CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-221

SUMMARY REVIEW

Division Director Review of NDA 22-221

Date	October 7, 2008
From	Wiley A. Chambers, M.D.
NDA#	22-221
Applicant	Akorn, Inc.
Date of Submission	August 11, 2008
PDUFA Goal Date	October 11, 2008
Name	Akten (lidocaine hydrochloride ophthalmic gel) 3.5%
Dosage forms / Strength	ophthalmic gel
Proposed Indication(s)	Ocular surface anesthesia during ophthalmic procedures
Action:	Approval

1. Introduction

Lidocaine, the first amino amide-type local anesthetic was 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.

Akorn is the holder of approved ANDA 40-433, for Lidocaine hydrochloride jelly, USP, 2%.

The current application under review, NDA 22-221 is submitted as a 505(b)(2) referencing the reference listed product for ANDA 40-433. This current application is recommended for approval for ocular surface anesthesia during ophthalmic procedures once adequate quality controls (chemical testing for and identification of, extractables from the container closure system and the limits on leachables into the drug formulation during storage) and revised labeling have been provided.

2. Background

Lidocaine has similar side effect profile as the other amide local anesthetics. Drugs in this class can have systemic dose related side effects which result from high plasma levels.

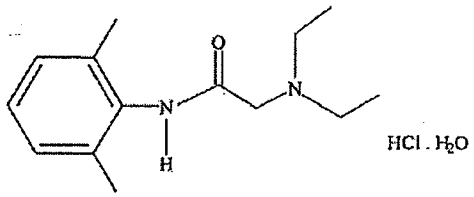
The major sources of clinical data utilized in the Medical Officer's review include:

- Akorn sponsored clinical trial 06AKO001
- Literature references citing ophthalmic uses of lidocaine

Study 06AKO001 was designed to describe the safety and efficacy of lidocaine 3.5% gel in achieving surface anesthesia when applied to the conjunctiva. This was a two day, multi-centered, randomized, prospective, sham controlled study conducted at 7 study sites to assess the effectiveness of topical Akten 1.5%, 2.5% and 3.5% as the sole anesthetic agent to achieve ocular surface anesthesia. Participants were randomized 1:1:1:1 to sham, Akten 1.5%, Akten 2.5%, or Akten 3.5%.

3. CMC

DRUG SUBSTANCE: Lidocaine hydrochloride 3.5% (35 mg/mL)
The active drug, lidocaine hydrochloride is designated chemically as 2-(Diethylamino)-2',6'-acetoxylidide, monohydrochloride, monohydrate with an molecular formula of $C_{14}H_{22}N_{20}.HC1\cdot H_20$ 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. Lidocaine is manufactured by [ ] 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. The applicant 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 [ ] — in the ophthalmic gel. Hypromellose is used [ ] [ ] Purified water is used as — Sodium hydroxide and/or hydrochloric acid are used for pH adjustment. 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(4)

DRUG PRODUCT COMPOSITION:

Lidocaine Hydrochloride	35 mg/mL
Hypromellose	—
Sodium chloride	—
HCl/NaOH	[ ]
Purified Water	

b(4)

All facilities inspections have been completed and the Office of Compliance and New Drug Quality have determined these facilities are acceptable.

CMC RECOMMENDATIONS:
This application is recommended for approval from the Chemistry, Manufacturing, and Controls perspective. All previous deficiencies have been resolved.

4. Nonclinical Pharmacology/Toxicology

This NDA is for a new ophthalmic gel formulation of Akten (lidocaine hydrochloride ophthalmic gel) 3.5%, for ocular surface anesthesia. The applicant has requested that the Division use its previous finding of safety from NDAs for lidocaine HCl to support the current NDA as permitted under section 505(b)(2) of the Federal food, Drug and Cosmetic Act. Lidocaine has been used as local anesthetic for labor/delivery, dental procedure, lumbar analgesia, surgical analgesia, obstetric procedures and postherpetic neuralgia. Lidocaine is available for intravenous and spinal injection as well as oral and topical administrations. Lidocaine is also available as ophthalmic drops. The recommended dose for lidocaine drops is 2 drops of 4% solution in both eyes, 6 times, 60 minutes prior to surgery. Assuming that roughly 100 uL of the lidocaine gel will be used, the human dose is roughly 60 μg/kg lidocaine.

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

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 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.

No clinical PK studies evaluating the systemic absorption of the ophthalmic gel have been conducted. The applicant 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 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.

7. Clinical/Statistical - Efficacy

The primary outcome variable for clinical trial 06AKO001 was the percentage of subjects who achieved ocular surface anesthesia within 5 minutes post-application of the anesthetic gel.

Analysis of Primary Efficacy Endpoint-Clinical Trial 06AKO001 (ITT Population)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=52)	Akten 3.5% (N=51)
Percent Achieving Anesthesia Within 5 Minutes of Dosing	12 (22%)	45 (88%)	46 (88%) *	47 (92%)
P value		<0.001	<0.001	<0.001

*Excludes 1 subject with anesthesia duration of 7192 seconds. Efficacy analyses were performed on 208 of the 209 subjects in the ITT population and 207 subjects in the PP population because subject 06/0026 in the 2.5% group was excluded from the efficacy analyses because this patient was an outlier.

Analysis of Secondary Efficacy Endpoints-Clinical Trial 06AKO001 (ITT Population)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=52)	Akten 3.5% (N=51)
Mean Duration of Anesthesia (secs.)	171.2	614.3	700.6	801.8
Standard Deviation	433.5	458.5	605.9	497.5
Min.	0	0	0	0
Max.	2062	2360	3280	2080
P value		<0.001	<0.001	<0.001
Mean Time to Anesthesia (secs.)	85.0	46.6	60.6	58.2
Standard Deviation	101.7	57.2	90.1	80.0
Min.	20	15	20	20
Max.	300	301	360	302

*Excludes 1 subject with anesthesia duration of 7192 seconds. Efficacy analyses were performed on 208 of the 209 subjects in the ITT population and 207 subjects in the PP population because subject 06/0026 in the 2.5% group was excluded from the efficacy analyses because this patient was an outlier.

Summary of Duration of Anesthesia Among Subjects Who Achieved Anesthesia

Time (secs.)	Sham (N=12)	Akten 1.5% (N=45)	Akten 2.5% (N=46)	Akten 3.5% (N=47)
Mean	770.3	696.2	792	870
SD	633.9	425	585	456
Median	560	580	580	860
Min.	40	224	235	260
Max.	2062	2360	3280	2080

Subject 06/0026 in Akten 2.5% group excluded from summary statistics.

Cumulative Frequency of Subjects Achieving Anesthesia by Onset Time and Treatment

Onset Time (secs.)	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
20	3 (25%)	16 (35.6%)	24 (52.2%)	16 (34.0%)
40	6 (50%)	34 (75.6%)	36 (78.3%)	35 (74.5%)
60	10 (83.3%)	43 (95.6%)	40 (87%)	41 (87.2%)
300	12 (100%)	45 (100%)	45 (97.8%)*	47 (100%)
Anesthesia Not Achieved	42	6	6	4

*Excludes one subject who achieved anesthesia at 360 seconds. This patient (0172) had the 5 minute dosing assessment delayed to 6 minutes.

8. Safety

Clinical Studies Used to Evaluate Safety

Two major sources of clinical data were utilized in this review 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. Labeling

Labeling revisions have been recommended by the review team and have been incorporated into the latest submission of the package insert.

b(4)

2 Page(s) Withheld

____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 1

approximately 55% of subjects experienced anesthesia for 10 minutes or longer and 27% experienced anesthesia for 15 minutes or longer. The anesthetic effect of additional applications of Akten™ has not been evaluated.

16 HOW SUPPLIED/STORAGE AND HANDLING

Akten™ (lidocaine hydrochloride ophthalmic gel) 3.5% is supplied as a clear gel for single patient use as follows:

5mL fill in a 10mL natural, round plastic dropper bottle

(NDC 17478-792-10).

Storage
Store at 15° to 25° C (59° to 77° F)

Keep container closed and protected from light in the original carton until use. Discard after use.

Rx Only

Akorn
Manufactured by:
Akorn Inc.
Lake Forest, IL 60045

U.S, Patent No.: 11/491,611 Pending
U.S, Patent No.: 11/745,207 Pending

AN00N Rev. 09/08

10. Regulatory Action

NDA 22-221, Akten (lidocaine hydrochloride ophthalmic gel) should be approved.

Wiley A. Chambers, MD
Acting Division Director
Division of Anti-Infective and Ophthalmology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
10/7/2008 04:10:10 PM
MEDICAL OFFICER

Wiley Chambers
10/7/2008 04:11:37 PM
MEDICAL OFFICER

Division Director Review of NDA 22-221

Date	June 2, 2008
From	Wiley A. Chambers, M.D.
NDA#	22-221
Applicant	Akorn, Inc.
Date of Submission	June 29, 2007
PDUFA Goal Date	June 2, 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:	Approvable

1. Introduction

Lidocaine, the first amino amide-type local anesthetic was 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.

Akorn is the holder of approved ANDA 40-433, for Lidocaine hydrochloride jelly, USP, 2%.

The current application under review, NDA 22-221 is submitted as a 505(b)(2) referencing the reference listed product for ANDA 40-433. This current application is recommended for approval for ocular surface anesthesia during ophthalmic procedures once adequate quality controls (chemical testing for and identification of, extractables from the container closure system and the limits on leachables into the drug formulation during storage) and revised labeling have been provided.

2. Background

Lidocaine has similar side effect profile as the other amide local anesthetics. Drugs in this class can have systemic dose related side effects which result from high plasma levels.

The major sources of clinical data utilized in the Medical Officer's review include:

- Akorn sponsored clinical trial 06AKO001
- Literature references citing ophthalmic uses of lidocaine

Study 06AKO001 was designed to describe the safety and efficacy of lidocaine 3.5% gel in achieving surface anesthesia when applied to the conjunctiva. This was a two day, multi-

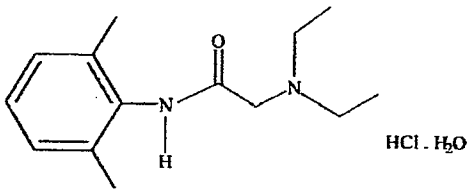
centered, randomized, prospective, sham controlled study conducted at 7 study sites to assess the effectiveness of topical Akten 1.5%, 2.5% and 3.5% as the sole anesthetic agent to achieve ocular surface anesthesia. Participants were randomized 1:1:1:1 to sham, Akten 1.5%, Akten 2.5%, or Akten 3.5%.

3. CMC

DRUG SUBSTANCE:

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

The active drug, lidocaine hydrochloride is designated chemically as 2-(Diethylamino)-2',6'-acetoxylidide, monohydrochloride, monohydrate with an molecular formula of $C_{14}H_{22}N_{20}.HC1{\cdot}H_20$ 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. Lidocaine hydrochloride used in manufacturing of the exhibit batches of AKTEN is manufactured by ⌐ ⌋ 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. The applicant evaluated the impurity profile for the drug substance and drug product during the validation studies as well. b(4)

DRUG PRODUCT:

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 ⌐ ⌋ in the ophthalmic gel. Hypromellose is used ⌐ ⌋ Purified water is used as — Sodium hydroxide and/or hydrochloric acid are used for pH adjustment. The formulation does not contain a preservative b(4)

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.

DRUG PRODUCT COMPOSITION:

From the original CMC review, page 17.

Composition of Akten (lidocaine hydrochloride ophthalmic gel)

Lidocaine Hydrochloride	35 mg/mL	
Hypromellose	[redacted]	b(4)
Sodium chloride	[redacted]	
HCl/NaOH	[redacted]	
Purified Water	[redacted]	

REGULATORY SPECIFICATIONS:

Amended Finished Product Specifications and Amended Stability Specifications from the original CMC review, page 35:

Table 18: Amended Finished Product Specifications

APPEARANCE	Clear, colorless, viscous gel, free from undissolved material.		
ASSAY LIDOCAINE HYDROCHLORIDE (35 mg/ml)	NLT: [redacted] and NMT: [redacted]		
LIDOCAINE IMPURITIES/DEGRADANTS	[redacted] Largest unspecified degradant: NMT: [redacted] Total: NMT: [redacted]		b(4)
IDENTIFICATION	The IR absorption spectrum of the preparation of the test specimen, exhibits maxima only at the same wavelengths as that of a similar preparation of the corresponding USP Reference Standard.		
pH <791>	[redacted]		
MINIMUM FILL <755>	NLT: [redacted] of the target volume of 5 ml		
SPECIFIC GRAVITY <841>	[redacted]		
VISCOSITY	[redacted]		
STERILITY <71>	To pass the test		
BACTERIAL ENDOTOXIN <85>	NMT: [redacted]		

Table 19: Amended Stability Specification

APPEARANCE	Clear, colorless viscous gel, free from undissolved material.		
ASSAY	Lidocaine Hydrochloride (35 mg/ml) NLT: — and NMT: —		
LIDOCAINE IMPURITIES/DEGRADANTS	[redacted] Largest unspecified degradant: NMT: — Total: NMT: —		
pH	[redacted]		
MINIMUM FILL <755>	NLT: — of the target volume of 5 ml		
STERILITY	To pass the test.		

b(4)

All facilities inspections have been completed and the Office of Compliance and New Drug Quality have determined these facilities are acceptable.

CMC RECOMMENDATIONS:

From the original CMC review, page 7:

This application is recommended for an approvable (AE) action 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 applicant did not provide a comprehensive study on the semi-permeable container closure system. The lack of leachable and extractable studies presents a safety risk that is unacceptable. In addition to the specification requested, there should be a control on the particulate matter.

4. Nonclinical Pharmacology/Toxicology

This NDA is for a new ophthalmic gel formulation of Akten (lidocaine hydrochloride ophthalmic gel) 3.5%, for ocular surface anesthesia. The applicant has requested that the Division use its previous finding of safety from NDAs for lidocaine HCl to support the current NDA as permitted under section 505(b)(2) of the Federal food, Drug and Cosmetic Act. Lidocaine has been used as local anesthetic for labor/delivery, dental procedure, lumbar analgesia, surgical analgesia, obstetric procedures and postherpetic neuralgia. Lidocaine is available for intravenous and spinal injection as well as oral and topical administrations. Lidocaine is also available as ophthalmic drops. The recommended dose for lidocaine drops is 2 drops of 4% solution in both eyes, 6 times, 60 minutes prior to surgery. Assuming that roughly 100 uL of the lidocaine gel will be used, the human dose is roughly 60 ug/kg lidocaine.

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

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.

Noclinical PK studies evaluating the systemic absorption of the ophthalmic gel have been conducted. The applicant 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 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.

7. Clinical/Statistical - Efficacy

The primary outcome variable for clinical trial 06AKO001 was the percentage of subjects who achieved ocular surface anesthesia within 5 minutes post-application of the anesthetic gel.

Analysis of Primary Efficacy Endpoint-Clinical Trial 06AKO001 (ITT Population)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=52)	Akten 3.5% (N=51)
Percent Achieving Anesthesia Within 5 Minutes of Dosing	12 (22%)	45 (88%)	46 (88%) *	47 (92%)
P value		<0.001	<0.001	<0.001

*Excludes 1 subject with anesthesia duration of 7192 seconds. Efficacy analyses were performed on 208 of the 209 subjects in the ITT population and 207 subjects in the PP population because subject 06/0026 in the 2.5% group was excluded from the efficacy analyses because this patient was an outlier.

Analysis of Secondary Efficacy Endpoints-Clinical Trial 06AKO001 (ITT Population – Outlier Patient)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=52)	Akten 3.5% (N=51)
Mean Duration of Anesthesia (secs.)	171.2	614.3	700.6	801.8
Standard Deviation	433.5	458.5	605.9	497.5
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Max.	2062	2360	3280	2080
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Max.	300	301	360	302

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Summary of Duration of Anesthesia Among Subjects Who Achieved Anesthesia

Time (secs.)	Sham (N=12)	Akten 1.5% (N=45)	Akten 2.5% (N=46)	Akten 3.5% (N=47)
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Min.	40	224	235	260
Max.	2062	2360	3280	2080

Subject 06/0026 in Akten 2.5% group excluded from summary statistics.

Cumulative Frequency of Subjects Achieving Anesthesia by Onset Time and Treatment

Onset Time (secs.)	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
20	3 (25%)	16 (35.6%)	24 (52.2%)	16 (34.0%)
40	6 (50%)	34 (75.6%)	36 (78.3%)	35 (74.5%)
60	10 (83.3%)	43 (95.6%)	40 (87%)	41 (87.2%)
300	12 (100%)	45 (100%)	45 (97.8%)*	47 (100%)
Anesthesia Not Achieved	42	6	6	4

*Excludes one subject who achieved anesthesia at 360 seconds. This patient (0172) had the 5 minute dosing assessment delayed to 6 minutes.

8. Safety

Clinical Studies Used to Evaluate Safety

Two major sources of clinical data were utilized in this review 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. Labeling

Labeling revisions have been recommended by the review team and have been incorporated into the following recommended labeling listed below:

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 2

10. Regulatory Action

An approvable letter should be issued for NDA 22-221, Akten (lidocaine hydrochloride ophthalmic gel) requesting:

1. Information, either directly or by reference to a DMF, on the components and composition of the immediate container label, adhesive and printing ink.

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

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

6. Revised labeling as listed in this review.

Wiley A. Chambers, MD
Acting Division Director
Division of Anti-Infective and Ophthalmology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
6/2/2008 11:43:02 PM
MEDICAL OFFICER

Wiley Chambers
6/2/2008 11:43:36 PM
MEDICAL OFFICER