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APPLICATION NUMBER:

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PHARMACOLOGY 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:	206276
Supporting document/s:	SDN014 (eCTD013)
Applicant's letter date:	1/22/2015
CDER stamp date:	1/22/2015
Product:	Olopatadine hydrochloride ophthalmic solution, 0.77%
Indication:	Treatment of signs and symptoms of allergic conjunctivitis
Applicant:	Alcon Research Ltd 6201 South Freeway MS TC 45 Fort Worth, TX 76134
Review Division:	Division of Transplant and Ophthalmology Products
Reviewer:	Aaron M Ruhland, PhD
Supervisor/Team Leader:	Lori Kotch, PhD, DABT
Division Director:	Renata Albrecht, MD
Project Manager:	Lois Almoza

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1 Executive Summary

1.1 Introduction

The subject of this NDA is olopatadine hydrochloride ophthalmic solution, 0.77% administered as a once daily topical ocular drop for the treatment of ocular itching associated with allergic conjunctivitis. A nonclinical review of the approvability of the NDA application has been conducted (dated 12-31-2014). This review represents reconsideration of Section 8 of the labeling following a counterproposal by the applicant. Specifically, the applicant contends that labeling language in Section 8 describing increased embryolethality and cleft palate in rats following oral administration of 60 mg/kg olopatadine during gestation falls within or near historical control values. The applicant submitted historical control data from nonclinical embryo-fetal studies to support these arguments .

1.2 Brief Discussion of Nonclinical Findings

- The applicant's argument that increased embryolethality following daily oral olopatadine doses of 60 mg/kg in pregnant rats falls within the historical control range is supported by the data submitted. The FDA proposed labeling has been amended in support of these findings.
- The applicant's argument that (b) (4) . The FDA proposed labeling has not been amended in support of these findings.
- It was suggested in internal discussion that (b) (4) be deleted from the labeling to reduce potential confusion when comparing this multiple to that of the 1 mg/kg/day based on comparison of exposure (i.e. 45 – 150 fold).
- The human exposure (AUC_{0-12}) to Pazeo following the recommended dosing regimen reported in Section 12.3 of the labeling was changed based upon the Clinical Pharmacology reviewer's calculations (changed from (b) (4) to 9.7 ng·hr/mL). The human AUC reported in Section 8 and resultant safety margin calculations have been revised to reflect this change.
- During ongoing revision, the applicant suggested the addition of the following statement to Section 8.3:
    - "An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose."

1.3. Labeling

1.3.1 Former FDA proposed labeling (see letter dated 12-31-2014)

8.1 Pregnancy

Risk Summary
There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD)). There was no toxicity in rat offspring at (b) (4) times MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced (b) (4) cleft palate at 60 mg/kg/day (1080 times the MRHOD), and reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day (b) (4). A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were (b) (4) times higher than the observed human exposure (b) (4) following administration of the recommended human ophthalmic dose.

8.3 Nursing Mothers
Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PAZEO is administered to a nursing mother.

1.3.2. Applicant's proposed amended labeling (SDN014; 1-22-2015)

Blue double-underlined text represents applicant's proposed additions to the labeling; Red strikethrough text represents applicant's proposed deletions from the labeling:

8.1 Pregnancy

Risk Summary
There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 10, (b) (4) 0 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD)). There was no toxicity in rat offspring at (b) (4) times MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced decreased embryofetal viability and (b) (4) reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day (b) (4). A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were (b) (4) times higher than the observed human exposure (b) (4) following administration of the recommended human ophthalmic dose.

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1.3.3 Data submitted by applicant to support proposed labeling changes

Morita, H., *et al*., 1987; "Spontaneous malformations in laboratory animals: Frequency of external, internal and skeletal malformations in rats, rabbits, and mice", *Cong Anom*, 27: 147 – 206.

Embryolethality

Following review of data from Study A-89-52, an embryo-fetal toxicity study in rats submitted to support the NDA, it was concluded that the (b) (4) dose caused

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