CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208144Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208144
Supporting document/s:	17
Applicant's letter date:	27 February 2017
CDER stamp date:	27 February 2017
Product:	Brimonidine tartrate ophthalmic solution, 0.025%
Indication:	Eye redness due to minor irritation
Applicant:	Bausch & Lomb/Valeant Pharmaceuticals 400 Somerset Corporate Blvd. Bridgewater, NJ 08807
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
Team Leader:	Jane J. Sohn, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Jung E. Lee, RPh

Disclaimer

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1 Executive Summary

1.1 Introduction

NDA 208144 is a 505(b)(2) application that proposes market registration of a brimonidine tartrate ophthalmic solution, 0.025%, for relief of eye redness due to minor irritations in the OTC setting. The application relies in part on prior FDA findings of 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.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical data were submitted in support of this application.

1.3 Recommendations

1.3.1 Approvability: Yes

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: No nonclinical safety concerns identified.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 70359-46-5

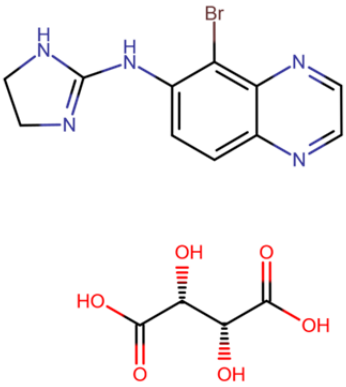
Generic Name: Brimonidine tartrate

Code Name: N/A

Chemical Name: 6-Quinoxalinamine, 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1)

Molecular Formula/Molecular Weight: $C_{11}H_{10}BrN_5 \bullet C_4H_6O_6$/442.2244

Structure:



Pharmacologic Class: Alpha adrenergic agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 020613; IND 108524

2.3 Drug Formulation

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 2.3.P.1–1 Qualitative and quantitative composition of Brimonidine Tartrate Ophthalmic Solution

Component	Reference to Quality Standard	Function	Concentration	
			mg/mL	% w/w[f]
Brimonidine Tartrate[a]	In-house	Active	0.25	0.025
Glycerin	USP	(b) (4)		
Sodium Borate Decahydrate	NF			
Boric Acid	NF			
Potassium Chloride	USP			
Calcium Chloride Dihydrate	USP			
Sodium Chloride	USP			
Benzalkonium Chloride (BAK), (b) (4)[b, c, d]	NF			
(b) (4) Sodium Hydroxide[e]	NF			
Hydrochloric Acid[e]	NF			
Water for Injection	USP			

a (b) (4)
b
c
d
e
f

USP = United States Pharmacopeia
NF = National Formulary
qs = quantity sufficient

2.4 Comments on Novel Excipients

All excipients included in the DP formulation are compendial. In addition, while each excipient is listed in the FDA IID 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.

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

2.5 Comments on Impurities/Degradants of Concern

The Sponsor conducted a leachable/extractable analysis of the container closure system (3.2.P.2.4), white LDPE bottles with white [redacted] dropper tips and two component child-resistant closures [redacted] inner portion and purple [redacted] outer portion). The results of the analysis indicated [redacted]. The Sponsor submitted a safety assessment addressing the risk posed by the presence of these [redacted] leachables, which was based on their interpretation of the ICH M7 guidance and published literature data.

The findings of the assessment include that "The existing scientific literature, as summarized in the [OECD Screening Information Dataset, SIDS] review, indicates that [redacted] can be classified as a Class 5 (nongenotoxic) impurity based on the absence of mutagenicity in standard genotoxicity assays, and supporting data for structurally similar molecules that are not carcinogenic in rodent bioassays." Published data were also available describing direct ocular administration to humans in an eye irritation study, wherein instillation of 0.04 mL of a [redacted] solution "...([redacted] ppm; equivalent to [redacted]mg) produced a mild transient sensory irritation (30-45 seconds), hyperemia of conjunctival vessels and a small increase in intraocular pressure, with effects resolving within 2 hours" resulting in a classification of non-irritating. The assessment further notes that '[redacted], a structurally similar compound to [redacted]], is not carcinogenic in rodents and is not genotoxic in *in vivo* and *in vitro* tests."

Based on their assessment, the Sponsor proposes a DP specification for [redacted] of NMT [redacted]%). At this proposed specification, the Sponsor estimates a worst-case patient exposure as follows:

- [redacted]
- [redacted]

Such an exposure would equate to approximately [redacted] µg/kg/day in a reference 60-kg person.

Internal consultation with CDER/OTS confirmed a lack of bacterial mutagenicity potential for [redacted] (**Appendix 1**). In addition, DTOP (Lori Kotch, PhD) was also consulted regarding standard practices and policies with respect to management of leachable/extractable impurities in ophthalmologic drug products. Dr. Kotch confirmed that NMT [redacted]% would be considered an acceptable qualification threshold for a non-genotoxic impurity in such a proposed ophthalmic drug product.

Thus, based on the Sponsor's submitted assessment, other publicly available information identified by this reviewer, and the noted internal consultation findings, the proposed specification of NMT [redacted]% is considered to be reasonably safe and acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

The drug product is intended for the relief of eye redness due to minor eye irritations in the OTC setting in adults and children five years and older. The recommended dosing regimen is to instill one drop in the affected eye(s) every 6-8 hours with a maximum of four times daily.

2.7 Regulatory Background

NDA 208144 was originally received on 31 March 2015, following development under IND 108524. The NDA was not filed at that time due to a lack of adequate post-marketing safety data for review (Refusal to File letter, 29 May 2015). On multiple occasions during development, the Sponsor has inquired of the Agency whether any additional nonclinical data would be required to support market approval for their drug product. The Agency has consistently responded that no additional data would be required in the absence of excipient or impurity safety concerns or identification of some safety signal during clinical trials (cf. IND 108524 Pre-NDA Meeting Minutes, 10 November 2014). The Sponsor indicates their reliance for nonclinical safety support on published literature and FDA's prior findings of safety for the listed prescription drug product, Alphagan (brimonidine tartrate, 0.2%), under NDA 020613 (approved 6 September 1996). The marketing of this product has now been discontinued for reasons other than safety or effectiveness, though other brimonidine products remain on the market.

3 Studies Submitted

No nonclinical studies were submitted in support of this application.

3.3 Previous Reviews Referenced

- NDA 208144: Pharmacology/Toxicology Filing Checklist for NDA, Xinguang (Cindy) Li, PhD, 29 May 2015
- NDA 208144: CDER/OTS Genotoxicity Consult: [redacted] 26 July 2017.

11 Integrated Summary and Safety Evaluation

NDA 208144 was originally received on 31 March 2015 as a 505(b)(2) application proposing market registration of a brimonidine tartrate ophthalmic solution, 0.025%, for relief of eye redness due to minor irritations in the OTC setting. The application was initially not filed due to a lack of adequate post-marketing safety data for review. The current resubmission relies in part on prior FDA findings of 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.

In multiple communications to the Sponsor during development, the Agency has consistently stated that no additional nonclinical data would be required to support an NDA in the absence of excipient or impurity safety concerns or identification of some safety signal during clinical trials. Consistent with these communications, the current submission contains no original nonclinical data in support of the application.

The drug product formulation contains only compendial excipients that have been previously used in approved ophthalmic solution drug products. The proposed in-product use levels of these excipients do not raise safety concerns from a nonclinical perspective.

A leachables/extractables assessment of the container closure system by the Sponsor indicated [redacted] The Sponsor submitted a safety assessment addressing the risk posed by the presence of these [redacted] leachables, which was based on their interpretation of the ICH M7 guidance and published literature data. Based on the Sponsor's submitted assessment, other publicly available information identified by this reviewer, and findings from internal consultation with OTS and DTOP, the proposed specification of NMT [redacted]% is considered to be reasonably safe and acceptable.

In conclusion, based on the totality of the information described above, NDA 208144 is considered to be approvable from a nonclinical safety perspective.

12 Appendix/Attachments

Appendix 1

CDER/OTS Genotoxicity Consult

To: Charles Thompson
cc: Jane Sohn
From: CDER/OTS/OCP/DARS: The Chemical Informatics Program
Re: NDA 208144
Date: July 26, 2017

(b) (4) was evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (Q)SAR models. Three software programs were used: *Derek Nexus* 5.0.2 (*DX*), *Leadscope Model Applier* 2.2.1-1 (*LMA*), and *CASE Ultra* 1.6.2.1 (*CU*). To maximize sensitivity and negative predictivity, a positive prediction from any one software program was used to justify an overall positive prediction. All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.

The (Q)SAR assessment of mutagenic potential for the compound is consistent with recommendations described in the final ICH M7 guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). Based on the entire weight of evidence, (b) (4) (b) (4) is predicted to be negative for bacterial mutagenicity.

Bacterial Mutagenicity (Q)SAR Predictions[1]

(b) (4)	Software	*Salmonella* Mutagenicity	*E. coli*/ TA102 Mutagenicity
	Derek Nexus	-	-
	Leadscope Model Applier	-	-
	CASE Ultra	-	-
	Overall Software Prediction	-	-
	Overall Expert Prediction	-	-

(b) (4) is predicted to be negative for bacterial mutagenicity. Furthermore, (b) (4) has been experimentally tested in *Salmonella* strains TA98, TA100, TA1535, TA1537, and *E. coli* WP2 and WP2 *uvrA* in the presence and absence of S9 (NTRL OTS0520390).

Reference:
National Technical Reports Library (NTRL). Toxicity Studies with (b) (4) Tests for in Vitro Genotoxicity with Attachments, Cover Sheets and Letter dated (b) (4) Accession Number (b) (4)

This report has been reviewed and approved by CDER/OTS/OCP/DARS.

[1] + = positive; – = negative; Eqv = equivocal; NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

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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/

DONALD C THOMPSON
09/28/2017

JANE J SOHN
09/28/2017
I concur.