CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208144Orig1s000

PRODUCT QUALITY REVIEW(S)

1.12.14 Environmental Analysis

Bausch & Lomb, a division of Valeant Pharmaceuticals North America LLC, hereby claims that the action requested of approval of this new drug application (NDA) for brimonidine tartrate ophthalmic solution, 0.025%, , qualifies for a categorical exclusion and therefore does not require the submission of a full environmental assessment per 21 CFR 25.31(b).

This is an additional brimonidine tartrate-containing drug product that will have little to no contribution to the aquatic or terrestrial environment, compared to the 1.0 PPB threshold outlined in 21 CFR 25.31(b). The calculation below is from the FDA *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications", July 1998*, and is used to estimate the potential concentration of the substance at the point of entry into the aquatic environment.

Basic assumptions

- Compound in use is brimonidine tartrate
- Quantity of active per proposed commercial and sample use is (b) (4) per year

The expected introduction concentration (EIC) of brimonidine tartrate into the aquatic environment is calculated as follows:

EIC Aquatic (PPB) = A*B*C*D

A = kg/year of product use

B = 1/liters per day entering publicly owned treatment works (POTW) (1.214 X 10^{11} liters per day standard)

C = year/365 days

D = 10^{9} µg/kg (conversion factor)

Brimonidine tartrate calculation:

A = (b) (4)

(b) (4)

B = (b) (4)

C =

D =

Result: A*B*C*D = (b) (4)

This result is well below the 1.0 PPB threshold outlined in 21 CFR 25.31(b). Therefore, a categorical exclusion from further environmental assessment under 21 CFR 25 is requested.

(b) (4)

(b) (4)

3/13/15

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/s/

MELISSA V CHHANGTE
01/02/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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Executive Summary Review #2 Addendum

Date: December 30, 2017
From: **Swapan K De, Ph.D.**
CMC Team Lead, CDER/OPQ/ONDP/DNDP II/Branch VI
Application Technical Lead (NDA 208144)

Subject: **Addendum to NDA 208144 executive summary review (**brimonidine tartrate ophthalmic solution 0.025%)

1. Proprietary Name: Following a T-con dated November 07, 2017 between FDA and Bausch & Lomb regarding safety concern and confusion of the proposed proprietary name Luminesse™ with another product, the applicant requested withdrawal of the name Luminesse™ on 11/14/2017. The applicant has submitted a proprietary name (Primary name: (b) (4), Alternate: Lumify) review document on 11/16/2017. The Agency considered the document as a complete submission, thus set up a user fee goal date, February 14, 2018 to review the request for proprietary name.
2. Labeling: Discard Statement: OPQ quality review (dated 11/6/17) granted the proposed labeling storage statement "discard 120 days after opening the bottle" based on the submitted in-use stability study conducted for a period of 120 days. The study results show that the multi-dose ophthalmic product remains within specifications when opened and used as indicated for the study period. DMEPA (review dated 11/8/17) recommended to keep the discard statement to the PDP. However, DTOP (Division of Transplant and Ophthalmology Products) clinical review (dated 11/27/17) advised that the discard statement "should not be retained". The basis for the recommendation was that "the data does not support any differences between the in-use stability data and the un-opened standard storage condition stability data". OPQ agrees with the DTOP statement up to 120 days, but advises that no data are available for in-use conditions after 120 days. The subject was discussed on November 20, 2017 and OPQ microbiology review was updated with an addendum (November 27, 2017) to state that "from a microbiological perspective, the risk to the patient due to microbial contamination after product opening is considered low" based on submitted data and to recommend "that standard labeling practices concerning discarding opened multi-dose ophthalmic products be followed." Multi-dose ophthalmic over-the-counter products such as Refresh Liquigel and Optive (90 days) as well as Blink (45 days) include a discard statement, while others such as Visine do not.

3. Labeling: Storage Statement: OPQ quality review (dated 11/6/17) recommended strengthening the storage statement by adding a warning against storage at high temperatures e.g. "discard if the product if stored at any temperature above 30°C (86°F)". The recommendation was based on changes in the pH, osmolality and concentration of the drug product seen in stability results and was made to assure that the quality of the product remained within specifications similar to the reference listed drug (RLD) when used by the consumer in an over-the counter setting. However, DTOP (Division of Transplant and Ophthalmology Products) clinical review (dated 11/27/17) advised that the warning statement "is not warranted from a clinical prospective" since "changes in pH and osmolality do not reach levels that are likely to affect the safety or efficacy of the drug product". Thus, OPQ defers decision regarding the discard statement to the DNDP labeling team.

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