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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 re
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. A 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 nonclinical safety for the approved listed drug product, Alphagan 0.2% (brimonidine tartrate 0.2%, NDA 0206 approved in 1996 for the treatment of glaucoma and increased intraocular pressure (IOP) in adults and children 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 Noven approved replacement name is pending at the time of this review, although the sponsor has proposed "(b) (4) with "Lumify" as a backup.

- The sponsor conducted 2 pivotal clinical efficacy trials, 1 safety trial, and a label interpretation study in suppor An additional study contributed safety information, yielding safety data from 4 clinical studies with 426 subjec on placebo. This application relies in part on the safety and efficacy established for NDA 20613, as well as sup 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 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 of tachyphylaxis or rebound congestion with an OTC ophthalmic vasoconstrictor to relieve redness of the eye i advantage for the OTC consumer.

Dimension	Evidence and Uncertainties	Conclusi
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 nega which may have ey it. Also, eye redness individual and othe 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 h treatment for conju fact that most suffe irritations, highligh treatments for contr symptoms.

Dimension	Evidence and Uncertainties	Conclusi
	• 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 o established for conc or to relieve eye red experience eye redn allergies may need product incorporati This combination p additional choice fo due to lack of sleep contact lenses and c
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 tartrat profile in the prescr on 14 years of clini experience in the U

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