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APPLICATION NUMBER:

22-221

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-221
Submission Date	July 2, 2007
Brand Name	Akten
Generic Name	Lidocaine hydrochloride
Primary Reviewer	Sarah Robertson, Pharm.D.
Team Leader	Charles R. Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Akorn
Relevant IND(s)	73,445
Submission Type; Code	Original NDA
Formulation; Strength	3.5% ophthalmic gel
Indication(s)	Ocular surface anesthesia during ophthalmic procedures

EXECUTIVE SUMMARY

Lidocaine hydrochloride is a local anesthetic agent that stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The only ocular anesthetic currently approved by the FDA is proparacaine. The current proposed product is a preservative-free gel solution of lidocaine 3.5% developed for topical ocular anesthesia. The proposed dose is 2 drops applied to the ocular surface in the area of the planned ophthalmic procedure.

The proposed gel formulation contains hypromellose to allow extended contact with the cornea, which is theorized to result in extended anesthesia at lower concentrations. The gel formulation is also theorized to result in significantly reduced or eliminated passage of anesthetic through the nasolacrimal system, thereby resulting in undetectable or negligible systemic exposure of lidocaine. However, no clinical PK studies evaluating the systemic absorption of the ophthalmic gel have been conducted. The Sponsor has requested a waiver of the requirement to demonstrate the in vivo bioavailability for lidocaine hydrochloride 3.5% ophthalmic gel under 21 CFR 320.22. Based on the total ocular dose to be administered, 3.5 mg lidocaine hydrochloride per 2 drops of gel, the maximum attainable lidocaine blood concentration, in the unlikely event the entire ocular dose is systemically absorbed, would be approximately 50 ng/mL. This value is ~ 1/30 the therapeutic concentration necessary for the treatment of cardiac arrhythmias, for which the recommended dose of lidocaine is 50-100 mg by IV bolus, followed by 1-4 mg/minute by continuous infusion. As the proposed indication of lidocaine ophthalmic gel is for acute use during ophthalmic procedures, there is not expected to be any systemic accumulation due to chronic, repeat administration.

The Sponsor's request for a waiver of the requirement for submission of evidence of the in vivo bioavailability is granted, based on the expected low systemic exposure of lidocaine following the ophthalmic administration of lidocaine hydrochloride 3.5% gel.

RECOMMENDATION

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant is acceptable. The request for a waiver of the in vivo bioavailability requirement is granted based on the expected low systemic exposure of lidocaine following the ophthalmic administration of lidocaine hydrochloride 3.5% gel.

The reviewer's changes to the proposed label should be forwarded to the Sponsor.

PHASE IV COMMITMENTS

No Phase IV commitments are recommended

9 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

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/s/

Sarah M. Robertson
1/23/2008 02:00:37 PM
BIOPHARMACEUTICS

Charles Bonapace
1/24/2008 09:09:59 AM
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