CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-221

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
NDA 22-221

Date	June 2, 2008
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-221
Applicant	Akorn, Inc.
Date of Submission	August 11, 2008
PDUFA Goal Date	October 11, 2008
Proprietary Name / Established (USAN) names	Akten (lidocaine hydrochloride ophthalmic gel) 3.5%
Dosage forms / Strength	ophthalmic gel
Proposed Indication(s)	Ocular surface anesthesia during ophthalmic procedures
Recommended:	Approval

1. Introduction

Lidocaine, the first amino amide-type local anesthetic, was developed by Nils Löfgren and Bengt Lundqvist in 1943 and first marketed in 1948. Over the past 60 years, lidocaine injection, oral solution, and topical gel have been found to be safe and effective for a variety of indications.

While all currently marketed ophthalmic preparations of topical anesthesia are in solution form, a lidocaine gel formulation is theorized to have longer contact time with pain-sensitive ocular structures that could lead to better anesthesia. This led to the development of Akten, a preservative-free, single-use ophthalmic preparation.

NDA 22-221 received an approvable letter on June 2, 2008. With the resolution of all remaining Chemistry and Manufacturing issues, the application for Akten (lidocaine hydrochloride ophthalmic gel) 3.5% is now recommended for approval for ocular surface anesthesia during ophthalmologic procedures.

2. Background

The approvable letter issued on June 2, 2008, cited the following issues:

1. Provide information, either directly or by reference to a DMF, on the components and composition of the immediate container label, adhesive and printing ink.
2. Provide a completed comprehensive study of leachable and extractable substances from the immediate container, and from the label and secondary packaging, and provide a toxicological evaluation of the substances to determine safe exposure levels.

3. Propose a test and acceptance criterion in parts-per-million for any leachable substance above a level that is of toxicologic concern.

4. Provide data to indicate whether there is a difference in leachable substances for samples stored in both the horizontal and upright orientations with the preprinted shrink wrap.

5. Provide a revised amended Stability Protocol and Commitment to include a test and acceptance criterion for particulate matter, weight loss/gain and viscosity.

3. CMC

Revised labeling and the five remaining Chemistry and Manufacturing issues cited in the June 2, 2008, approvable letter have been addressed by the applicant in amendments dated September 16, 2008, August 29, 2008, August 8, 2008, July 9, 2008, June 26, 2008, and June 13, 2008. For detailed information regarding each of the five deficiencies, see the CMC review dated September 26, 2008:

Per the CMC review dated September 26, 2008:

> This application is recommended for approval (AP) from the Chemistry, Manufacturing, and Controls perspective.
>
> **Basis for Approvability**
> Akorn, Inc. submitted this NDA for Aktentm (lodicaine hydrochloride) Ophthalmic Gel, 3.5% in accordance with section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The NDA submission describes a novel gel dosage form of lidocaine hydrochloride for ophthalmic use. The reference listed drug (RLD) for this NDA submission is identified as Xylocaine Injectable Solution, (1-2% lidocaine hydrochloride, NDA# 006488, APP Pharms) and Xylocaine Jelly, (2% lidocaine hydrochloride, NDA# 008816, APP Pharms) approved in 1948 and 1953 respectively.
>
> The manufacturing sites were found "Acceptable" by the Office of Compliance (12-Sep-2007). The applicant's request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable.

Previously, the NDA was reviewed and found inadequate from CMC perspective. The applicant was notified in advance of the NDA review and via AE (Approvable) action letter of the pending CMC deficiencies. An NDA amendment (May 20, 2008) was received prior to the NDA action indicating a complete extractable and leachable study had not been performed on the proposed container closure system. The amendment indicated that complete assessment of the suitability would be determined based on the proposed protocol submitted therein. The proposed study protocol was to use the sample container closure system obtained for the three months accelerated stability data. The applicant committed to continue the study for 3 months at 40°C and declared the final report will be submitted to the NDA as a supplement/annual report. Stated in the AE letter was that a completed study should be included in the NDA submission.

The re-submission with letter date August 8, 2008, as noted by the applicant contains the final report for leachable/extractable compounds from container, label and secondary packaging for the samples with the entire immediate container/closure system and the secondary packaging. Also included in the submission is the safety update report since the last submission dated May 5, 2008. Draft copies of the introductory promotional materials are also included in the submission.

The appropriate review discipline has provided evaluation of the additional reports and information. Several discussions with the applicant have taken place and have resulted in the amendments submission being reviewed as listed under section 6 of the review data sheet.

The applicant has amended the stability protocol to provide testing for viscosity testing and to provide for demonstration of compatibility of the container closure system. The applicant has provided and will continue to provide information required for adequate documentation of suitability, quality control and stability of the container closure system. The control for the extract/leachable substances is a critical part of quality that will result in a safer drug product. Agreement with the recommended revised drug product specification and the revised stability protocol primarily are based on the route of administration, several referenced guidances and review team input.

4. Nonclinical Pharmacology/Toxicology

Per the original Division Director's review for the first cycle review of this product:

No new nonclinical studies were requested by the Division or performed by the applicant. The applicant provided literature studies and a reference to the agency's previous findings for lidocaine to support the required labeling sections. There are no objections to approval of this NDA from the pharmacology/toxicology perspective based on the nonclinical information provided in this application.

5. Clinical Pharmacology/Biopharmaceutics

Per the original Division Director's review for the first cycle review of this product:

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.

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 applicant'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.

6. Sterility Assurance

The product is a single use, unpreserved, sterile product. A review for sterility assurance has been conducted and found to be satisfactory in the first review cycle for this drug product.

7. Clinical/Statistical - Efficacy

Two major sources of clinical data were utilized in the clinical review of this drug product to establish efficacy:

- The results of one clinical trial (06AKO001)
- Literature references citing ophthalmic uses of lidocaine.

In clinical study 06AKO001 lidocaine 3.5% provided a statistically significant amount of anesthesia when compared to sham. The published studies discussed in the Medical Officer's original review further support the efficacy of lidocaine as an anesthetic for the use during ophthalmic procedures.

8. Safety

Two major sources of clinical data were utilized in the clinical review of this drug product to establish safety:

- The results of one clinical trial (06AKO001)
- Literature references citing ophthalmic uses of lidocaine.

The safety profile was consistent with other ophthalmic anesthetic agents.

9. Advisory Committee Meeting

Not applicable; this product is a non-NME.

10. Pediatrics

Safety and efficacy in pediatric patients has been extrapolated from studies in older subjects and studies in pediatric patients using different formulations of lidocaine.

11. Other Relevant Regulatory Issues

With the resolution of all remaining Chemistry and Manufacturing issues cited in the June 2, 2008, approvable letter, the application for Akten (lidocaine hydrochloride ophthalmic gel) 3.5% is recommended for approval for ocular surface anesthesia during ophthalmologic procedures.

12. Labeling

Labeling revisions have been recommended by the review team and have been incorporated into the recommended labeling.

See Appendix 1 for the recommended labeling for the drug product.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

With the resolution of all remaining Chemistry and Manufacturing issues, the application for NDA 22-221 Akten (lidocaine hydrochloride ophthalmic gel) 3.5% is now recommended for approval for ocular surface anesthesia during ophthalmologic procedures.

RISK BENEFIT ASSESSMENT:

The benefits of using this drug product outweigh the risks for the indication of anesthesia during ophthalmic procedures.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Cross Discipline TL Review- 1

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/s/

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