies with brimonidine tartrate ophthalmic solution, 0.025% demonstrate that brimonidine tartrate 0.025% provides rapid and effective relief for ocular redness, while minimizing the side effects of tachyphylaxis (tolerance or loss of effectiveness) or rebound congestion that are commonly associated with OTC products currently on the market for reduction of ocular redness and that restrict long-term use.	The effectiveness of the product has been established for conditions other than glaucoma or to relieve eye redness. Consumers who experience eye redness related to seasonal allergies may need other therapy such as a product incorporating an antihistamine. This combination product provides an additional choice for consumers to eye redness due to lack of sleep, minor irritation from contact lenses and other minor eye irritants.
Risk	• For a risk assessment in this application, the sponsor submitted a Summary of Clinical Safety (ISS) and Postmarket safety data from December 2011 to December 2016, plus a 4-month safety update.	Brimonidine tartrate has a satisfactory safety profile in the prescription environment based on 14 years of clinical use and postmarketing experience in the United States.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Exposure was adequate in clinical trials: subjects in studies 11-100-0015 and 13-100-0005 were dosed 4 times daily (QID) for approximately four weeks. Subjects in study 13-100-0006 were dosed QID for approximately four weeks and subjects in study 13-100-0007 were dosed QID for approximately one week. • Serious adverse events have been reported infrequently for the product in adults in the postmarket setting. See Clinical, Section 7 of this review and Dr. Kelty's review. • The most common adverse events are related to the site of administration and include Ocular Hyperemia, Eye Irritation, Intraocular Pressure Increased (maybe drug ineffective), and Eye Pain. Non-ocular events reported across 4 databases include Dizziness, Fatigue, Headache, and Hypotension. In the clinical development program, the most common non-ocular adverse events were Nasopharyngitis and Sinusitis, both below 1%. Bradycardia; hypotension; iritis; miosis; skin reactions (including erythema, eyelid pruritus, rash, and vasodilation); and tachycardia. Apnea, bradycardia, hypotension, hypothermia, hypotonia, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solution 0.2%. • Brimonidine tartrate is a Pregnancy Category B drug. Studies in rats with oral doses 189 times higher than seen in humans after multiple ophthalmic doses revealed no evidence of fetal harm This drug is excreted in breast milk. • Safety in pediatric patients ≤ 2 years of age as not been established at 0.2%. SAEs have been reported with 0.2% brimonidine tartrate ophthalmic solution.	Serious adverse events (SAEs) are uncommon with labeled use in adults for lowering of intraocular pressure at a 0.2% strength. For the pediatric age group, SAEs were uncommon in clinical trials down to age 5 at a 0.025% strength used as an eye redness reliever. The potential for alpha agonist effects, local or centrally mediated from absorption, is generally low in the doses contained in the proposed product. Relative safety of the prescription strength brimonidine tartrate ophthalmic solution 0.1-0.2% has been established in adults. The safety of brimonidine tartrate ophthalmic solution 0.025% for OTC use is supported by the clinical studies and overall safety profile demonstrated in the evaluation of postmarketing safety data and published literature from the higher concentration prescription brimonidine tartrate ophthalmic products (0.1-0.2%).

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Brimonidine tartrate ophthalmic solution 0.025% shows no difference from placebo in its effect on IOP in subjects with normal IOP.	
Risk Management	• The proposed OTC labeling has the essential warnings translated from the current Alphagan Rx label (brimonidine tartrate 0.2%) into the OTC Drug Facts Label (DFL). Some of the warnings are translated into the DFL out of an abundance of caution, since they refer to a higher strength (Rx).	Warnings provided in the proposed OTC labeling may help mitigate the risk of serious adverse events.

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2. Background

Current Submission NDA 208144
The sponsor, Bausch & Lomb, submitted a 505(b)(2) application as a 505(b)(2) under NDA 208144 on February 27, 2017 to market brimonidine tartrate ophthalmic solution 0.025% under the proposed name Luminesse, for the treatment of red eye, or relieving redness of the eye due to minor eye irritations.

The sponsor relied on FDA's prior findings of safety and efficacy for the approved product under NDA 020613, brimonidine tartrate 0.20% ophthalmic solution (Alphagan). Alphagan was withdrawn from marketing but not for safety or effectiveness, and is still a RLD. Several generics (5 as of November 22, 2017 per the Orange Book) with brimonidine tartrate 0.2% will remain on the market with no changes to the current approved Rx labeling for the treatment of glaucoma and ocular hypertension.

CDTL Comment
The majority of safety data comes from the Rx drug which has been on the market for approximately 20 years. For this switch, efficacy also needed to be established, which DTOP assessed as being proven in 2 pivotal trials.

Source of CDTL Review Information
This review is written from the following primary FDA reviews in Table 1 below:

Table 1: Primary reviews reflected in this CDTL review

Materials Reviewed	***Name of Discipline Primary Reviewer***
DMEPA Human Factors Name Review	Grace P. Jones, PharmD, BCPS
DNDP Labeling Review	Arlene Solbeck, BS
DNDP Medical Officer Review	Jenny Kelty, MD
DNDP Pharmacology/Toxicology Review	Donald C. Thompson, PharmD, PhD
DNDP Social Science Review	Amanda Pike-McCrudden, MAA
Office of Biostatistics Review	Joo-Yeon Lee, PhD
Office of Clinical Pharmacology Review	Amit Somani, PhD
OPQ CMC	Swapan De, PhD (and 5 others from OPQ)
DTOP	Martin Nevitt, MD, MPH
DTOP-Statistics	Wonyul Lee, PhD
OSI (inspection)	Sharon Gershon, PhD

OPQ CMC = Office of Pharmaceutical Quality: Chemistry, Manufacturing and Controls
DMEPA = Division of Medication Error Prevention and Analysis
DNDP = Division of Nonprescription Drug Product
DTOP = Division of Transplant and Ophthalmology Drug Products
OSI = Office of Scientific Investigation (Compliance)

Pre and Post Submission Regulatory Activity

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Six meetings were held with the sponsor regarding this application since September 2010. These major milestone meetings and select discussions from 5 other meetings are summarized in Table 2 below.

Table 2. Key Interactions with the Applicant under NDA 208144

Date	Meeting Type	Key Discussion Points/Action Items
September 1, 2010	Pre-IND Meeting	• Ora (agent for Eye Therapies) will file an IND with a study protocol using the Conjunctival Allergen Challenge (CAC) model • Ora will provide clarification that it does not seek an OTC claim for IOP reduction and will submit information about brimonidine tartrate IOP reduction dose response
December 20, 2010	IND 108524 opened by Eye Therapies, LLC	• Prepare for CAC model study
November 15, 2011	Pre-NDA Meeting	• Ora agreed to repeat the CAC study for onset and duration of action. • Ora agreed to submit actual use data if there is a disparity between dosing directions and duration of action. • Safety issues raised by FDA included: a) use in geriatric subjects b) safety in pediatric subjects, c) potential somnolence and lethargy d) potential "overuse" issues
May 15, 2013	End of Phase 2 Meeting	• Ora agreed to provide an initial Pediatric Study Plan (iPSP) within 60 days of this End-of-Phase 2 meeting • Ora agreed to utilize daily subject diaries
August 5, 2013	Transfer of IND to Bausch & Lomb	• Business reasons
October 24, 2014	Pre-NDA Meeting (first meeting with Bausch & Lomb)	• FDA recommended that the dosing regimen match the efficacy data of the proposed product. • FDA expressed concern that the proposed product might be accidentally ingested by children. The sponsor confirmed that its product will be packaged with a child-resistant cap. • FDA stated there have been case reports involving misuse of similar products as date rape drugs. The sponsor agreed to search for AEs and literature regarding misuse. • The sponsor requested FDA's comments regarding a label interpretation study to support inclusion of the phrase [redacted] (b) (4)" on the principal display panel (PDP). FDA noted that claims beyond what is stated in the Drug Facts Label (DFL) are not allowed on the PDP. While truthful and non-misleading claims may be permissible on the PDP, [redacted] (b) (4)" was probably not acceptable as it may overstate efficacy.
March 31, 2015	NDA 208144 filed	• NDA submitted
May 29, 2015	Refusal to File (RTF) Letter	• Reason for RTF: failure to provide post marketing data critical for an adequate safety review of the proposed product for use in the OTC consumer population.

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July 29, 2015	Post-Refusal to File Meeting	• FDA requires additional analyses, and specific AE information for the postmarketing surveillance/database. The literature review was to provide synthesized conclusions about safety with a focus on topics of special interest such as CNS depression, respiratory depression, and issues of misuse. More detailed safety narratives were to be included for discontinuations due to AEs. • CMC issues included the provision of in-use stability data for the different presentations of the product, the proposed change in the color of the child-resistant cap, and the submission of validation and sterilization information associated with drug product manufacturing.

December 17, 2015	tcon	• FDA requested the addition of terms rape, sexual assault, victim, victim of sexual abuse, date rape to the postmarketing search strategy.
		• FDA requested safety topics of special interest including breakdowns of AEs by preferred terms, serious and non-serious AE reports separately, inclusion of a discussion of medically significant AEs, even if rare, and a discussion of how these would/would not impact the suitability of the drug product for an OTC environment with labeling implications also to be addressed.
		• FDA agreed to time period of January 1, 2001 through July 31, 2015 for the literature and database searches based on a projected NDA resubmission date of March 2016
		• The sponsor agreed to include the following safety issues in the postmarketing safety analysis:
		  • CNS depression
		  • Respiratory depressive effects, especially in young children and elderly
		  • Drug misuse and abuse

February 27, 2017	NDA resubmission*.	• Review cycle initiated

IOP = intraocular pressure
* NDA resubmitted by Bausch & Lomb, a subsidiary of Valeant Pharmaceuticals International, Inc.
Source: Dr. Kelty's review

Information about the Prescription (Rx) Drug Product

Brimonidine is an α2 adrenergic receptor (α2-AR)-specific agonist with an α2-AR/α1-AR binding affinity ratio ~1000:1.

The brimonidine tartrate-containing ophthalmic solutions are approved with concentrations of 0.1%, 0.15%, and 0.2% at a dose of one drop three times daily (TID) for lowering intraocular pressure (IOP). In addition to Alphagan, generic formulations of brimonidine tartrate 0.15% and 0.2% are approved at the same dosages.

Long term ophthalmic dosing (two or three times daily dosing over years) with brimonidine tartrate 0.2% has been shown to be safe and effective in lowering IOP.

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CDTL Comment
The approved ocular prescription-strength of brimonidine tartrate is 4-8 fold higher than the concentration proposed in this application, adding a margin of safety for the proposed OTC drug to be used to relieve eye redness.

Nature of the proposed OTC condition (eye redness) and type of drug product
Ocular redness can be caused by an inflammation in the conjunctiva which may be due to exposure to allergens, environmental irritants, or a reaction to infectious agents, such as a bacterium or virus). Topical vasoconstrictor agents are commonly used to relieve ocular redness, particularly non-allergic and non-infectious redness caused by minor eye irritations.

These vasoconstrictor agents are all α-adrenergic receptor (AR) agonists and induce contraction of smooth muscle. The α-ARs are further divided pharmacologically into α1-ARs and α2-ARs, both of which can induce vasoconstriction through different mechanisms. Brimonidine tartrate is an imidazoline 2-adrenergic receptor (AR) agonist, a chemical class well known to cause vasoconstriction and that includes the active component in several over-the-counter (OTC) vasoconstrictors (e.g., Visine LR, Naphcon Forte, see Tables 4 and 5 below).

Specific Drug Product Information
The proposed drug product is a preserved topical ophthalmic solution of composition as summarized in the Sponsor's Table 2.3.P.1-1 below. The drug product will be packaged as nominal 2.5 and 7.5 mL fill volumes in 10 mL LDPE bottles using (b) (4) tips and two-piece child-resistant closures.

Table 3 below summarizes the drug product information for the proposed OTC brimonidine tartrate ophthalmic solution, including the drug class, proposed dosing regimen, chemical structure, and formulation ingredients.

Table 3. Drug product information (proposed OTC)

Product Name	Brimonidine Tartrate Ophthalmic Solution
Applicant	Bausch & Lomb
Class	Selective α-2 adrenergic agonist
Formulation	0.025% ophthalmic solution
Dosing Regimen	Adults and children ≥ 5 years: 1 drop in affected eye(s) Q6-8 hrs, no more than 4x/day
Proposed Indication	Relieve redness of the eye due to minor eye irritations
NDA Type	505(b)(2)

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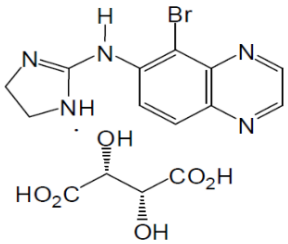
Chemical Structure	 White powder freely soluble in water. Molecular Weight 442.22 g/mol

Source: Dr. Kelty's and Dr. De's review
Product Composition: see Table 8 below and the CMC section of this review
See CMC primary review for further details about nomenclature and molecular formula

Examples of OTC NDA eye redness relievers

Dr. Kelty's clinical review listed the some currently available OTC *NDA or ANDA* (generic) eye redness relievers (Table 4 below).

Table 4. Currently available OTC NDA or ANDA drug products for relief of eye redness

Product	Active Ingredients	Indication	Sponsor	Approval Date
Visine A N020485	0.025% naphazoline HCl 0.3% pheniramine maleate	Temporarily relieves itchy, red eyes due to: • pollen • ragweed, • grass, • animal hair and dander	J & J	1 31/96
Opcon-A N020065 A078208	0.02675% naphazoline HCl 0.315% pheniramine maleate		Bausch & Lomb	6 8/94
Naphcon A N020226 A202795	0.025% naphazoline HCl 0.3% pheniramine maleate		Alcon	6 8/94
Visine LR N019407	0.025% oxymetazoline HCl	Relief of redness of the eye due to minor eye irritations	J & J	3 31/89
Ocuclear N018471	0.025% oxymetazoline HCl		Bayer	5 30/86

Source: Dr. Kelty's clinical review

Dr. Kelty's review also listed some OTC *monograph* eye redness relievers (Table 5 below).

Table 5. OTC Final Monograph Ophthalmic Drug Products (21 CFR 349): GRASE* Ophthalmic Vasoconstrictors

Ephedrine HCl	0.12%
Naphazoline HCl	0.01-0.03%
Phenylephrine HCl	0.08-0.2%
Tetrahydrozoline HCl	0.01-0.05%

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Indication	Relieves redness of the eye due to minor eye irritations
Dosage	1-2 drops in affected eye(s) every 6 hours up to 4 times/day
Population	Adults and children ** 6 years
Maximum Duration of Use	Unspecified
Warnings	Discontinue use for: • eye pain • vision changes • condition worsens/persists for >72 hours Do not use • *glaucoma* • if solution becomes cloudy • Overuse may produce increased redness of eye

*GRASE general recognition of safety and effectiveness
** OTC monograph vasoconstrictor eye drops typically are marketed with dosing down to 6 years of age; however, the monograph does not specify a lower age limit for use
Source: Dr. Kelty's clinical review

CDTL Comments

1. Table 5 above shows that OTC ophthalmic vasoconstrictors have dosing down to age 6; however, the sponsor requests dosing down to age 5 for brimonidine tartrate 0.025% ophthalmic solution.

2. Dr. Kelty's review addressed the difference between the lower age dosing for OTC ophthalmic vasoconstrictors by noting:
"At the EOP2 Meeting held on May 15, 2013, it was agreed that adult findings of efficacy could be extrapolated to pediatric patients down to age 6 years provided safety is demonstrated. In the agreed initial Pediatric Study Plan (iPSP), the sponsor proposed that efficacy in pediatric patients 5-17 years of age can be extrapolated from brimonidine tartrate ophthalmic solution, 0.025% adult studies; and the Division agreed. There is unlikely to be a significant difference in efficacy with use of the proposed product between a 5 year old and a 6 year old child for the proposed indication".

Clinical Studies to Support OTC Use:
Six clinical studies were conducted to evaluate the safety and effectiveness of brimonidine tartrate ophthalmic solution, 0.025% in relieving ocular redness. These included: one dose-ranging safety and efficacy (phase 2) study; two safety and efficacy studies (one phase 2 and one phase 3 study); one intraocular pressure lowering study; one safety (phase 3) study; and one pharmacokinetics (phase 1) study. An overview of the clinical studies is summarized in Table 6 below.

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Table 6. Clinical Studies of Brimonidine Tartrate Ophthalmic Solution, 0.025%

Study Number, Title	Type of Study/ Population (N subjects)	Study Title	Drug Treatment Duration
10-100-0008	Phase 2 safety and efficacy (duration of action) Adult (68)	A Single-center, Randomized, Double- Masked, Placebo and Active Controlled, Dose-Ranging Evaluation of the Duration of Action of Brimonidine Tartrate Ophthalmic Solution in the Prevention of Ocular Redness Induced by Conjunctival Allergen Challenge (CAC)	14 days screening + single doses administered over 42 days of enrollment
11-100-0015	Phase 2 safety and efficacy Adult (45) Geriatric	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	28 days
12-150-0001	Pilot IOP study (safety) Adult (15)	A Single-Center, Randomized, Double-Masked, Cross-Over Pilot Study Evaluating Safety and IOP Lowering Response of Brimonidine Tartrate 0.025% Ophthalmic Solution versus Vehicle in Subjects with Open Angle Glaucoma or Ocular Hypertension	~1-5 weeks screening + 4 weeks QID dosing
13-100-0005 B&L Number 861	Phase 3 safety and efficacy Adult (50) Geriatric (10)	A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Used Four Times Daily in a Population of Adult and Geriatric Subjects with Ocular Redness	~5 weeks
13-100-0006 B&L Number 862	Phase 3 safety Pediatric (50) Adult (408) Geriatric	A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Used Four Times Daily in a Population of Pediatric, Adult, and Geriatric Subjects.	~4 weeks
13-100-0007 B&L Number 863	Phase 1 safety Adult (14)	A Prospective, Single- Center, Open-Label Study of the Plasma Pharmacokinetics and Safety following Topical Administration of Brimonidine Tartrate Ophthalmic Solution 0.025% Used Four Times Daily in Healthy, Adult Subjects	7 days

Source: Adapted from sponsor's Table 1 Clinical Studies of Brimonidine Tartrate Ophthalmic Solution 0.025%, ISE.

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Study 11-100-0015 and 13-100-0005 are the efficacy studies contributing to basis of approval for OTC strength, along with safety study 13-100-0006 (see Section 8 of this review).

Proposed Dosing regimen
The sponsor proposed the dose of one drop in each affected eye every 6-8 hours while symptoms persist, no more than 4 times in any 24- hour period. (b) (4).

CDTL Comment
The DTOP review evaluates and confirms the efficacy of the drug and dosing regimen for the relief of eye redness.

Financial Disclosures
Financial interest and arrangement information was collected from the clinical investigators and there was no disclosable financial information reported.

3. Product Quality

The Product Quality review was written jointly by multiple disciplines listed in Table 7 below. Swapan De, PhD from was the Application Technical Lead (Chemistry, Manufacturing, and Controls; CMC) and recommended **approval.**

Table 7. Quality Review Team Members

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Anne Marie Russell, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Tarun Mehta	OPF/DPAII/Branch VI
Microbiology	Elizabeth Bearr, Ph.D.	OPF/DMA/MABI
Facility	Donald L Lech	OPF/DIA/IABIII
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MD
Environmental Assessment	N/A	

Dr. De noted that the chemical composition of the drug product, with one active ingredient (brimonidine tartrate) and 10 excipients, is shown in Table 8 below.

Table 8. Chemical Composition (sponsor's Table 3.2.P.1-1)

Component	Reference to Quality Standard	Function	Concentration	
			mg/ mL	% w/w
Brimonidine Tartrate	In house	Active	0.25	0.025
Glycerin	USP	(b) (4)	(b) (4)	

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Sodium Borate Decahydrate	NF	(b) (4)
Boric Acid	NF	
Potassium Chloride	USP	
Calcium Chloride Dihydrate	USP	
Sodium Chloride	USP	
Benzalkonium Chloride (b) (4)	NF	
(b) (4) Sodium	NF	
Hydrochloric	NF	
Water for Injection	USP	

Source: CMC review and sponsor's data.
USP = United States Pharmacopoeia
NF = National Formulary
qs = quantity sufficient

CDTL Comment
The CMC review noted that in Table 8 above, "no excipient exceeds the FDA Inactive Ingredients Database (IID) Limits for the route of administration."

The CMC review team discussed the container closure and the expiration date and storage conditions, as noted below.

Container Closure:
The product is packaged in a 10mL round white low-density polyethylene (LDPE) bottle fitted with a (b) (4) dropper tip and closed with a child resistant cap composed of a purple (b) (4) outer and a (b) (4) (b) (4) inner closure. Primary packaging components are tested and sterilized with (b) (4).

The bottle is fitted with a clear tamper resistant neckband and an adhesive label, then packaged in a carton.

Expiration Date & Storage Conditions
Dr. De noted that the "Proposed expiry of 15 months for the 2.5mL fill and 24 months for the 7.5mL fill product is acceptable and supported by the real-time stability data from for 3 registration lots for each fill, plus one clinical lot and one commercial lot for each fill. And, "Based on in-use stability data for both 2.5 mL and 7.5 mL configurations, 120 day in-use period is granted. "Discard 120 days after opening the bottle" is suggested to be in the label".

Elizabeth Bearr, PhD from CMC-micro initially concurred with keeping the discard statement in the label: "From the micro perspective, we do not recommend removing the discard statement from the label". However, in a follow-up memorandum (November 27, 2017) Dr.

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Bearr reconsidered based on the in-use study and the drug stability study noted below, and concluded "Based on these data, DMA (Division of Microbial Assessment) recommends that standard labeling practices concerning discarding opened multi-dose ophthalmic products be followed."

- An in-use study was conducted wherein 2 drops of the drug product were dispensed every other day for 121 days. The drug product was capable of passing AET after 121 days of simulated use.
- AET was performed on drug product stability samples stored unopened at 25ºC for 24 months (i.e. expiry for the "worst case" 7.5 mL drug product) and the samples met the acceptance criteria.

Dr. De summarized as "regarding Chemistry Manufacturing and Controls, the application may be approved. And, **"**Regarding quality aspects of the application the drug substance, drug product, process, microbiology and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 15 months for the 2.5mL fill and 24 months for the 7.5mL fill product configuration. In addition, 120 day in-use period is granted (i.e. once the bottle is opened it should be discarded after 120 days)".

See the Chemistry review for additional details.

CDTL Comments
1) At a team labeling meeting held on November 20, 2017, DNDP, DTOP, and the Product Quality (CMC and microbiology) team discussed the data and need or lack of need for a "discard 120 days after opening" statement. CMC recommended the statement because there is some water loss from the bottle after opening, leading to the concentration the preservative, (b) (4) *being out of specifications after approximately 120 days. DTOP commented that a discard statement was atypical for an ophthalmic solution. Dr. Bearr from OPQ-microbiology commented that the preservative was still active at day 120 even at 10% of the concentration in the proposed drug product. Although actual antimicrobial activity/microbial growth was not measured after day 120 (following opening), the risk of bacterial contamination after day 120 is extremely low. Dr. Bearr commented she saw reason to either include or not include the discard statement.*

2) This CDTL reviewer believes that the discard statement is not needed on this OTC drug product based on the microbiology opinion that microbial growth is likely to be inhibited after 120 days given that microbial growth was inhibited at day 120 at a preservative concentration 10% of the actual in the OTC drug product.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology / Toxicology review was conducted by Donald Thompson, RPh, PhD, DABT., who recommended **approval**. Dr. Thompson noted that no new nonclinical data were submitted with the application and the "application relies in part on prior FDA findings of

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nonclinical safety for the approved listed drug product, Alphagan 0.2% (NDA 020613), a product whose marketing was discontinued for reasons other than safety or effectiveness".

CDTL Comment
As noted earlier, Alphagan NDA 020613 (brimonidine tartrate 0.2%) remains as a RLD (November 22, 2017), which it is eligible for because of the Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons.

Regarding excipients or inactive ingredients, Dr. Thompson commented that "All excipients included in the DP (drug product) formulation are compendial. In addition, while each excipient is listed in the FDA IID (inactive ingredient database) as having previously been used in approved ophthalmic solution drug products (see summary table below), their proposed use levels in the current product cannot be definitively confirmed in each case to be at or below previously approved levels on an MDD basis because droplet volume has not been specified for all the supporting formulations. However, published references (cf. https://www.medicinescomplete.com/mc/excipients/current/) confirm that each excipient is widely used in ophthalmic drug products at comparable levels. Thus, the proposed excipients and their corresponding use levels do not appear to raise safety concerns".

Table 9 below shows the inactive ingredients and the application approval as support (or qualified) for that level in a drug product.

Table 9. Inactives in brimonidine tartrate ophthalmic solution 0.025%

Inactive Ingredient	DP Use (% w/w)	MDD (mg) (at 0.4 mL/day)	IID Max Potency (% w/w) (Ophth. Soln; usage)	Approved Application No.
Glycerin	(b) (4) [redacted]			
Sodium Borate Decahydrate				
Boric Acid				
Potassium Chloride				
Calcium Chloride Dihydrate				
Sodium Chloride				
Benzalkonium Chloride				

DP = drug product
MDD = maximum daily dose
IID = FDA Inactive ingredient database
gtt = drop
Source: Dr. Thompson's review

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CDTL Comment
Per Dr. Thompson's review, all of the excipients are safe for use in the drug product. Table 9 does not include sodium, hydrochloric, or water that are in the CMC Table 8 above because these ingredients are present only to adjust pH and (b) (4) *as needed.*

5. Clinical Pharmacology

The Clinical Pharmacology review was written by Amit Somani, B., PharmD, who recommended **approval**.

Dr. Somani reviewed the PK Study 863 (13-100-0007) which assessed the systemic exposure to brimonidine following a single dose and four times a day (QID) dosing in each eye for five days with brimonidine tartrate ophthalmic solution, 0.025%, in healthy subjects. Blood samples were collected from all subjects for the determination of brimonidine in plasma at the specified time points on Day 1 (within 1 hour prior to dosing and post-dose at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 hours), Day 2 (24 hours from the single dose administered on Day 1), Day 7 (within 1 hour prior to dosing and post-dose at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 hours), and Day 8 (24 hours from the single dose administered on Day 7).

Blood samples were analyzed using an LC/MS/MS method for the quantitation of brimonidine that was developed and validated over the concentration range of 0.0250 to 50.0 ng/mL. Only one subject in the PK population (n=14) had a detectable plasma brimonidine tartrate concentration (0.0253 ng/mL, one hour post-instillation) which was close to the lower limit of quantitation (LLOQ 0.025 ng/mL); all other blood samples collected from this subject and all blood samples from all other subjects had plasma brimonidine concentrations below the LLOQ at every time point pre-and post-instillation of brimonidine tartrate 0.025%. Given the available data, the Applicant concludes that the plasma concentrations of brimonidine remain below the lower limit of quantitation (LLOQ) in most subjects (13/14) during and after five days of bilateral QID topical administration of the study drug and were not able to characterize the PK of brimonidine.

Dr. Somani concluded that:
"Based on the findings of PK Study 863 (13-100-0007), the reviewer agrees with the Applicant's conclusion that the plasma concentrations of brimonidine are below the LLOQ (0.025 ng/mL) in most subjects following the topical instillation of a single dose and QID dosing of brimonidine tartrate ophthalmic solution, 0.025%".

In addition, Dr. Somani concluded that:
"PK and safety were assessed following the topical ocular instillation of Brimonidine tartrate ophthalmic solution, 0.025%, as a single dose and QID in healthy, adult subjects. The completed PK Study 863 (13-100-0007) confirmed that the systemic exposure to brimonidine is low following topical instillation of single or multiple-dose of Brimonidine tartrate ophthalmic solution, 0.025%".

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CDTL Comment
Per Dr. Somani's review, systemic absorption is minimal from installation of the proposed drug product under the maximum labeled use for 5 days, which is a sufficient number of days to study.

6. Clinical Microbiology

The CMC review included a quality microbiology input. A separate clinical microbiology review was not needed for this application. See section 3 (Product Quality) above for a comment from Elizabeth Bearr, PhD regarding a potential "discard statement 120 days after opening" on the label.

7. Clinical Efficacy

The efficacy review was written by the DTOP team. Martin Nevitt, MD, MPH who reviewed the clinical aspect and recommended **approval.** Wonyul Lee, PhD reviewed the statistics aspect and concurred. This section combines their reviews.

In support of efficacy for the treatment of eye redness, the sponsor conducted a dose response study (10-100-0008) and two pivotal studies: Study 861/13-100-0005 or study "05" and Study 11-100-0015 or study "15" (both highlighted in red), as shown in Table 10 below.

Table 10. Dose response study plus 2 efficacy studies

Study ID	Objective(s)	# of Subjects	Site
10-100-0008	Evaluate the safety, efficacy and dose response of BT 0.01% and 0.025% ophth soln vs placebo in the prevention of allergen-induced conjunctival redness using a conjunctival allergen challenge (CAC) model.	68	Ora, Inc. Gail Torkildsen, MD
*11-100-0015	Evaluate the efficacy and safety of BT 0.025% ophth soln vs vehicle in the relief of ocular redness in healthy adults and geriatric subjects	57	Ora, Inc. Gail Torkildsen, MD
*13-100-0005	Compare efficacy of BT 0.025% ophth soln vs vehicle for treating ocular redness in adult and geriatric patients	60	Total Eye Care, PA Eugene McLaurin, MD

Source: adapted from sponsor submission

Drs. Nevitt and Lee described the 2 efficacy study designs as follows:

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The efficacy studies 5 and 15 had similar designs. They were randomized, single-center, double-blind, vehicle controlled, superiority studies. Each study randomized approximately 60 adults in a 2:1 ratio to brimonidine or vehicle. Subjects received in-office drug instillation at the day of randomization (Visit 1), 2 weeks after randomization (Visit 2), and 4 weeks after randomization (Visit 3). In addition, subjects were instructed to apply one drop bilaterally, four times a day, until Visit 3.

The common primary efficacy endpoint in the two studies (5 and 15) was mean change in ocular redness assessed by the study investigator at 5, 15, 30, 60, 90, 120, 180, and 240 minutes after study drug instillation at Visit 1. Ocular redness was assessed by a 0-4 scale.

Study 15 had another primary efficacy endpoint; ocular redness evaluated by the study subject and recorded in dosing diaries throughout the 4 weeks treatment period. This endpoint was one of the secondary efficacy endpoints in Study 05.

In both studies, subjects in the brimonidine groups had significantly lower average ocular redness score at Visit 1 after drug instillation compared to that of subjects in the vehicle groups: 0.62 vs. 1.49 in Study 05 and 0.31 vs. 1.67 in Study 15 (Table 11 below).

Table 11. Average ocular redness score over post-instillation time points at Visit 1: intent to treat (ITT) population

	Brimonidine	Vehicle	Difference (95% CI)	p-value
Study 11-100-0015				
Average Ocular redness, Mean (SD)*	0.31 (0.060)	1.67 (0.086)	-1.36 (-1.57, -1.16)	<.0001
Change from pre-instillation, Mean (SD)*	-1.56 (0.060)	-0.20 (0.086)	-1.36 (-1.57, -1.16)	<.0001
Study 861/13-100-0005				
Average Ocular redness, Mean (SD)*	0.62 (0.074)	1.49 (0.105)	-0.87 (-1.12, -0.61)	<.0001
Change from pre-instillation, Mean (SD)*	-1.16 (0.074)	-0.30 (0.105)	-0.87 (-1.12, -0.61)	<.0001

* SD: Standard deviation; Mean and SD were estimated from mixed model repeated measure (MMRM) models.
Source: Table 9 of the clinical study report for Study 11-100-0015 and Table 11-3 of the clinical study report for Study 861/13- 100-0005.
Source: Dr. Wonyul Lee's review

Dr. Nevitt assessed both studies as showing "a statistically significant difference in ocular redness scores at a P-value < 0.001 for all time points in both studies. The mean difference was approximately 1 at the time of onset and is considered clinically significant".

Dr. Nevitt commented that a secondary endpoint assessing ocular redness scores at 1, 360, and 480 minutes after drug instillation: "Clinical significance, usually defined as 1 unit on the scale used in this study, is not reached at 1 minute, but is reached by 15 minutes in both clinical trials".

<u>Statistical Review of Efficacy Studies</u>:

Wonyul Lee, Ph.D. described the design and primary endpoint(s) of the sponsor's 2 pivotal efficacy studies shown in Table 12 below.

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Table 12. Design and primary endpoints of two pivotal efficacy studies of brimonidine tartrate used as an eye redness reliever

	Study 11-100-0015 (Phase 2)	Study 861/13-100-0005 (Phase 3)
Design	Single center, randomized, double-blinded, vehicle-controlled Study (5 Weeks) Efficacy and safety measures were assessed at Visit 1 (Day 0), Visit 2 (Day 14 ± 2), Visit 3 (Day 28 ± 2), and Visit 4 (Day 35 ± 1)	
Arms	Brimonidine Tartrate, 0.025% QID Vehicle QID	
Primary Endpoint(s)	Ocular redness score assessed by the investigator (0-4 unit scale) at 5, 15, 30, 60, 90, 120, 180, and 240 minutes after investigational drug instillation at Day 0	
	Ocular redness evaluated by the subject as captured in subject's dosing diaries throughout the treatment period (4 weeks).	

Table 13 below shows the time course of average eye redness as assessed by subjects in study 11-100-0015. Table 14. Shows the average ocular redness assessed by the subject in diaries in study 861/13-100-0005

CDTL Comment
Tables 13 and 14 below show that brimonidine tartrate has less average redness than does the vehicle throughout the period of observation (30 days)

Tables 13 and 14. Time course of average eye redness as assessed by subjects in study 11-100-0015 average ocular redness assessed by the subject in diaries in study 861/13-100-0005.

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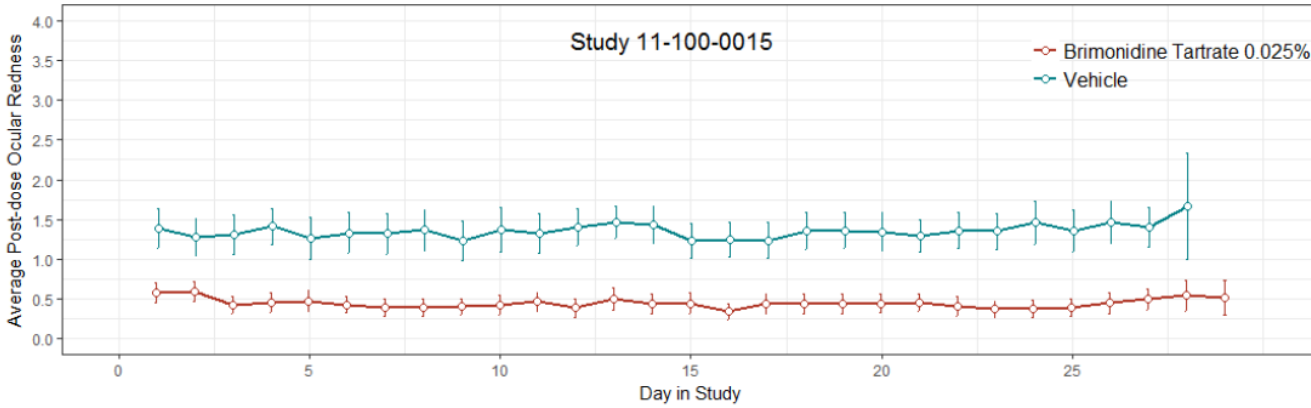

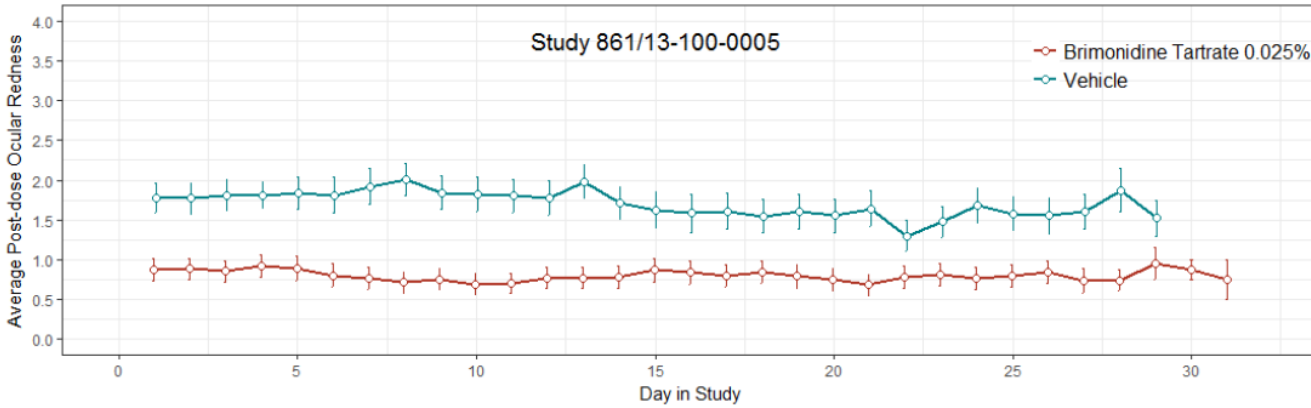

Source: Dr. Wonyul Lee's review

Overall, Dr. Nevitt's clinical ophthalmology review confirmed that the sponsor's studies demonstrated that brimonidine tartrate ophthalmic solution, 0.025% provides rapid and effective relief for ocular redness, while minimizing the side effects of tachyphylaxis (tolerance or loss of effectiveness) or rebound congestion that are commonly associated with OTC products currently on the market for reduction of ocular redness and that restrict long-term use.

Regarding two topics related to labeling:

- Drs. Nevitt and Lee confirmed that the sponsor's efficacy studies supported a statement regarding the onset of action ("works in 1 minute") and the duration of action ("lasts up to 8 hours")
- Removal of the [redacted] (b) (4)

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CDTL Comment
Studies 11-100-0015 and 13-100-0005 are the pivotal efficacy studies contributing to the basis of approval for OTC brimonidine tartrate ophthalmic solution 0.025%, along with the safety study 13-100-0006 (see Section 8 of this review).

8. Safety

The clinical safety review was written by Dr. Jenny Kelty who recommended **approval**, and is supplemented by the safety portion of Dr. Nevitt's efficacy review**.**

This section discusses the safety data from clinical trials performed for the current submission. Postmarket safety data is discussed in Section 9 of this review.

Safety Data Sources
The sponsor focused on safety from 4 studies it conducted for this submission:

- Study 13-100-007, 1 week PK study, subjects dosed for 5 days, both eyes
- Study 862/13-100-0006 or "Study 06", a 4-week safety study
- Studies 11-100-0015 and 13-100-0005, both 5-week efficacy studies
- Postmarketing safety databases
  - FAERS, VPII, WHO, NPDS, DAWN
- Published literature review
  - EMBASE, MEDLINE, BIOSIS Preview

Pooling of studies
Studies 11-100-0015 (efficacy), 13-100-0005 (efficacy), 13-100-0006 (dedicated safety), and 13-100-007 (PK study) were pooled to support the safety of brimonidine tartrate ophthalmic solution 0.025% compared to the vehicle ophthalmic solution.

Two additional studies were not pooled:

- Study 10-100-0008 was a CAC study with limited dosing and safety results may be confounded with the CAC procedure.
- Study 12-150-0001 was a study in a different population than the intended population for this NDA.

Extent of Exposure to Active Drug
The safety population consisted of a total of 426 subjects who were exposed to active drug in the 4 clinical studies in the ISS, with mean drug exposure of 27.2 days. The age range for the subjects was 5 to >65 years of age. Table 15 below shows this number of subjects exposed to drug (426), and vehicle (209).

Table 15. Exposure to study drug (safety population)

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Exposure (Subject-Days)	Brimonidine Tartrate, 0.025%	Vehicle (N=209)	All Subjects (N=635
N	426	209	635
Mean (SD)	27.2 (6.35)	28.6 (3.49)	27.7 (5.61)
Median	29.0	29.0	29.0
Min - Max	1, 35	1, 38	1, 38
Total	11597	5985	17582

*N in the headers represents the total number of subjects enrolled in each respective treatment group within the Safety Population. Exposure was calculated as Date of Last Dose - Date of First Dose + 1, where Date of First Dose was assumed to be the Day 1 Date. Total (11597, 5985, 17582 across table) represents the total number of subject-days of exposure in the treatment group.

Expected exposure was 5 weeks for Studies 11-100-0015 and 13-100-0005, four weeks for Study 13-100-0006, and one week for Studv 13-100-0007.
Source: ISS Table 14.3.9.1

Dr. Nevitt noted that there were 10 withdrawals in the 4 studies "due to non-serious events" and "Of those subjects who discontinued from clinical trials for safety, no trend was observed."

CDTL Comment
1) The total number of subjects exposed to active drug (426) over 4 studies is reasonable, given the previous experience with the Rx drug at higher strengths.

2) Approximately 1.6% dropouts (10/635) is expected for clinical trials.

The most commonly reported ocular TEAEs are summarized in Table 16 below.

Table 16. TEAEs by System Organ Class and Preferred Term Occurring in >1% of Subjects: ISS Analysis Set

System Organ Class (SOC) Preferred Term (PT)	Brimonidine Tartrate 0.025% (N=426)		Vehicle (N=209)		All Subjects (N=638)	
	Events	Subjects	Events	Subjects	Events	Subjects
Total TEAEs	122	96 (22.5%)	58	45 (21.5%)	180	141 (22.2%)
Eye Disorders	60	51 (12.0%)	28	25 (12.0%)	88	76 (12.0%)
Visual Acuity Reduced	18	17 (4.0%)	9	9 (4.3%)	27	26 (4.1%)
Conjunctival Hyperemia	12	11 (2.6%)	6	6 (2.9%)	18	17 (2.7%)
Ocular Hyperemia	5	5 (1.2%)	2	2 (1.0%)	7	7 (1.1%)
General Disorders and Administration Site	11	10 (2.3%)	4	4 (1.9%)	15	14 (2.2%)
Instillation Site Pain	7	7 (1.6%)	4	4 (1.9%)	11	11 (1.7%)
Infections and Infestations	15	12 (2.8%)	8	8 (3.8%)	23	20 (3.1%)
Nasopharyngitis	3	3 (0.7%)	4	4 (1.9%)	7	7 (1.1%)
Nervous System Disorders	7	7 (1.6%)	5	5 (2.4%)	12	12 (1.9%)
Headache	5	5 (1.2%)	4	4 (1.9%)	9	9 (1.4%)

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Source: Dr. Kelty's review p.26

The most commonly reported TEAEs were eye disorders, reduced visual acuity, conjunctival hyperemia, instillation site pain, headaches, ocular hyperemia, and nasopharyngitis. All of the reduced visual acuity and conjunctival hyperemia TEAEs were deemed not related to study treatment. All instillation site pain TEAEs were deemed related to study treatment. A similar percentage of subjects in each treatment group reported mild to moderate headaches which were deemed related to study treatment.

Regarding the AEs reported across the clinical trials in the ISS, Dr. Kelty stated "No safety concerns, including somnolence, were noted in the pediatric, adult, and geriatric populations studied". And, in the dedicated safety study 06, "there were no severe ocular TEAEs in the brimonidine treatment group".

Potential Safety Issues for Drugs in the Class

Drug-Drug Interactions (DDIs)
Per the Rx Label

- Antihypertensives/cardiac glycosides may lower blood pressure
- Use with CNS depressants may result in an additive or potentiating effect
- Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine
- Monoamine oxidase inhibitors may result in increased hypotension

Respiratory depressive effects
This adverse event may be seen especially in young children and the elderly and drug misuse and abuse (including sexual abuse and overdose).

CDTL Comment
See Dr. Kelty's review for a complete discussion of potential safety issues with this class of drug.

Deaths in Clinical Trials
The clinical trials did not report any deaths and only one study (Study 862) reported serious adverse events (gastroenteritis, methicillin-resistant *Staphylococcus aureus*), in two patients, which were unrelated to brimonidine tartrate. The outcome was resolved for both events.

Safety in Geriatric Population
The proposed DFL does not place an upper age limit on use.

Ocular Rebound and Tachyphylaxis:
Tachyphylaxis and rebound congestion are common with ophthalmic vasoconstrictors and restrict their chronic use. Currently marketed OTC vasoconstrictors are α1-AR or mixed α1/α2-AR selective, but brimonidine is selective for α2-ARs. Therefore, brimonidine is less likely to be associated with tachyphylaxis because of its reduced binding to α1-ARs.

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Rebound congestion is thought to be related to generalized ischemia and secondary release of an inflammatory cascade brought about by vasoconstriction.[1,2] Ocular rebound was assessed in Study 11-100-0015 and Study 13-100-0005 based on ocular redness scores by the investigator at Visit 4 and on subject diary data in the follow-up period after dosing had ceased. No rebound was detected.

CDTL Comment
The lack of tachyphylaxis and rebound with this product are a potential advantage for the OTC consumer.

Postmarket Safety

The information in this section is based on Dr. Kelty's review of postmarket data submitted by the sponsor. The sponsor submitted a 120-day safety update after the NDA submission (see below).

Dr. Kelty noted that "There is no previous marketing experience with brimonidine tartrate ophthalmic solution, 0.025%. Brimonidine tartrate ophthalmic solution has not yet been marketed as an OTC drug product in any country. The postmarketing safety evaluation was based on experience with the higher concentration prescription brimonidine ophthalmic products indicated for treatment of increased intraocular pressure".

External Databases
The sponsor provided postmarket safety data from external databases including the FDA Adverse Event Reporting System (FAERS), the Valeant Pharmaceutical International Inc. database (VPII), the World Health Organization (WHO Vigibase), National Poison Data System (NPDS), and Drug Abuse Warning Network (DAWN) from 1/01/01-7/31/15, except DAWN 2004-2011. The 120-day safety update covered 7/1/15 or 8/1/15 to 12/31/16.

Table 17 below summarizes the number of reports submitted with the NDA and with the 120-day safety report.

Table 17. Postmarketing Safety Database Reports Time Periods

Safety Database	Submitted in NDA	120 Day Safety Update	Total # of Reports
FAERS	1/1/01-6/30/15	7/1/15-12/31/16	4245
VPII	1/1/01-7/31/15	8/1/15-12/31/16	409
WHO VigiBase	1/1/01-7/31/15	8/1/15-12/31/16	2474
NPDS	1/1/01-7/31/15	8/1/15-12/31/16	174

[1] Isenberg, S and B Green, 1984, Effect of Phenylephrine Hydrochloride on Conjunctival PO2, Arch Ophthalmol, 102(8):1185-1186.
[2] Fratelli, M and A De Blasi, 1987, Agonist-induced Alpha 1-Adrenergic Receptor Changes – Evidence for Receptor Sequestration, FEBS LETT, 212(1):149-153.

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DAWN*	2004-2011	NA	113

*Data collection for DAWN ceased in 2011.

Most Common Adverse Events Across the Safety Databases
Overall, adverse events relating to the site of administration appear to be most prevalent among all databases. Commonly reported Preferred Terms (PTs)were ocular local events including Eye irritation, Ocular hyperemia, Eye pain, and Vision blurred. These four PTs all appear on the label for the Rx strength brimonidine tartrate ophthalmic solution. Common systemic events included Dizziness, Fatigue, Headache and Hypotension. In VigiBase and VPII, where report origin is identified as US vs. Ex-US, types of PTs were similar by region.

FDA requested the sponsor analyze postmarket reports for the following safety topics of interest.

- Death
- CNS Depression (including loss of consciousness)
- Respiratory depression (especially young and elderly)
- Drug Misuse and abuse
- Accidental and intentional overdose

In addition, FDA asked the sponsor to note any reports of sexual assault, date rape or victim of rape.

Deaths in Postmarketing Databases
There were 30 death reports in FAERS and 10 death reports in VigiBase. None of the FAERS death reports contained a preferred term associated with any safety topic of interest. The other three databases contained no death reports. Among the deaths reported in FAERS, there were 3 cases contained the Preferred Term (PT) CNS depression, 1 case contained the PT loss of consciousness, 1 case contained the PT respiratory depression, 1 case contained the PT misuse/abuse, and no cases contained the PT accidental/intentional overdose.

Dr. Kelty summarized the 30 death reports as follows:
"In the cases summarized above, there is either inadequate information or it is unlikely based on the information available to made a causative association between brimonidine tartrate ophthalmic solution and death. Most of the deaths occurred in patients greater than 65 years of age with comorbid conditions and concomitant medication uses. The youngest death case occurred in a 42 year old man with a history of coronary artery disease and glaucoma who had cardiac arrest…. and considered unrelated to Combigan (brimonidine tartrate; timolol maleate)".

Other Serious Adverse Events in Postmarketing Databases

CNS Depression
CNS events typically occurred within two days of initial exposure, per the FAERS and VigiBase data. Dizziness, fatigue, and somnolence were the most frequently reported preferred terms defining CNS depression adverse event reports in FAERS and VigiBase, ranging from 18.5% to 35.3% each. In VPII, there were 21 (6.6%) cases of CNS depression. Dizziness and

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fatigue were the most common CNS depression preferred term in VPII. In NPDS, 20.3% (n=31 cases) of the brimonidine tartrate ophthalmic solution reports involved CNS depression. Among the brimonidine tartrate ophthalmic solution-only CNS depression reports in NPDS, 88.9% (n=27 cases) were unintentional exposures. In NPDS, most CNS depression cases were children 0 to 5 years of age (n=30 cases). Quantities fell between 0.1-0.3 mL for 15 of 27 (55.6%) brimonidine tartrate ophthalmic solution-only CNS depression reports in NPDS where dosage was available. Among the 22 cases for which treatment was known, 13 were treated and released from a non-healthcare facility, 3 went to critical care, and 3 went to noncritical care.

Respiratory Depression (RD)
The sponsor found nine cases (5.9%) of RD in NPDS, of which five (62.5%) were among children 0 to 5 years of age. Of the 94 reports of RD in VigiBase, 41 (43%) were serious. The PT dyspnea was recorded in 64.7% of FAERS cases of RD and was the only PT that was reported in >2% of all brimonidine tartrate ophthalmic solution case reports. There were six (1.9%) cases of RD reported in VPII. RD could not be defined in DAWN.

Misuse/Abuse
The sponsor found three reports of misuse/abuse found in VPII and 45 reports in FAERS. In NPDS, there were three cases of misuse/abuse listed below:

- 29 y.o. woman with Intentional-suspected suicide
- 79 y.o. man with Intentional-misuse
- 52 y.o. woman with Other-malicious use.

In DAWN, there were five cases (4.4%) of misuse/abuse, all in adults 21 years of age and older. At least one half of the misuse/abuse reports in FAERS, VigiBase, and VPII also contained the PT off label use.

Accidental/Intentional Overdose
The sponsor found five cases each of accidental/intentional overdose in FAERS and VigiBase and one case in VPII. Of the 141 brimonidine tartrate ophthalmic solution-only cases in NPDS, 125 (88.6%) reported unintentional exposures (accidental ingestions). Among the 125 cases with known age, 51 (40.8%) were children 0-5 years old and 47 (37.6%) were adults over 65 years old. The estimated dose quantities ranged from 0.1 mL to 15 mL. There was one multi-substance exposure case with a reported dose of 6 to 10 mL.

In FAERS, there was one case of accidental ingestion by a toddler and four cases of inadvertent oral administration of brimonidine tartrate ophthalmic solution to infants. See Dr. Kelty's review for a description of these case reports.

In the NPDS database, four of the six hospitalizations were to a critical care setting (among the 50 cases with a known treatment facility) and are listed below:

- 2007: An infant girl less than 1 year of age with accidental exposure, CNS depression, respiratory depression
- 2014: 2 y.o. boy with accidental exposure, CNS depression, respiratory depression
- 2014: 2 y.o. girl with accidental exposure, CNS depression, respiratory depression

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- 2014: 77 y.o. man with unintentional general use

DAWN contained seven reports of accidental ingestion, four of which were among children 0 to 5 years of age.

Sexual Assault, Date Rape or Victim of Rape
The sponsor found no reports of sexual assault, date rape, or victim of rape in FAERS, VPII, WHO, NPDS, or DAWN.

Factors such as age and dosage in AE reports
Age
Among FAERS reports, the sponsor found that a majority of cases 0 to 5 years of age reported CNS depression (78.1%) and/or RD (56.3%). While the prescription product is contraindicated for children < 2 years, there were 27 cases reported among infants under 1 year of age. Also, with the exception of one case, all the CNS and RD reports for children aged 0 to 5 years, were among children <1 year of age. For DAWN, 6 of 113 (5.3%) emergency department visits were from patients aged ≤ 20 years.

Dosage
The sponsor reports that available dosage information was limited in the safety databases. In FAERS, there were 130 case reports (5%) that included information needed to calculate dosage. Of these, all but one case reported dosages of 1-6 drops per day. Nearly all VigiBase reports of safety topics of interest in which dosage was available were in the indicated daily dosage range (0.1-0.3 mL). DAWN does not contain dosage data.

Summarizing the FAERS, WHO, DAWN, and NPDS data:
There were no new or unexpected safety findings from the reports from the FDA/AERS and WHO databases. Most of the commonly reported AE terms either reflected lack of efficacy or represented terms which are listed events. Further, no information from DAWN through 2011 indicates that there is any drug abuse concern with this product.

CDTL Comments

1) Postmarketing data have limitations, including overlap or duplication of reports within databases, incomplete reports, underreporting, unknown number of people exposed, lack of a control group to provide baseline rate of occurrence of event, and stimulated reporting from lawsuits or media reports.

2) The sponsor analyzed postmarket safety data for the Rx product which is 8-fold stronger than the proposed OTC product and this analysis did not reveal any preponderance of adverse events that would affect the labeling for the OTC product.

3) Review of the databases above did not reveal reports of overdose cases that would imply adverse safety for the proposed OTC product which is 1/8th the strength of the Rx drug.

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4) Summarizing the FAERS, WHO, DAWN, and NPDS data: there were no new or unexpected safety findings from the reports from the FDA/AERS and WHO databases. Most of the commonly reported AE terms either reflected lack of efficacy or represented terms which are listed events. Further, no information from DAWN through 2011 indicates that there is any drug abuse concern with this product.

120-day Safety Update

The 120-day Safety Update showed the following case reports from the VPII, FAERS, WHO, and NPDS databases.

VPII – 89 cases
- 40 serious cases: most common "Other Medically Important Event"
- 2 life threatening events; no deaths
- 5 cases of CNS depression (depressed level of consciousness, dizziness, fatigue, lethargy)
- 3 cases of LOC
- 4 cases of respiratory depression
- 2 cases of misuse/abuse

FAERS – 1742 cases with BT as primary or secondary suspect drug
- 497 cases of serious AE and/or associate with death, 14 deaths
- 13% CNS depression
- 13 cases of LOC
- 49 cases of respiratory depression
- 58 cases of misuse/abuse
- 5 cases of unintentional exposures
- Majority of cases reported in the 0-5 yrs were serious involving infants <1 yr

WHO VigiBase – 576 cases with BT as primary or secondary suspect drug
- 4 deaths
- 9.9% CNS depression
- 14 cases of respiratory depression
- 3 cases of LOC
- 10 cases of misuse/abuse
- 1 case of unintentional exposures

NPDS – 21 calls to poison centers regarding BT
- 1 serious event, no deaths
- 6 cases of CNS depression
- 2 cases of misuse/abuse
- 16 cases of unintentional exposures

*Dr. Kelty agreed with the sponsor and concluded from the 120-day safety update: "*There are no new safety signals."

Literature Review

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The sponsor submitted a literature search it conducted from January 1, 2001 through July 31, 2015 identifying 3822 citations of which 37 were pertinent to the following categories of interest:

- CNS Depression/Respiratory Depression (13 references)
- Accidental Ingestions (5 references)
- Uveitis (1 reference)
- Charles Bonnet Syndrome (3 references)

Three of the references related to accidental ingestion are described below from Dr. Kelty's review (verbatim) because they outline the more serious AEs related to ingestion of the Rx product:

Accidental Ingestions

1) **Lai Becker, M, N Huntington, and A Woolf, 2009, Brimonidine Tartrate Poisoning in Children: Frequency, Trends, and Use of Naloxone as an Antidote, Pediatrics, 123:e305-e311.** All brimonidine exposures in children 0 to 5 years of age between 1997 and 2005 were retrieved from the American Association of Poison Control Centers' Toxic Exposure Surveillance System database and FAERS database. There were 413 brimonidine reports in the Toxic Exposure Surveillance System and 340 in FAERS. Approximately half of all exposures occurred in children aged five years and younger with ingestion being the most common route of exposure. Drowsiness was the predominant symptom of exposure. Although the potential for misuse/abuse with other imidazoline derivatives exist, misuse and intentional abuse with brimonidine tartrate has not been reported anywhere in the literature. The authors calculated that the mean dose in 31 cases was 1.11mg/kg body weight.

2) **Soto-Perez-de-Celis, E, D Skvirsky, and B Cisneros, 2007, Unintentional Ingestion of Brimonidine Antiglaucoma Drops, Pediatr Emergency Care, 23 (9):657-8.** This is a case report of a 19 month old boy who unintentionally ingested approximately 1.5 mL (3 mg) of topical brimonidine ophthalmic solution (2 mg/mL). Approximately 20 minutes after ingestion, he was found unresponsive, pale, lethargic, and hypopneic. He was treated in the emergency department and hospitalized. He was treated with activated charcoal and intravenous fluids. Symptoms resolved within 6 hours.

3) **Hoffman, U, S Kuno, G Franke et al, 2004, Adrenoceptor Agonist Poisoning After Accidental Oral Ingestion of Brimonidine Eye Drops, Ped Critical Care Med, 5(3):282-285.** This is a case report of a 2-year-old boy who presented with severe cardiorespiratory symptoms, including lethargy and shallow infrequent respirations, within 20 minutes of ingesting 2 mL of brimonidine ophthalmic solution 0.2%.

Dr. Kelty Commented:

1) "CNS and respiratory depression are known potential adverse effects of exposure to brimonidine at higher concentrations in young children. The proposed product will not be labeled for use in children <5 years of age".

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2) "The OTC Drug Facts label for all OTC redness relievers warns against continued use if redness persists or worsens after 72 hours of use. Therefore, uveitis should not be an AE seen in consumers in the OTC setting. The lower strength and limited duration of use should minimize or eliminate any risk of uveitis in consumers".

CDTL Comment re: Accidental Ingestion
Reference 2 above (Soto-Perez-de-Celis 2007) demonstrates that when a 19-month old child ingested 3 mg of brimonidine tartrate it made him unresponsive, but he recovered with medical care. The largest proposed bottle for OTC use is 7.5 mL of a 0.025% solution; however, a volume of 12 mL would be needed to achieve the 3 mg of brimonidine tartrate (12 mL = 12000 mg, 12000 mg x 0.00025 = 3 mg). This gives support to the relative safety of the largest proposed OTC product (7.5 ml) in an accidental ingestion by a small child.

Overall, these references, which were pertinent to the Rx product, have reports and assessment that support the relative safety of the less potent proposed OTC drug product.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this drug product since other drug products with the indication of eye redness reliever are already OTC.

10. Pediatrics

The application triggers the Pediatric Research Equity Act (PREA) because it proposes a new dosing regimen and new indication for the drug (eye redness reliever).

An initial pediatric study plan (iPSP) was submitted to IND 108524 on October 31, 2013. The Agency confirmed an Agreed iPSP on January 16, 2014. A partial waiver of studies in pediatric patients 0 to 4 years of age was granted on the basis that evidence strongly suggests this drug would be unsafe in this age group (potential CNS depression in young children with the Rx drug, albeit at a higher strength).

The Division also agreed to the extrapolation of the efficacy of brimonidine tartrate 0.025% for reducing eye redness down to age 5 years of age provided that safety was demonstrated. The proposed labeling does not include dosing instructions for children down to, but not less than, 5 years of age.

CDTL Comments

1) *Brimonidine tartrate ophthalmic solution 0.2% (Rx) is contraindicated in children under the age of 2 years.*

2) *The sponsor studied children down to age 5 with its brimonidine tartrate 0.025% ophthalmic solution and, per the reviews of Drs. Nevitt and Kelty, demonstrated effectiveness and safety for the relief of eye redness.*

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11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues aside from the (initial) conditional approval of the name "Luminesse" and the subsequent safety concerns from the clinical reviewers from DNDP and DTOP leading to withdrawal of the name (see Section 12 below and Appendix 1).

12. Labeling

Proprietary Name
The Division of Medication Error Prevention and Analysis (DMEPA) conducted the review of the proprietary name. DMEPA conditionally approved the proprietary name "Luminesse" during the first review cycle and again during the current review cycle on May 3, 2017. However, during the current review cycle, the DTOP and DNDP teams raised concerns about potential confusion of the name "Luminesse" with the cosmetic named "Luminess" (spelled without an "e" at the end), which is used as an airbrush system to apply facial foundation makeup.

DMEPA re-engaged the sponsor with DNDP and DTOP via a tcon on November 7, 2017 to express the new concerns. On November 17, 2017, the sponsor proposed the name "(b) (4) with Lumify as a backup. DMEPA is evaluating the name (b) (4) at the time of this review.

See Appendix 1 for a discussion of the DNDP and DTOP concerns with the name Luminesse.

Label Interpretation Study re: "(b) (4)"
Ms. Amanda Pike-McCrudden conducted the social science review of the sponsor's "Label Interpretation Study". Ms. Pike noted that a Label Interpretation Study (LIS) is in general less rigorous than a Label Comprehension Study and has a limited focus. In this instance, the LIS had the following objectives:

Overall Study Objective:
To evaluate consumers understanding of the term "(b) (4)"

- Primary Objective: to evaluate the ability of consumers to correctly interpret (b) (4) to mean redness relief.
- Secondary Objective: to understand why consumers interpreted the claim correctly/incorrectly.

- Interpretation questions:

(b) (4)

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(b) (4)

Statistical Review of Label Interpretation Study

The statistical review was done by Joo-Yeon Lee, Ph.D., who did not make an approval or complete response recommendation. Dr. Lee reviewed the Label Interpretation study (see Ms. Amanda Pike-McCrudden's review) and concluded: "We could reproduce the sponsor's primary and subgroup analyses results. We noted that the sponsor's report did not provide details on subject disposition. Therefore, it is not clear how many subjects were screened and whether all those screened completed the study".

For further information, including the secondary objective, see Ms. Pike-McCrudden's review and Dr. Lee's review.

Drug Facts Labeling Review

The labeling review of the DFL was written by Ms. Arlene Solbeck who looked at the labeling statements on the proposed DFL and the Principal Display Panel (PDP). See her review for additional details and recommendations. Key points Ms. Solbeck made were as follows:

On the DFL

(b) (4)

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(b) (4)

Other DFL Consideration

A "discard statement" such as " discard remaining product 120 days after use", was favored by chemistry, not favored by DTOP, with microbiology initially neutral. (b) (4) . See the CDTL comment in Section 3 (Product Quality) of this review regarding it is OK to omit a discard statement without affecting safety for the consumer. In addition, see the clinical opinion from DTOP (Dr. Chambers) in an addendum review dated November 26, 2017, which in short states:

"*The OPQ review also notes that "The carton discard statement of 120 days for both fill configurations is supported by in-use and stability data." While this statement is technically true, the data does not support any differences between the in-use stability data and the un-opened standard storage conditions stability data. 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). No quality issues have been documented in the opened product. The necessity of discarding the product 120 days after opening is not supported. The statement "Discard remaining product 120 days after opening" should not be retained".*

On the PDP

a) Remove the term (b) (4),,

Reason: the sponsor did not submit data showing (b) (4) *(only that redness is relieved)*

b) Remove (b) (4),,

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[redacted] (b) (4)

CDTL Comment

1) *I agree with the labeling recommendations by Ms. Solbeck.*

2) *Removing '* [redacted] (b) (4)

3) *Dosing directions down to age 5 are appropriate. Per Dr. Kelty's review, although most OTC eye redness reducers (e.g., Visine) may provide dosing down to 6 years of age, the monograph does not specify a lower age cutoff. 21 CFR 349.75: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=349.75*

13. Postmarketing Recommendations

I have no special postmarket requirements or commitments to recommend for this application.

14. Recommended Comments to the Applicant

I recommend approval of this application involving brimonidine tartrate ophthalmic solution 0.025% for OTC use by consumers age 5 and older.

The additional recommendation that the sponsor considers a name other than Luminesse was met when the sponsor formally withdrew the name Luminesse, and then on November 17, 2017 the sponsor proposed a new name "[redacted] (b) (4) with "Lumify" as a backup. DMEPA is evaluating the new name "[redacted] (b) (4) at the time of this review.

Potential comments to the applicant regarding labeling, are described in Section 11 above.

APPEARS THIS WAY ON ORIGINAL

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Appendix 1. Labeling

CDTL Comment
This appendix documents the concern from DNDP and DTOP for why the (initially) proposed name Luminesse for brimonidine tartrate ophthalmic solution 0.025% would lead to risk of confusion with the cosmetic product Luminess.

DNDP Safety Concern
Regarding Similarity of Proposed Proprietary Name for Luminesse (brimonidine tartrate ophthalmic solution) 0.025% to Luminess Airbrush Foundation:

As Dr. Kelty noted in her review: "Consumers could accidentally administer the Luminess (no "e") cosmetic product into their eyes thinking that it is Luminesse eye drops. Administration of the Luminess cosmetic into the eye could result in chemical conjunctivitis and severe irritation leading to considerable consumer discomfort. Luminess cosmetic refills are sold online in individual bottles that look like eye drop containers and not necessarily copackaged with the airbrush makeup system." In addition, Dr. Nevitt wrote in his DTOP clinical review "…the similarity in names between the proposed drug product Luminesse (brimonidine tartrate ophthalmic solution 0.025%) and Luminess Airbrush Foundation will result in confusion of the two products with potential misapplication of the liquid cosmetic foundation into the eye. Although the Luminess Air Airbrush foundation applicator is a mechanical device as opposed to a bottle, the refill of the foundation is packaged in an LDPE opaque bottle with a dropper tip almost identical to the drug product Luminesse."

DTOP Safety Concern:
Regarding Similarity of Proposed Proprietary Name for Luminesse (brimonidine tartrate ophthalmic solution) 0.025% to Luminess Airbrush Foundation:
"The Division of Transplant and Ophthalmology Products (DTOP) has concerns that the similarity in names between the proposed drug product Luminesse (brimonidine tartrate ophthalmic solution) 0.025% and Luminess Airbrush Foundation will result in confusion of the two products with potential misapplication of the liquid cosmetic foundation into the eye. Although the Luminess Air Airbrush foundation applicator is a mechanical device as opposed to a bottle, the refill of the foundation is packaged in an LDPE opaque bottle with a dropper tip almost identical to the drug product Luminesse". See photo below (bottle on right is Luminesse drug product, cosmetic is on the left).

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"The tall cap of the Luminess Air Airbrush foundation is not an identifier for a cosmetic product. It is similar in size and shape to Latisse (bimatoprost ophthalmic solution) 0.03%, a drug product". See photo below.

"In summary, DTOP believes there is significant risk of confusion between the two products based on their almost identical names and packaging. We do not recommend the acceptance of Luminesse as a proprietary name for brimonidine tartrate ophthalmic solution 0.025%".

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5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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

/s/

STEVEN F OSBORNE

11/29/2017

CDTL Review NDA 208144 brimonidine tartrate ophthalmic solution 0.025% for OTC use by consumers age 5 and older. Approval recommended. Proprietary name still pending, (b) (4) proposed after Luminesse was withdrawn by sponsor.