Office of Clinical Pharmacology Memo

NDA or BLA Number	208144
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Submission Date	03/31/2015
Resubmission Date	02/27/2017 (Following Refuse to File on 05/29/2015)
Submission Type	505(b)(2) NDA; Standard Review
PUDFA Goal Date	12/27/2017
Brand Name/Generic Name	Luminesse / Brimonidine tartrate
Product/Formulation; Strength(s)	Brimonidine tartrate ophthalmic solution, 0.025%
Route of Administration	Topical delivery to the eye
Proposed Indication	To relieve redness of the eye due to minor eye irritations
Applicant	Bausch and Lomb Inc.
Associated IND	108524
OCP Review Team	Amit Somani, B. Pharm., Ph. D. Clinical Pharmacology Reviewer, DCP IV Philip Colangelo, Pharm. D., Ph. D. Clinical Pharmacology Team Leader, DCP IV
OCP Division	DCP IV
OCP Final Signatory	Philip Colangelo, Pharm. D., Ph. D.

SUMMARY

This NDA 208144 is for Luminesse, Brimonidine tartrate ophthalmic solution, 0.025%. The 0.025% Brimonidine tartrate ophthalmic drug product is a clear, colorless to slightly yellow, sterile, preserved ophthalmic solution formulated for topical delivery to the eye. The Applicant is seeking approval of this product as an over-the-counter (OTC) application to relieve redness of the eye due to minor eye irritations. The proposed dosing regimen in adults and children 5 years and older is to instill 1 drop in the affected eye(s) every 6-8 hours, no more than four times daily. Brimonidine tartrate ophthalmic solutions (e.g. Alphagan®P and Combigan™; Allergan) are FDA-approved for prescription use at concentrations of 0.1%, 0.15%, 0.2%, and 0.5% at a dose of one drop three times a day for the treatment of increased intraocular pressure.

Brimonidine is minimally absorbed after topical application to the eye. To compare prior known systemic exposure information for the previously approved ophthalmic products containing brimonidine tartrate to the proposed 0.025% brimonidine tartrate ophthalmic solution, the Applicant conducted a pharmacokinetic (PK) Study 863 (13-100-0007) to evaluate the systemic PK exposure to brimonidine following topical ocular administration of the 0.025% brimonidine tartrate ophthalmic solution.

Study 863 (13-100-0007) was performed to assess 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 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 Luminesse. Given the available data, the Applicant concludes that the plasma concentrations of brimonidine remain below 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.

Reviewer's Comment: *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 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%.*

RECOMMENDATION

The Clinical Pharmacology team has reviewed the application and recommends the approval of NDA 208144, Luminesse (Brimonidine tartrate ophthalmic solution, 0.025%) as an OTC ophthalmic drug product to relieve redness of the eye due to minor eye irritations. The approval recommendation is based on the results from the PK Study 863 (13-100-0007), where the plasma

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%.

LABELING COMMENTS

None. There is no Clinical Pharmacology relevant information in the proposed label.

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/s/

AMIT A SOMANI
10/31/2017

PHILIP M COLANGELO
10/31/2017