

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

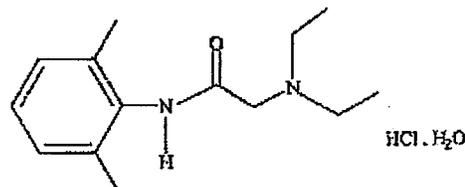
**22-221**

**CHEMISTRY REVIEW(S)**



**NDA 22-221**

**Akten™ (lidocaine hydrochloride) Ophthalmic Gel**



**Akorn Inc.  
2500 Millbrook Drive  
Buffalo Grove, IL 60089**

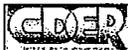
**Milton J. Sloan, Ph.D.  
ONDQA Pre-Marketing Assessment Division II Branch IV**

**For Division of Anti-Infective and Ophthalmology Drug  
Products**



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# Chemistry Review Data Sheet

1. NDA 22-221
2. REVIEW #: 3
3. REVIEW DATE: 08-Aug-2008
4. REVIEWER: Milton J. Sloan, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original  
Amendment (BC)  
Amendment (BC)  
Amendment (BC)  
Amendment (BC)  
Amendment (BC)

Document Date

02-July-2007  
17-July-2007  
12-March-2008  
11-April-2008  
20-May-2008  
13-June-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment (BC)  
Amendment (AC)  
Amendment (BF)  
Amendment (BC)  
Amendment (BC)  
Amendment (BC)  
Amendment (BC)

Document Date

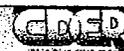
09-July-2008  
08-August-2008  
29-August-2008  
29-August-2008  
16-September-2008  
19-September-2008  
22-September-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Akorn Inc.  
Address: 2500 Millbrook Drive  
Buffalo Grove, IL 60089



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Representative: Sam Boddapati, VP Reg. Affairs

Telephone: (847) 353-4909

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Akten (lidocaine hydrochloride) Ophthalmic Gel, 3.5%.

b) Non-Proprietary Name (USAN): lidocaine hydrochloride

c) Code Name/# : AK 1015

d) Chem. Type/Submission Priority :

- Chem. Type: 3
- Submission Priority: S

#### 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

#### 10. PHARMACOL. CATEGORY: local anesthetic agent

#### 11. DOSAGE FORM: sterile ophthalmic gel

#### 12. STRENGTH/POTENCY: 3.5%

#### 13. ROUTE OF ADMINISTRATION: ocular

#### 14. Rx/OTC DISPENSED: Rx OTC

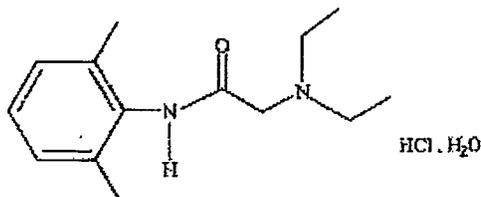
#### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

#### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-(Diethylamino)-2',6'-acetoxyllidide, monohydrochloride, monohydrate



Molecular Formula: C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O · HCl · H<sub>2</sub>O



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

Molecular Weight: 288.8

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	II			1, 3	Adequate	02/08/2008	R. Powers, Quality Reviewer
—	III			1, 3	Adequate	06/22/2006	J. Jee, Quality Reviewer
—	III			1, 3	Adequate		
—	III			1, 3	Adequate	01/14/2005	Y. Lu, Review Chemist
—	III			1, 3	Adequate	N/A	NAI
—	III			1, 3	Adequate	N/A	NAI

b(4)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73,445	Initial Phase II Study
IQA Review (27-July-2007)	NDA 22-221	Initial Quality Assessment of PAL (Linda Ng, Ph.D.)
Review (02-July-2007)	NDA 22-221	NDA Fileability Checklist



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Review (22-Jan-2008)	NDA 22-221	NDA review #1
Review (15-July-2008)	NDA 22-221	NDA review #2 Memo to File

#### 18. STATUS:

##### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	
EES	Overall Acceptable	12-Sep-2007	S. Adams
Pharm/Tox	N/A	N/A	
Biopharm	N/A	N/A	
LNC	N/A	N/A	
Methods Validation	Not requested per ONDQA policy	N/A	M. Sloan
DMETS	Comments to Sponsor	28-Feb-2008	J. Park
EA	Claim of Categorical Exclusion is acceptable	21-Apr-2008	M. Sloan
Quality Microbiology	Adequate	21-Apr-2008	J. Metcalfe

# The Chemistry Review for NDA 22-221

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application is recommended for approval (AP) from the Chemistry, Manufacturing, and Controls perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

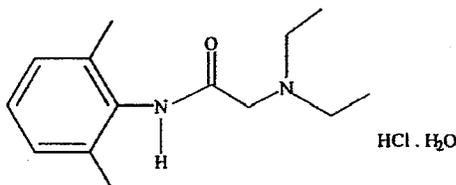
None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Lidocaine hydrochloride 3.5% (35 mg/mL)

The active drug, lidocaine hydrochloride is designated chemically as 2-(Diethylamino)-2',6'-acetylidide, monohydrochloride, monohydrate with a molecular formula of  $C_{14}H_{22}N_2 \cdot HCl \cdot H_2O$  and molecular weight of 288.8. The structural formula of lidocaine hydrochloride monohydrate is as follows:



Lidocaine hydrochloride is a white, odorless, crystalline powder, having a slightly bitter taste; very soluble in water and in alcohol; soluble in chloroform; insoluble in ether. Lidocaine hydrochloride used; in manufacturing of the exhibit batches of AKTEN is manufactured by  $\Gamma$  and is the subject of DMF — The Drug Master File (DMF) was reviewed and is adequate for support of this NDA. The technical data provided by the manufacturer specify the impurities related to the drug substance.

b(4)



## CHEMISTRY REVIEW



### Executive Summary Section

#### Drug Product:

Akten™ (lidocaine hydrochloride) Ophthalmic Gel, 3.5% is a sterile, aqueous product, containing lidocaine hydrochloride as an active and hypromellose, sodium chloride, and purified water as inactive ingredients. Lidocaine hydrochloride is a local anesthetic agent and administered topically for ophthalmic use. Sodium chloride functions as a \_\_\_\_\_ in the ophthalmic gel. Hypromellose is used to \_\_\_\_\_ Purified water is used \_\_\_\_\_ Sodium hydroxide and/or hydrochloric acid is used for pH adjustment. The manufacturing process for sterile Akten™ (lidocaine hydrochloride) 3.5% ophthalmic gel briefly involves \_\_\_\_\_

b(4)

\_\_\_\_\_ The formulation does not contain a preservative because the product is to be used as unit dose. Akten™ Ophthalmic Gel is available in a single strength, 3.5% in 5ml fill size. The active drug substance is present as a hydrochloride and therefore the name and strength are linked in terms of the salt. The strength (3.5%) is in terms of the amount of hydrochloride salt (35 mg) and the name appropriately expresses the salt in the nomenclature.

#### **B. Description of How the Drug Product is Intended to be Used**

Akten™ is a local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures, including cataract surgery, intravitreal injections, refractive surgery including LASIK, supplemental topical anesthetic after peribulbar or retrobulbar block, contact lens exam of retina, etc.. Akten™ stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthesia and occurs between 20 seconds to 1 minute and persists for 5 to 30 minutes or more. The gel formulation of Akten™ is expected to reduce or eliminate the passage of anesthetic through the nasolacrimal system. Therefore, systemic levels of Akten™ should be significantly lower compared to systemic levels of other topical ocular anesthetics applied as liquid drops. The recommended dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure. Additional anesthesia may be reapplied as needed. The gel formulation is supplied in 10 mL bottles that are capped with a 15 mm round tip with a 0.016 pierced dropper tip. The new formulation does not contain a preservative because the product is to be used as unit dose. The drug product has been found to be stable when stored at 25°C (77°F)/ 40% RH. The recommended expiry date for this drug product is 24 months.



## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

Akorn, Inc. submitted this NDA for Akten™ (lidocaine 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 sponsor'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 sponsor 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 sponsor 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 sponsor 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. Noted was that the proposed labeling for Akten™ was submitted on June 6, 2008. The appropriate review discipline has provided evaluation of the additional reports and information. Several discussions with the sponsor have taken place and have resulted in the amendments submission being reviewed as listed under section 6 of the review data sheet.

The sponsor has amended the stability protocol to provide testing for viscosity testing and to provide for demonstration of compatibility of the container closure system. The sponsor 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.



## CHEMISTRY REVIEW



### Executive Summary Section

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

Chemist: Milton J. Sloan, Ph.D.

Date: September 15, 2008

Final Revision: September 25, 2008

Branch Chief: Norman Schmuff, Ph.D.

Date:

#### C. CC Block

Project Manager: Jane Dean

19 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**  
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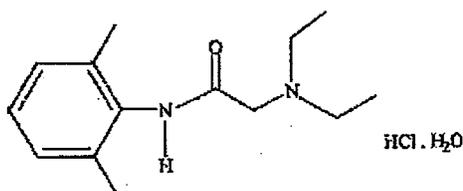
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Milton Sloan  
9/26/2008 12:46:52 PM  
CHEMIST  
Recommend AP

Norman Schmuff  
9/26/2008 09:00:30 PM  
CHEMIST



**NDA 22-221**

**Akten™ (lidocaine hydrochloride) Ophthalmic Gel**



**Akorn Inc.  
2500 Millbrook Drive  
Buffalo Grove, IL 60089**

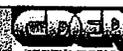
**Milton J. Sloan, Ph.D.  
ONDQA Pre-Marketing Assessment Division II Branch IV**

**For Division of Anti-Infective and Ophthalmology Drug  
Products**



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A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block .....	10
<b>Chemistry Assessment.....</b>	<b>11</b>
<b>I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....</b>	<b>11</b>
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# Chemistry Review Data Sheet

1. NDA 22-221

2. REVIEW #: 1

3. REVIEW DATE: 22-Jan-2008

4. REVIEWER: Milton J. Sloan, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment (BC)

Amendment (BC)

Amendment (BC)

Document Date

02-July-2007

17-July-2007

12-March-2008

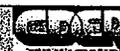
11-April-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Akorn Inc.  
Address: 2500 Millbrook Drive  
Buffalo Grove, IL 60089  
Representative: Sam Boddapati, VP Reg. Affairs  
Telephone: (847) 353-4909



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Akten™ (lidocaine hydrochloride) Ophthalmic Gel, 3.5%.
- b) Non-Proprietary Name (USAN): lidocaine hydrochloride
- c) Code Name/# : AK 1015
- d) Chem. Type/Submission Priority :
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: local anesthetic agent

11. DOSAGE FORM: sterile ophthalmic gel

12. STRENGTH/POTENCY: 3.5%

13. ROUTE OF ADMINISTRATION: ocular

14. Rx/OTC DISPENSED:  Rx  OTC

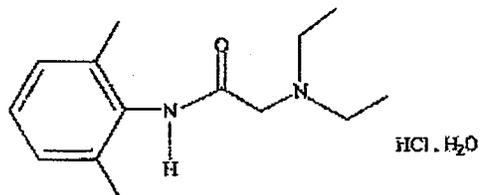
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

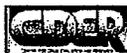
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-(Diethylamino)-2',6'-acetoxylidide, monohydrochloride, monohydrate



Molecular Formula: C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O · HCl · H<sub>2</sub>O

Molecular Weight: 288.8



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
—	II			1, 3	Adequate	02/08/2008	J. Powers, Quality Reviewer
—	III			1, 3	Adequate	06/22/2006	J. Jee, Quality Reviewer
—	III			1, 3	Adequate		
—	III			1, 3	Adequate	01/14/2005	Y. Lu, Review Chemist
—	III			1, 3	Adequate	N/A	N/A
—	III			1, 3	Adequate	N/A	N/A
—	III			1, 3	Adequate	N/A	N/A

b(4)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73,445	Initial Phase II Study



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	
EES	Overall Acceptable	12-Sep-2007	S. Adams
Pharm/Tox	N/A	N/A	
Biopharm	N/A	N/A	
LNC	N/A	N/A	
Methods Validation	Not requested per ONDQA policy	N/A	N/A
DMETS	Comments to Sponsor	28-Feb-2008	J. Park
EA	Claim of Categorical Exclusion is acceptable	21-Apr-2008	M. Sloan
Microbiology	Adequate	21-Apr-2008	J. Metcalfe

# The Chemistry Review for NDA 22-221

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

1. This application is recommended for approvable (AE) from the Chemistry, Manufacturing, and Controls perspective, pending acceptable responses from deficiency comments. The NDA lacks adequate safety controls (chemical testing for and identification of, extractables from the container closure system and the introduction of leachables into the drug formulation during storage) for the compatibility of packaging components. The sponsor did not provide a comprehensive study on the  $I^-$  container closure system. The lack of leachable and extractable studies presents a safety risk that is unacceptable.

b(4)

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

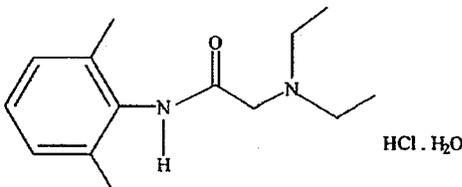
N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Lidocaine hydrochloride 3.5% (35 mg/mL)

The active drug, lidocaine hydrochloride is designated chemically as 2-(Diethylamino)-2',6'-acetoxyllidide, monohydrochloride, monohydrate with an molecular formula of  $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$  and molecular weight of 288.8. The structural formula of lidocaine hydrochloride is as follows:



Lidocaine hydrochloride is a white, odorless, crystalline powder, having a slightly bitter taste; very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.



## CHEMISTRY REVIEW



### Executive Summary Section

Lidocaine hydrochloride used in manufacturing of the exhibit batches of AKTEN is manufactured by [redacted] and is the subject of DMF [redacted]. The Drug Master File (DMF) was reviewed and is adequate for support of this NDA. The technical data provided by the manufacturer specify the impurities related to the drug substance. The sponsor evaluated the impurity profile for the drug substance and drug product during the validation studies as well.

b(4)

#### Drug Product:

Akten™ (lidocaine hydrochloride) Ophthalmic Gel, 3.5% is a sterile, aqueous product, containing lidocaine hydrochloride as an active and hypromellose, sodium chloride, and purified water as inactive ingredients. Lidocaine hydrochloride is a local anesthetic agent and administered topically for ophthalmic use. Sodium chloride functions as a [redacted] used to [redacted] in the ophthalmic gel. Hypromellose is [redacted]. Purified water is used [redacted]. Sodium hydroxide and/or hydrochloric acid are used for pH adjustment. A brief description of the manufacturing process for sterile Akten™ (lidocaine hydrochloride) 3.5% ophthalmic gel involves [redacted].

b(4)

b(4)

[redacted] The formulation does not contain a preservative because the product is to be used as unit dose. Akten™ Ophthalmic Gel is available in a single strength, 3.5% in 5ml fill size.

#### **B. Description of How the Drug Product is Intended to be Used**

Akten™ is a local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures, including cataract surgery, intravitreal injections, refractive surgery including LASIK, supplemental topical anesthetic after peribulbar or retrobulbar block, contact lens exam of retina, ALTISLT lasers, retinal lasers, retinal cryoretinopexy, pneumatic retinopexy, scleral depression examinations, conjunctival or corneal foreign body removal, gonioscopy, suture placement, removal of corneal sutures, removal of conjunctival sutures, removal of lid sutures, anterior chamber paracentesis, placement of electroretinographic lenses, lens placement for YAG laser, vitreous biopsy, conjunctival biopsies, minor lid procedures, pterygium surgery, strabismus adjustment surgery, conductive keratoplasty, pars plana vitrectomy, and trabeculectomy. Akten™ stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic and occurs between 20 seconds to 1 minute and persists for 5 to 30 minutes or more. The gel formulation of Akten™ is proposed to reduce or eliminate the passage of anesthetic through the nasolacrimal system. Therefore, systemic levels of



Executive Summary Section

Akten™ may be significantly lower compared to systemic levels of other topical ocular anesthetics applied as liquid drops. The recommended dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure. Additional anesthesia may be reapplied as needed. The gel formulation is supplied in 10 mL bottles that capped a 15 mm round tip with a 0.016 pierced dropper tip. The new formulation does not contain a preservative because the product is to be used as unit dose. Stability indicating attributes tested were the assay of drug substance, level of impurities, minimum fill, pH, sterility, and appearance. Based on these test, the sponsor has concluded the drug product to be stable when stored at 25°C (77°C); excursions permitted to 15-30°C (59-86°C).

**C. Basis for Approvability or Not-Approval Recommendation**

Akorn, Inc. has submitted this NDA for Akten™ (lidocaine 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 have all been found "Acceptable" by the Office of Compliance (12-Sep-2007). The applicant request for a categorical exclusion from the preparation of an Environmental Assessment provided under 21 CFR § 25.31(a) is acceptable. The proposed specifications have not been found adequate and suitable for a quality drug product. Specific concerns were communicated to the sponsor (02-April-2008). The sponsor submitted a response to the information request on 11-April-2008. Their responses were reviewed and not found satisfactory. Tests for physico-chemical and toxicology to determine product specific safety of all material components should have been performed much earlier in product development to qualify use and to justify not monitoring on stability. The sponsor has not provided basic information on the adhesive or ink to be used for bottle label. Additionally, information on the proposed printed shrink band covering the neck of the bottle and the closure as tamper evidence has not been provided. The proposed container/closure system (section P.7) uses at

Although the individual resins have been used in approved ophthalmic drug products and are the subject of adequate and supportive DMFs, the NDA lacks information to support the suitability of these materials in combination with the drug product. The proposed stability protocol does not include a test for viscosity, a critical quality attribute of gel dosage forms. The sponsor has essentially concluded that several deficiencies cannot be completed within the PDUFA time frame. Without a comprehensive study of the container closure system, Akorn Inc. has not demonstrated via CMC data submitted in the application that this new formulation is stable throughout the proposed shelf life of the drug product.

b(4)



Executive Summary Section

The drug product review sections of the NDA submission for Product Development, Manufacture, Control of Drug Product, Container Closure, and Stability were all found inadequate for support a quality drug product. Pending satisfactory responses to all the comments sent to the sponsor, and those presently recommended, the proposed specifications may be adequate and suitable for a quality drug product.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist: Milton J. Sloan, Ph.D.

Date: April 15, 2008

Final Draft: May 5, 2008

Branch Chief: Norman Schmuff, Ph.D.

Date:

**C. CC Block**

Project Manager: Jane Dean

39 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Milton Sloan  
5/6/2008 02:38:35 PM  
CHEMIST

Norman Schmuff  
5/8/2008 09:39:44 AM  
CHEMIST

## NDA FILEABILITY CHECKLIST

**NDA Number:** 22-221

**Applicant:** Akorn Inc.

**Stamp Date:** 02-Jul-2007

**Drug Name:** Akten™ (lidocaine hydrochloride) ophthalmic gel, 3.5%

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	<input type="radio"/>		The CMC section of the NDA is organized in CTD format to allow substantive review.
2	Is the section indexed and paginated adequately?	<input type="radio"/>		
3	On its face, is the section legible?	<input type="radio"/>		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	<input type="radio"/>		
5	Is a statement provided that all facilities are ready for GMP inspection?	<input type="radio"/>		A statement has been provided. CMC PM Linda Athey has submitted EER with concurrence from reviewer(8/15/07).
6	Has an environmental assessment report or categorical exclusion been provided?	<input type="radio"/>		A claim for categorical exclusion has been requested.
7	Does the section contain controls for the drug substance?	<input type="radio"/>		The controls for the USP grade drug substance has been referenced to DMF# <u>      </u>
8	Does the section contain controls for the drug product?	<input type="radio"/>		
9	Has stability data and analysis been provided to support the requested expiration date?		<input type="radio"/>	Data is not detailed or substantial to give clear indication of support for the requested shelf life.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input type="radio"/>		
11	Have draft container labels been provided?	<input type="radio"/>		
12	Has the draft package insert been provided?	<input type="radio"/>		
13	Has an investigational formulations section been provided?	<input type="radio"/>		A pharmaceutical development report has been included.

b(4)

NDA: 22-221  
Akten™ (lidocaine hydrochloride) Ophthalmic gel, 3.5%

Akorn Inc.

14	Is there a Methods Validation package?	<input type="checkbox"/>		
15	Is a separate microbiological section included?	<input type="checkbox"/>		

If the NDA is not fileable from a manufacturing and controls perspective, state why it is not.

\_\_\_\_\_  
Milton J. Sloan, Ph. D., Review Chemist:

\_\_\_\_\_  
Date:

\_\_\_\_\_  
Norman Schmuff, Ph.D., Branch Chief:

\_\_\_\_\_  
Date:

cc:  
Original NDA 22-221  
Division File  
Chem/Sloan  
Chem/Ng  
ONDQA/Schmuff  
PM/Dean

Have all DMF References been identified?

DMF Number	Holder	Description	LOA Included	Status
			Yes	Current/Adequate

**b(4)**

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/s/  
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Milton Sloan  
8/17/2007 04:13:22 PM  
CHEMIST  
No filable issues identified

Linda Ng  
8/20/2007 09:22:54 AM  
CHEMIST  
Signing for Norman Schmuff

Initial Quality Assessment  
Branch IV  
Pre-Marketing Assessment Division II

**OND Division:** Division of Anti-Infective and Ophthalmology Products  
**NDA:** 22-221  
**Applicant:** Akorn Inc  
**Stamp Date:** June 29, 2007  
**PDUFA Date:** May 2, 2008  
**Trademark:** Akten  
**Established Name:** Lidocaine hydrochloride Ophthalmic gel  
**Dosage Form:** Ophthalmic gel 3.5%  
**Route of Administration:** topical  
**Indication:** Local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures

**PAL:** Linda Ng, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

### Summary and Critical Issues:

#### Summary

In general, this NDA, 3S, dated June 29, 2007, is straightforward. The product is claimed to be a novel formulation of lidocaine hydrochloride ophthalmic gel at 3.5% for potentially achieving local ocular anesthesia with longer surface contact time. No preservative is used in the formulation. The drug product was clinically studied using the 1.5% and 3.5% strengths. This is a 505(b)(2) NDA, submitted in CTD format. NDA 22,221 has been accepted as a standard NDA.

The drug substance, lidocaine hydrochloride monohydrate, a white odorless, slightly bitter crystalline powder, is manufactured by [redacted] and supplied by [redacted]. The DMF [redacted] has been reviewed for other products. The Letters of Authorization for the drug substance and for the container and closure system is provided in section 1.4.1. b(4)

This is a single use drug product using a 10 mL natural [redacted] round bottle with 15 mm natural dropper tip and natural color unknown material cap. Hypromellose is [redacted] for the gel formulation. [redacted] is the container closure supplier (DMF [redacted]). b(4)

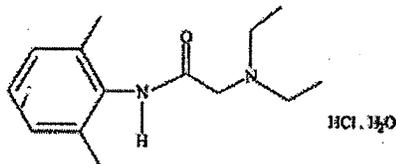
The drug product is manufactured and released by Akorn at Somerset, New Jersey. The target pH [redacted]

One batch with 12 months and two batches with 3 months at 25°C/40%RH and 6 months and 3 months at 40°C/25%RH respectively were submitted. Vertical and horizontal positions were included for the accelerated conditions. See section 32.P.8. A three-year marketing exclusivity and an expiry dating period of 24 months are requested.

The microbiology consult, the trade name request to DMET and the labeling consult to DDMAC have not been sent. The OND PM, Ms. Jane Dean will submit the latter two after the filing meeting of August 21, 2007. The microbiology consult will be submitted when the micro copy is tracked down.

The EER was submitted July 17, 2007 by the OND PM, Ms. Linda Athey.

The chemical structure is as follows:



Lidocaine hydrochloride

Chemical Name: - 2-( diethyl-amino )-N-(2,6-dimethylphenyl)-, monohydrochloride monohydrate

- 2-diethyl-amino-N-2,6-acetoxylididi, monohydrochloride monohydrate

Molecular Formula: C<sub>14</sub>H<sub>23</sub>ClN<sub>2</sub>O. H<sub>2</sub>O

Molecular Weight: 288.81

### **Critical issues for review**

- A USP monograph for the drug substance, lidocaine hydrochloride exists but none for the ophthalmic gel. The DMFs for all have not been evaluated by the IQA reviewer.
- All tests should be evaluated for meaningful conditions and criteria. In addition, a one-time intensive leachables study should be evaluated for the container and closure system.
- The release and stability testing sites for the drug substance and stability site for the drug product were not clearly stated. The OND PM, Linda Athey, followed up with the applicant to obtain the information. The EER was submitted by Ms. Athey
- The impurities test for the drug substance appears to be missing in section 3.2.S. It is suggested that a system suitability test to include a standard at the quantitation limit to ensure detectability of impurities at that level. The system suitability test should be included for both drug substance and drug product impurities test.
- It is not clear what material is used for the cap. The letter of authorization stated a trade name, but not the material. Information may be available in the DMF. However, the stability protocol states a \_\_\_\_\_ cap.
- Evaluate if freeze-thaw/stress studies were performed, mentioned in the stability protocol, to evaluate the physical/chemical stability of the gel formulation.

b(4)

**Initial Quality Assessment**

- The drug product specification should include a test and criterion for viscosity, and two non-specific identification tests or one specific test as per ICH Q6A. The format of listing the impurities should be evaluated.
- The stability protocol appears to have missed the commitment to inform the Review Division with testing failures, section 3.2.P.8.2.

- **Comments for 74-Day Letter**

None recommended.

**D. Review, Comments and Recommendation:**

Acceptable for filing. No team review is recommended. A single reviewer can review this NDA due to the fairly straightforward issues. Dr. Milton Sloan has been assigned to review the NDA.

Linda Ng, Ph.D.  
Pharmaceutical Assessment Lead

July 27, 2007  
Date

Norman Schmuff, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

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/s/

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Linda Ng  
7/30/2007 02:10:45 PM  
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Norman Schmuff  
7/30/2007 02:18:22 PM  
CHEMIST