Clinical Review #2 for NDA 208144

Application Type	NDA
Application Number(s)	208144
Submit Date(s)	February 27, 2017
Received Date(s)	February 27, 2017
Reviewer Name(s)	Wiley A. Chambers, MD
Review Completion Date	November 26, 2017
Established Name	Brimonidine tartrate ophthalmic solution, 0.025%
Therapeutic Class	α-2 adrenergic agonist
Applicant	Bausch & Lomb
Formulation(s)	Sterile solution
Dosing Regimen	1 drop in affected eye(s) every 6-8 hours, no more than 4 times a day
Indication(s)	Relieve redness of the eye due to minor eye irritations
Intended Population(s)	Adults and children ≥ 5 years

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 2

Recommendation on Regulatory Action 2

2 INTRODUCTION AND REGULATORY BACKGROUND 2

DRUG PRODUCT 2

3.1 Formulation 2

3.2 Revised release and shelf life specifications 3

4 LABELING RECOMMENDATIONS 5

1 Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

NDA 208144, Brimonidine tartrate ophthalmic solution, 0.025% (b) (4)

2 Introduction and Regulatory Background

See the Clinical Review for NDA 208144, dated November 2, 2017. This is a 505(b)(2) application. The applicant identifies the listed drug product that is the basis for the submission as Alphagan (brimonidine tartrate ophthalmic solution) 0.2%, NDA 20-613.

See also the Office of Pharmaceutical Quality (OPQ) Combined Summary Review for NDA 208144 dated November 6, 2017.

Drug Product

3.1 Formulation

Component	Function	mg/mL	% w/w**
Brimonidine tartrate	Active	0.25	0.025
Glycerin	(b) (4)		
Sodium Borate Decahydrate			
Boric Acid			
Potassium Chloride			
Calcium Chloride Dihydrate			
Sodium Chloride			
Benzalkonium Chloride, (BAK), (b) (4)			
(b) (4) Sodium Hydroxide			
(b) (4) Hydrochloric Acid			
Water for Injection			

(b) (4)

Reviewer's Comment: *Acceptable.*

3.2 Revised release and shelf life specifications

Test	Procedure	Release Criteria	Shelf Life Criteria
Description	(b) (4)		
Visible particulates			
Identification by UPLC			
Identification by UV			
pH			
Osmolality			
Particulate Matter			
Assay			
Related substances			
Leachables Total (b) (4)			
Benzalkonium Chloride (BAK) Assay			
Sterility			
Antimicrobial Effectiveness			
Weight Loss/Gain			
Fill Volume			

Reviewer's Comment: *The applicant originally proposed wider specifications. The OPQ Reviewer notes:*

> *"The attributes of pH and osmolality are important monitors of stability since the 2.5mL fill product exhibits significant weight loss on stability due to water loss from permeation through the semi-permeable container. This loss affects pH, osmolality, brimonidine tartrate assay, BAK assay and weight loss (see Stability section). The water loss is observed in the lowest fill configuration (2.5mL) of the registration lots at a much higher rate than reported for higher fill configurations in the clinical (5mL fill and 10mL fill) and*

registration (7.5 mL fill) lots. Because of the higher fill and lower rate of water loss, stability data submitted for two clinical lots ((b) (4) lot 1550517 and B&L lot 184121) do not show much trend in pH and osmolality over 24 months at 25°C – the pH data remained constant (6.5 – 6.6 and 6.4 – 6.5 respectively) and osmolality changed a few points (312-317 and 305-314 mOsm/kg respectively). The clinical history does not support the proposed wider acceptance criteria for pH ((b) (4)) or osmolality (b) (4) mOsm/kg)."

However, the OPQ reviewer is not correct from a clinical prospective. The human eye comfortably tolerates pH values between 6 and 7.4, and osmolality values between 200 and 500. As described in the USP, monograph <771>: "Normal tears have a pH of about 7.4. The eye can tolerate products over a range of pH values from about 3.0 to about 8.6, depending on the buffering capacity of the formulation; and ophthalmic products may be tolerated over a fairly wide range of tonicity (0.5%–5% sodium chloride, equivalent to about 171–1711 mOsm/kg).

OPQ requested revised acceptance criteria:

"To accommodate stability trends due to water loss, the affected attributes may be controlled by tighter release acceptance criteria and wider shelf-life acceptance criteria which are supported by clinical lot stability data, registration lot release data and a comparative approved prescription product.

pH: Water loss decreases pH, so the proposed lower limit of the shelf-life acceptance criteria, (b) (4), is acceptable and achievable, but the upper range of (b) (4) should be reduced to (b) (4), the proposed release limit since it will not change on stability. See comment below to change the acceptance criteria.

Osmolality: This attribute is clinically important in ophthalmic products. The osmolality of human tears is in the range of 280 – 300 mOsm/kg. Product water loss increases osmolality. Patients received clinical product containing no more than 317 mOsm/kg in the two clinical lots submitted. Osmolality increased to no more than 330 mOsm/kg in the worst case (2.5mL fill) registration lots at 25°C for 18 months – the timepoint at which the lots first failed for weight loss exceeding the limit of (b) (4)%. The approved shelf-life acceptance criteria for osmolality of the comparative product is (b) (4) mOsm/kg. Considering all this, a shelf-life acceptance criteria of (b) (4) mOsm/kg is acceptable and achievable."

After two requests from the OPQ reviewer, the applicant submitted revised specifications with tightened criteria for related substances, pH and osmolality.

From a clinical prospective, the following comments related to the final specifications:

1. *Considering the container is opaque, it will not be possible to assess visible particles by visual inspection. The specification is not necessary.*
2. *The pH and osmolality specification is more stringent than needed for safe and effective use of the drug product. The USP notes in <771> that ophthalmic products may be tolerated over a fairly wide range of tonicity (0.5%–5% sodium chloride, equivalent to about 171–1711 mOsm/kg). Brimonidine tartrate ophthalmic solution, 0.15% has an acceptable osmolality range of 250-350 mOsm/kg. A pH specification of (b) (4) is also acceptable from a clinical prospective.*

4 Labeling Recommendations

The OPQ review includes the following comments concerning labeling:
"The carton storage statement for both configurations should be strengthened to include a warning to discard the product if it has been stored at any temperature exceeding 30°C (86°F). If the applicant wishes to label the 7.5 mL fill separately, the warning for that configuration should advise the consumer to discard the product if it has been stored at any temperature exceeding 30°C (86°F) for several days. These warnings are based on stability test results plus added margin to address risk and assure quality of the product when used by the consumer in an over-the-counter setting."

Reviewer's Comment: *The OPQ request is not warranted from a clinical prospective. The request is based on a concern that the pH, osmolality and concentration can be altered secondary to water loss when the bottle is exposed to temperatures greater than 25°C (77°F). As noted earlier in this review, the changes in pH and osmolality do not reach levels that are likely to affect the safety or efficacy of the drug product. In addition, the product is supported by lifetime use of concentrations of brimonidine 8 times greater than proposed in this product. The minor increase in concentration due to the water loss is negligible in comparison to the 8-fold safety margin.*

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.

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
11/27/2017