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APPLICATION NUMBER:

22-221

MEDICAL REVIEW(S)

Clinical Review
Sonal D. Wadhwa, MD
NDA 22-221
Akten (lidocaine hydrochloride ophthalmic gel) 3.5%

CLINICAL REVIEW

Application Type NDA
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Reviewer Name Sonal D. Wadhwa, MD
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Established Name lidocaine hydrochloride
ophthalmic gel 3.5%
(Proposed) Trade Name Akten ophthalmic gel
Therapeutic Class anesthetic
Applicant Akorn, Inc.

Priority Designation S

Formulation lidocaine hydrochloride
Dosing Regimen two drops to ocular surface
area
Indication Ocular surface anesthesia
during ophthalmic procedures
Intended Population patients undergoing
ophthalmic procedures

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 22-221 is recommended for approval with the labeling changes identified in this review. The clinical study and literature studies contained in this submission support the use of lidocaine hydrochloride 3.5% for the use of anesthesia during ophthalmic procedures.

1.2 Risk Benefit Analysis

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

1.3 Recommendations for Post-Marketing 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.

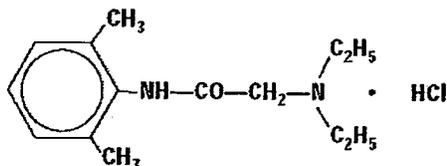
1.4 Recommendations for other Post-Marketing Activities/Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Akten™ Ophthalmic Gel 3.5% is designed chemically as acetamide, 2-(diethyl-amino)-N-(2,6-dimethylphenyl)-, monohydrochloride. The structural formula of the active ingredient is:



Akten is a preservative-free, single-use ophthalmic preparation for topical ocular anesthesia. Each mL of Akten ophthalmic gel 3.5% contains 35 mg of lidocaine

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hydrochloride. Akten also contains hypromellose, sodium chloride, and purified water. The pH may be adjusted with hydrochloric acid and/or sodium hydroxide.

2.2 Tables of Currently Available Treatments for Proposed Indications

Proparacaine is the only topical ocular anesthetic currently approved by the FDA for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Drug Name	Dosage Form	Indication(s)	RLD Mfr/NDA
Xylocaine 2% Jelly	Topical Gel	prevention and control of pain in procedures involving the male and female urethra, topical treatment of painful urethritis, anesthetic lubricant for endotracheal intubation (oral and nasal)	Abraxis Bioscience/ 008816
Xylocaine (various) 0.5% to 20%	Injection	production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostals, and by central neural techniques such as lumbar and caudal epidural blocks	Abraxis Bioscience/ 006488
Xylocaine Viscous 2%	Oral Solution	relief of pain and discomfort in connection with: irritated or inflamed mucous membranes of the mouth and pharynx. e.g., lesions following tonsillectomy; introduction of instruments and catheters into the respiratory and digestive tracts, e.g., bronchoscopy, esophagoscopy; painful diseases of the upper gastrointestinal tract e.g., esophagitis.	Abraxis Bioscience/ 009470
Xylocaine 4% Preservative Free	Topical Solution	parenteral or topical use for the production of local anesthesia of the mucous membranes of the respiratory tract or the genitourinary tract; injected transtracheally to anesthetize the larynx and trachea; administered by retrobulbar injection to provide anesthesia for ophthalmic surgery.	Abraxis Bioscience/ 010417

There is currently no approved NDA for lidocaine for surface anesthesia during ophthalmic procedures.

2.4 Important Safety Issues With Consideration to Related Drugs

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. Some of these side effects include: systemic (ie. hypersensitivity), CNS toxicity (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions), unconsciousness, respiratory depression,

and/or arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of CNS toxicity may be drowsiness merging into unconsciousness (and respiratory arrest), allergic (cutaneous lesions, urticaria, edema, or anaphylactoid reactions), and neurologic. There have been reported cases of permanent injury to extraocular muscles requiring surgical repair following retrobulbar administration. There have been rare reports of endotracheal tube occlusion associated with the presence of dried jelly residue in the inner lumen of the tube.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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. Recently, there has been an increase in the off-label use of lidocaine 2% gel for ophthalmic procedures. Initial interest in lidocaine gel preparations was reported in upper airway, dental, urogenital, and gastrointestinal procedures. A majority of these reports reported favorable patient-pain profiles with the use of lidocaine gel preparation as the sole anesthetic agent. 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, as the sole anesthetic agent to achieve ocular anesthesia.

2.6 Other Relevant Background Information

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for this study. Since lidocaine as a local anesthetic has been available for some time and it has been available in many formulations at varying strengths DSI recommended inspections only if the clinical data submitted by Akorn is suspect. Since there were no issues noted in the review of the clinical data, DSI did not perform an inspection.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trial was not conducted in compliance with good clinical practices.

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3.3 Financial Disclosures

Financial disclosure forms were reviewed. There were no investigators with proprietary interest or with any significant interest in the drug product.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Composition of Akten (lidocaine hydrochloride ophthalmic gel) 3.5%

Component	Reference to Quality Standard	Function	Amount per mL
Lidocaine Hydrochloride	USP	Drug Substance	35 mg
Hypromellose Sterile	USP	[]	[]
Sodium Chloride	USP	[]	[]
Hydrochloric Acid	NF	As Required for pH Adjustment	
Sodium Hydroxide	NF	As Required for pH Adjustment	
Purified Water	USP	[]	[]

b(4)

Components of the Drug Product

Akten is a sterile, aqueous product, containing lidocaine hydrochloride as an active and hypromellose, sodium chloride, and purified water as inactive ingredients. Hypromellose is used to [] Sodium chloride functions as [] in the ophthalmic gel. Purified water is used [] Sodium hydroxide and/or hydrochloric acid are used for pH adjustment.

b(4)

Drug Substance

The drug substance used in Akten (lidocaine hydrochloride ophthalmic gel) 3.5% is Lidocaine Hydrochloride, USP. Lidocaine hydrochloride is a local anesthetic agent and administered topically for ophthalmic use. Chemically lidocaine hydrochloride is 2-(diethylamino)-2',6'-acetoxylidide monohydrochloride monohydrate and has the molecular formula $C_{14}H_{23}ClN_2O \cdot H_2O$ and it has a molecular weight of 288.81. Lidocaine

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hydrochloride is a white crystalline powder and is freely soluble in water, soluble in alcohol and chloroform and insoluble in ether. 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.

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 container closure system. The lack of leachable and extractable studies presents a safety risk that is unacceptable.

b(4)

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

The sponsor has requested that the Division would 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 post-herpetic neuralgia. Lidocaine is available for intravenous and spinal injection as well as oral and topical administrations. Lidocaine has been used off-label as ophthalmic drops.

The inactive ingredients used for Akten Ophthalmic Gel formulation are hydroxypropylmethyl cellulose (HPMC) at _____ sodium chloride, and purified water. All the inactive ingredients in Akten Ophthalmic Gel have been used previously in other approved ophthalmic products at equal or higher concentrations. No new non-clinical studies were requested by the Division or performed by the sponsor. The sponsor 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 non-clinical information provided in this application.

b(4)

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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.

4.4.2 Pharmacodynamics

Not applicable. The drug product is topically applied to the site of action and has minimal systemic absorption. 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.

4.4.3 Pharmacokinetics

Not applicable. 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, the unlikely event the entire ocular dose is systemically absorbed, would be approximately 50 ng/mL. This value is approximately 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 was granted, based on the expected low systemic exposure of lidocaine following the ophthalmic administration of lidocaine hydrochloride 3.5% gel.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The following clinical trial was performed by the Applicant:

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage, Regimen, Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status, Type of Report
Efficacy	06AKO001	The goal of this multi-centered, randomized, sham-controlled study was to evaluate the achievement of ocular anesthesia using Akten applied to the conjunctiva	Two day, multi-centered, randomized, prospective, sham controlled study	Topical Akten 1.5%, 2.5% and 3.5% as the sole anesthetic agent	209	Subjects with condition that required ocular anesthesia	Variable	Completed; Full

Literature References Citing Other Lidocaine Preparations For Ophthalmic Efficacy

The following 27 clinical studies with lidocaine for ocular anesthesia during ophthalmic procedures have been conducted and published and submitted by the Sponsor. Nine (9) of the submitted references are with topical lidocaine 2% gel. Five (5) of the submitted references describe use with topical lidocaine 2-4% solution. The remaining studies describe intracameral injection or retrobulbar injection.

Studies With Topical Lidocaine Gel

Reference	Number of Patients	Number Treated With Lidocaine	Control Group	Outcome Measure	Was Outcome Measure Met?
1. Barducci A Ophthalmology 2003; 110:144-149. Double-blind, prospective, randomized, single-surgeon No long term follow-up/No mention of AEs	107	54-Topical lidocaine 2% gel	53-Topical, non-preserved lidocaine 4% solution AND 0.5 mL hydroxypropyl methylcellulose (to mask surgeon)	Mean intra-ocular level of aqueous lidocaine	Lidocaine gel-27.14 micrograms/mL Lidocaine solution-12.73 mg/mL (P<0.001)
				Mean intra-operative pain score using 0-10 visual analog scale assessed by patient	Lidocaine gel-1.46 Lidocaine solution-2.51 (P=0.007)
2. Solimann MM J Cataract Refract Surg 2004; 30:1716-1720. Single-blind, prospective, randomized,	90	30-Topical lidocaine 2% gel	30-Topical bupivacaine 0.5% drops 30-Topical benoxinate 0.4% drops	Mean 10 point verbal pain score (VPS) at time of application of anesthetic and intra-operatively	Intra-op complications-1 in each group Mean VPS at time of application 2.97, 1.53, 1.03 in lidocaine, bupivacaine and benoxinate groups, respectively (P<0.001) Mean VPS intra-op 1.6, 4.1, 7.1 in lidocaine, bupivacaine and benoxinate groups, respectively (P<0.001) No statistically significant difference between groups
				Mean duration of surgery	

single-surgeon No long-term follow-up/2 events of allergic reaction in lidocaine group	14 undergoing bilateral strabismus surgery (paired eyes of 14 pts.)	14-Topical lidocaine 2% gel AND saline drops	14-Amethocaine 1% eye drops AND placebo gel	No. of patients requiring supplemental anesthesia	Lidocaine-1 Bupivacaine-3 Benoxinate-24, (P<0.001)
				Patient satisfaction	Lidocaine-93.3% Bupivacaine-83.3% Benoxinate-30.0%, (P<0.001)
3. Yu CB Ophthalmology 2003; 110:1426-1429. Double-blind, prospective, randomized Follow-up at 2 weeks and 3 months. No AEs noted.	20 undergoing intravitreal injection	20-Topical lidocaine 2% gel topical	20-Subconjunctival lidocaine 2%	Surgical complications	None in any group
				Mean score on 10 point visual analog scale assessed by patient	Lidocaine gel-2.6 Amethocaine-5.3 (P=0.01)
4. Kozak I Retina 2005; 25:994-998. Un-blinded, prospective, single-surgeon No long-term follow-up/No AEs noted.	100 undergoing cataract	50-Topical lidocaine 2% gel	50-Topical tetracaine 0.5% drops	Mean score on 10 point visual analog scale assessed by surgeon	Lidocaine gel-2.2 Amethocaine-4.6 (P=0.01)
				No. of patients that required supplemental anesthesia	Lidocaine-3 Amethocaine-9
5. Amiel H J Cataract Refract Surg 2007; 33:98-				Pain score on scale 0-10 assessed by patient	No difference in groups
				Incidence of chemosis	More in injection group
				Incidence of subconjunctival hemorrhage	More in injection group
				Mean self-reported post-operative pain score on scale 0-5	Lidocaine-0.94 Tetracaine-1.02 (P=0.76)

<p>100. Double-blind, prospective, randomized, single-surgeon No long term follow-up/No mention of AEs.</p>	<p>surgery</p>	<p>12-Topical lidocaine 2% gel</p>	<p>13-Topical tetracaine 0.5% drops</p>	<p>No. of patients requiring supplemental anesthesia</p>	<p>1 patient in lidocaine group required supplemental anesthesia</p>
<p>6. Barquet IS J Cataract Refract Surg 1999; 25: 626-631. Double-blind, prospective, randomized, single-surgeon Post-operative course stated as uneventful it was stated that there were no complications related to anesthesia observed.</p>	<p>25 eyes undergoing cataract surgery</p>	<p>50-Topical oxybuprocaine 0.4% followed by topical lidocaine 2% gel AND intracameral lidocaine non-preserved 1%</p>	<p>50- Topical oxybuprocaine 0.4% followed by lidocaine 2% sub-tenon injection</p>	<p>Mean corneal sensitivity measured with aesthesiometer at time 0, 5 minutes after application, and at end of surgery using scale 0-6 No. of patients requiring supplemental anesthesia Percentage of patients reporting satisfactory level of comfort Percentage of patients perceived to achieve comfort perceived by surgeon Intra-op complications</p>	<p>Lidocaine-6, 0, 0 Tetracaine-5, 0, 0 Lidocaine-2 Tetracaine-4 Lidocaine-58% Tetracaine-61% (P=1.0) Lidocaine-58% Tetracaine-61% (P=1.0) 1 in tetracaine group</p>
<p>7. Sekundo W Eur J Ophthalmol 2004; 14:111-116. Single-blinded, prospective, randomized, single surgeon</p>	<p>100 patients undergoing cataract surgery</p>	<p>50-Topical oxybuprocaine 0.4% followed by topical lidocaine 2% gel AND intracameral lidocaine non-preserved 1%</p>	<p>Number of times during surgery patient felt pain Median intra-operative pain score using 0-10 visual analog scale assessed by patient</p>	<p>Topical group-67 times Subtenon's group-31 times Topical group-3 Subtenon's group-0 (P<0.0001)</p>	

No long term follow-up/No mention of AEs.				Mean score of the extent the surgeon was bothered by intra-operative motility on scale 1-3.	Lidocaine gel-1.5+/-0.6 Combination eyedrops-1.3 +/- 0.5 (P=0.62)
8. Thill M Ophthalmologica 2005; 219:167-170. Double-blind, prospective, randomized, single-surgeon No long term follow-up/No mention of AEs.	39 eyes undergoing cataract surgery	18-Topical lidocaine 2% gel AND intracameral non-preserved lidocaine 1%	21-Topical bupivacaine 0.5%, oxybuprocaine 1%, and diclofenac 1% eye drops AND intracameral non-preserved lidocaine 1%	Mean intra-operative pain score using 0-10 visual analog scale assessed by patient Mean intra-operative pain score using 0-10 visual analog scale assessed by surgeon	Lidocaine gel-0.65 +/- 0.31 Combined eyedrops-0.89+/-0.82 (P=0.57) Lidocaine gel-0.18 +/- 0.23 Combined eyedrops-0.80+/-0.97 (P=0.02)
9. Bourmas P Ann Ital Chir 2005; 76:383-389. Double-blind, prospective, randomized	874 patients undergoing cataract surgery	437-Group 1, topical lidocaine 2% gel and ropivacaine 0.75% AND viscoelastic without anesthetic	437-Group 2, topical lidocaine 2% gel and ropivacaine 0.75% AND viscoelastic with anesthetic (sodium hyaluronate and lidocaine 1%)	Patient reported pain during 5 steps of the procedure Absence of corneal edema on POD#1 Percentage of patients report as satisfied with anesthesia	Statistically significant less pain in group with viscoanesthetic during the following 3 steps of surgery: Infusion of Ach, placement of suture, and IOL insertion. No difference during immediate post-op pain and pain the night following surgery. Group 1-78.9% Group 2-82.1% Group 1-91.1% Group 2-97.3%

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Studies With Topical Lidocaine Solution

Reference	Number of Patients	Number Treated With Lidocaine	Control Group	Outcome Measure	Was Outcome Measure Met?
1. Martini E J Cataract Refract Surg 2002; 28:1018-1022. Double-blind, prospective, randomized, two-surgeon	64 patients undergoing cataract surgery	32-Topical ropivacaine 1%	32-Topical lidocaine 4%	Duration of surgery	Ropivacaine-21.84 min. +/-2.91 Lidocaine-22.09 min. +/-2.75 (P=0.798)
				Mean intra-operative pain score using 0-10 scale assessed by patient	Ropivacaine-1.84 +/-1.272 Lidocaine-2.41 +/-1.603 (P=0.179)
				Surgical complications	Similar rate and severity in both groups
2. Pablo LE J Glaucoma 2004; 13:510-515. Un-blinded, prospective, randomized No mention of AEs.	80 patients undergoing combined phaco/trab surgery	40-Topical lidocaine 2% solution AND Intracameral lidocaine 1%	40-Peribulbar 50:50 mixture lidocaine 2% and bupivacaine 0.75%	No. of patients requiring supplemental anesthesia	Lidocaine-5 Ropivacaine-4 (P>0.05)
				Mean endothelial cell density reduction at 2 months post-op	Lidocaine-672.06 +/-646.23 Ropivacaine-318.25 +/- 595.14 (P=0.031)
				Pain assessed by patients on scale 0-4 at different time points	Peribulbar group had higher rates of discomfort during anesthetic administration. No significant difference in pain between 2 groups during surgery or after surgery.
3. Jacobi PC Arch Ophthalmol 2000; 118:1037-1043. Un-blinded, prospective,	476 patients undergoing cataract surgery	238-Topical lidocaine 2%	238-Retrobulbar injection of 50:50 mixture of lidocaine 2% and bupivacaine 0.75% with hyaluronidase	Surgeon assessment of ease of surgery on 4 point scale	No difference between groups
				Intra-operative vital signs	No difference between groups
				Complications	Prolonged chemosis/conjunctival hemorrhage occurred more frequently in the peribulbar group
				Number of complications and adverse events	Lower vitreous loss in topical group. Similar rates of capsular tear, zonular tear, and iris prolapse in 2 groups
				Mean intra-operative pain score using 0-10 visual analog scale	Topical-0.84 +/-1.30 Retrobulbar-0.73 +/-1.50 (P=0.41)

randomized, two- surgeon	631 patients undergoing cataract surgery	352-Non-preserved topical lidocaine 4% AND tetracaine 0.5%	279-Non-preserved intracameral lidocaine 1%	assessed by patient	No significant difference between 2 groups
				Overall intra-operative conditions judged by surgeon on 5 point scale	
4. Masket S J Cataract Refract Surg 1998; 24:956-960. Retrospective chart review of single surgeon No mention of long-term f/u or AEs.	1893 patients undergoing cataract surgery	91.9-Topical lidocaine 2%	97.4-Topical ropivacaine 1%	Patient preference for anesthesia	Topical-91% Retrobulbar anesthesia-62%, (P=0.01)
				No. of patients requiring supplemental anesthesia	Topical-150 Intracameral-1 (P<0.0001)
5. Lo Martire N Minerva Anesthesiology 2002; 68:529-534. Double-blind, prospective, randomized No long-term f/u or AEs noted.				Absence of Corneal edema on POD #1	Topical-76.7% Intracameral-88.2%, however author proposed this could be secondary to switch in phaco technique (sculpting technique in topical group compared to chopping in intracameral group). (P<0.001)
				Mean intra-operative pain score using 0-10 visual analog scale assessed by patient	Statistically significant higher pain in lidocaine group at 4 of 5 measured time points during surgery.
				No. of patients requiring supplemental anesthesia	Lidocaine-12 Ropivacaine-9
				Degree of operability expressed by surgeon on 4 point scale	Recorded as good degree of operability (score of 1) Lidocaine-69.8% Ropivacaine-83.0%
				Complications	No significant complications noted by author.
				Patient satisfaction on 4 point scale	Recorded as high satisfaction (score of 1) Lidocaine-60.4%

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							Ropivacaine-86.6%
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Studies With Intracameral Lidocaine

Reference	Number of Patients	Number Treated With Lidocaine	Control Group	Outcome Measure	Was Outcome Measure Met?
1. Martin RG J Cataract Refract Surg 1998; 24:961-963. Prospective, randomized No mention of AEs.	93 patients undergoing cataract surgery	40-Topical proparacaine and topical lidocaine 4% AND intracameral unpreserved lidocaine 1%	53-Topical proparacaine and topical lidocaine 4% AND intracameral BSS	Percentage of patients reporting no sensation during surgery Post-op endothelial cell density parameters at 2- 3 months post-op Kowa Laser flare-cell measurements at 10 days post-op	Intracameral lidocaine-78% Control-56% (P=0.048) No significant difference between groups No significant difference between groups
2. Chuang LH J Cataract Refract Surg 2007; 33:293-296. Double-blind, prospective, randomized, single-surgeon	66 eyes (paired eyes of 33 patients) undergoing cataract surgery	33-Topical non-preserved lidocaine 2% AND intracameral non- preserved lidocaine 0.5%	33-Topical non- preserved lidocaine 2% AND intracameral BSS	Mean reduction in endothelial count measured by non- contact specular microscopy BCVA Mean intra-operative pain score using 0-10 visual analog scale assessed by patient	Intracameral lidocaine-7.17% BSS-6.82% Post-op BCVA significantly improved in both groups; no statistically significant difference between 2 groups Intracameral lidocaine-0.64 BSS-1.52 (P=0.001)
Mean f/u 7.8 mos. No reported AEs. 1 intra-op vit. Loss in BSS group.					
3. Shah AR Indian J Ophthalmology	106 patients undergoing cataract	53-Topical lidocaine 4% AND intracameral non-	53-Topical lidocaine 4% AND	No. of patients with descemet folds on POD #1	Intracameral lidocaine-4 BSS-5 (All corneas cleared at POD #7)

<p>2004; 52:133-138. Double-blind, prospective, randomized, single-surgeon No intra-op complications; 1 yr. f/u</p>	<p>surgery</p>	<p>preserved lidocaine 1%</p>	<p>intracameral BSS</p>	<p>Percentage of endothelial cell loss at 1 year</p>	<p>Intracameral lidocaine-4.9 +/- 2.53% BSS-4.49 +/- 3.09% (P=0.97)</p>
<p>4. Anders N Ophthalmology 1999; 106:1863- 1868. Un-blinded, prospective, randomized</p>	<p>200 eyes undergoing cataract surgery</p>	<p>100-Intracameral non- preserved lidocaine 1% AND topical oxybuprocaine</p>	<p>100-Peribulbar injection of prilocaine</p>	<p>Complications Duration of surgery Visual acuity ERG at 30 minutes post-op (only performed on 15 patients in each group)</p>	<p>Similar complications Lidocaine-11.8 +/- 3.8 minutes Peribulbar-9.5 +/- 4.5 minutes (P=0.0001) Lidocaine-Better visual acuity immediately after surgery but no difference at POD #1 No statistically significant difference between the 2 groups in implicit times and amplitude values</p>
<p>5. Roberts T Clin Experiment Ophthalmol 2002; 30:19-22. Double-blind, prospective, randomized, single-surgeon No mention of AEs. No intra-op complications.</p>	<p>135 patients undergoing cataract surgery</p>	<p>67-Intracameral non- preserved lidocaine 1% AND topical amethocaine 1%</p>	<p>68-Intracameral BSS AND topical amethocaine 1%</p>	<p>Mean intra-operative pain score using 0-10 visual analog scale assessed by patient Vital signs</p>	<p>Intracameral lidocaine-1.0 BSS-0.7 No statistically significant difference in systolic blood pressure, pulse, and oxygen saturation between 2 groups.</p>
<p>6. Boulton JE Ophthalmology 2000; 107:68-71.</p>	<p>200 patients undergoing cataract</p>	<p>Intracameral, non- preserved lidocaine 1% AND</p>	<p>Intracameral BSS AND topical</p>	<p>Mean intra-operative pain score using 0-10 visual analog scale</p>	<p>Lidocaine-1.29 +/- 1.24 Control-1.44 +/- 1.33 (P>0.35)</p>

Double-blind, prospective, randomized, three-surgeon No mention of AEs or f/u.	surgery	topical tetracaine 1%	tetracaine 1%	assessed by patient	
				Surgical complications	Lidocaine-4 Control-5
7. Gills JP J Cataract Refract Surg 1997; 23:545-550. Double-blind, prospective, randomized, single-surgeon No reported AEs.	303 patients undergoing cataract surgery	183-Intracameral, non-preserved lidocaine 1% AND topical proparacaine 0.5% and topical bupivacaine 0.75%	120-Intracameral BSS AND topical proparacaine 0.5% and topical bupivacaine 0.75%	No. of patients requiring supplemental anesthesia	Lidocaine-3 Control-2
				Patient reported pain on scale of 0-5	Lidocaine-9% had pain score of >=2 BSS-26% had pain score of >=2
8. Garcia A J Cataract Refract Surg 1998; 24:403-406. Un-blinded, prospective, randomized F/U 4 weeks. No mention of AEs.	59 patients undergoing cataract surgery	31-Topical oxybuprocaine AND intracameral non-preserved lidocaine 1%	28- Peribulbar injection 50:50 lidocaine 2% and bupivacaine 0.5%	Mean post-op endothelial cell loss measured by contact specular microscopy at 2-4 weeks post-op	Intracameral lidocaine-3.59% Peribulbar-4.37%
				Phaco ultrasound time	No significant difference between 2 groups.
9. Hosny M J Cataract Refract Surg 2002; 28:834-836. Double-blind,	70 eyes undergoing cataract surgery	35-topical amethocaine 1% AND intracameral hydroxypropyl methylcellulose (HPMC)	35- topical amethocaine 1% AND intracameral HPMC 2.25%	Median intra-operative pain score using 0-5 scale assessed by patient	No significant difference between the 2 groups

prospective, randomized, two-surgeon 10. Carino NS J Refract Surg 1998; 24:1602-1608. Double-blind, prospective, randomized, single-surgeon No long-term f/u; No mention of AEs.	60 eyes undergoing cataract surgery	2.25% and non-preserved lidocaine 1%	30-T-topical tetracaine 0.5% AND non-preserved intracameral lidocaine 1%	30-T-topical tetracaine 0.5% AND intracameral BSS	Mean reported pain score at end of surgery assessed by patient (4 point scale)	Lidocaine-0.21 +/- 0.4 BSS-0.60 +/-0.6 (P<0.014)
					Surgeon reported satisfaction with anesthesia (5 point scale)	Lidocaine-4.73 +/- 0.8 BSS-3.90 +/- 1.2 (P<0.0007)
No long-term f/u; No mention of AEs.	30 paired eyes of 15 patients	15-T-topical tetracaine 0.5% AND non-preserved lidocaine 2%	15-T-topical tetracaine 0.5% AND intracameral BSS	Patient reported satisfaction with anesthesia (5 point scale)	Lidocaine-4.70 +/- 0.6 BSS-4.60 +/-0.8	
				Mean central endothelial cell loss at 1 month post-op	Lidocaine-6.7 +/- 6% BSS- 6.1 +/- 8% (P=0.73)	
				BCVA at 1 month post-op	Rate of potential visual acuity recovery was similar in both groups [No statistically significant difference between 2 groups at any interval (1 day, 1 week, and 1 month)] Lidocaine-25.9 +/- 5.2 minutes BSS-25.3 +/- 7.0 minutes (P=0.81)	
11. Pang MP Ophthalmology 2001; 108:2018-2025. Single-blind, prospective, randomized, single-surgeon No long-term f/u; No mention of AEs.	30 paired eyes of 15 patients	15-T-topical tetracaine 0.5% AND non-preserved lidocaine 2%	15-T-topical tetracaine 0.5% AND intracameral BSS	Mean duration of Surgery	No difference between 2 groups	
				Degree of pain and photophobia (scale 0-4) ERG and VER performed POD #1.	Only performed in 5 patients. No significant difference between 2 groups in ERG amplitudes or prolonged latency. No significant difference in VER latencies.	

<p>12. Crandall AS Ophthalmology 1999; 106:60-66. Double-blind, prospective, randomized, single surgeon No mention of AEs.</p>	<p>136 patients undergoing cataract surgery</p>	<p>68-Topical non-preserved bupivacaine 0.75% AND intracameral non- preserved lidocaine 1%</p>	<p>68-Topical non- preserved bupivacaine 0.75% AND intracameral BSS</p>	<p>Mean intra-operative pain score using 0-10 visual analog scale assessed by patient at 3 time points</p>	<p>Mean pain score at delivery of anesthesia: Lidocaine-1.72 BSS-1.67, (P=0.902) Mean pain score during surgery: Lidocaine-0.86 BSS-1.2, (P=0.170) Mean pain score after surgery: Lidocaine-0.24 BSS-0.29, (P=0.680)</p>
<p>Patient assessment of pain during tissue manipulation on scale 0-2</p>	<p>Lidocaine-0.58 BSS-0.70 (P=0.021)</p>				
<p>Surgeon assessment of patient cooperation</p>	<p>Lidocaine-93% assessed as excellent BSS-81% assessed as excellent (P=0.043)</p>				
<p>Mean visual analog scale assessed by surgeon assessing overall operating conditions (0=poor and 10=excellent)</p>	<p>Lidocaine-8.99 BSS-8.85 (P=0.290)</p>				
<p>No. of patients that required supplemental anesthesia</p>	<p>Lidocaine-8 BSS-6 (P=0.573)</p>				
<p>Mean change in endothelial cell count at 3 months post-op (performed in 39 of the patients)</p>	<p>Lidocaine-9.1 +/- 5.5% BSS-8.1 +/- 6.9% (P=0.43)</p>				

Clinical Review
 Sonal D. Wadhwa, MD
 NDA 22-221
 Aken (lidocaine hydrochloride ophthalmic gel) 3.5%

Studies With Retrobulbar Lidocaine

Reference	Number of Patients	Number Treated With Lidocaine	Control Group	Outcome Measure	Was Outcome Measure Met?
1. Chin GN Ophthalmology 1983; 90:369-372. Double-blind, prospective, randomized No drug related complications noted.	128 eyes undergoing cataract surgery	32-Retrobulbar injection lidocaine 2% with epinephrine and hyaluronidase	96-Retrobulbar injection bupivacaine 0.75% +/-epinephrine +/- hyaluronidase	Onset time of adequate anesthesia at 15 minutes Mean duration of aknesia Need for post-op analgesia	No significant difference between 2 groups Lidocaine-4 hours Bupivacaine-11 hours Lidocaine-<40% did not require additional analgesia Bupivacaine-70-90% did not require additional analgesia

Literature references citing lidocaine preparations for non-ophthalmic use were also submitted in the NDA application. These studies were also reviewed but in order to be concise were not included in this review. Refer to Sponsor Submission for these articles.

The reviewer performed a Medline literature search and did not find any significant data regarding efficacy or safety that was not submitted to the NDA.

5.2 Review Strategy

The major sources of clinical data utilized in this review include:

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

5.3 Discussion of Individual Studies

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%.

Following baseline fluorescein corneal staining, study participants were given 2 drops of the gel preparation approximately 5 mm posterior to the limbus at the 6 o'clock position. Simultaneously, a timer was started. At the 20-second mark, the investigator tested the conjunctiva with a 0.3 forceps at the center of the applied gel. The study subject was instructed to state 'pain' if there was any pain with pinching of the conjunctiva with the forceps. If there was no pain or only pressure, the subject did not respond. This technique was to be repeated at 20-second intervals until anesthesia was achieved (no response from the study subject). Subjects who indicated they "had no pain" (indicating anesthesia) were then tested at 5-minute intervals starting at the 5-minute mark. The testing was concluded when the study subject reported 'pain' on two successive tests. If the study subject reported 'pain' at both the 20 second mark and 40 second mark, testing was performed at the 1 minute mark. If the subject reported 'pain' at 1 minute, testing was suspended until the 5 minute mark. If the subject reported 'pain' at the 5 minute mark, no more conjunctival pinching was performed and it was deemed that anesthesia was not achieved. Subjects returned to the clinical site on the day following treatment (Day 2) for follow-up examinations.

Investigators Who Enrolled Patients For Study 06AKO001

Site #	Principal Investigator	Location	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)	Overall (N=209)
1	Joseph Boone	Murfreesboro, TN	6 (11%)	6 (12%)	7 (13%)	6 (12%)	25 (12%)
2	William Davitt	El Paso, TX	8 (16%)	8 (15%)	8 (15%)	9 (18%)	33 (16%)
3	John O'Keefe	Richmond, VA	6 (11%)	6 (12%)	5 (9%)	5 (10%)	22 (11%)
4	Brett Rosenblatt	Hauppauge, NY	0	0	0	0	0
5	Michael Rotberg	Charlotte, NC	6 (15%)	6 (12%)	6 (11%)	6 (12%)	24 (11%)
6	Kenneth Sall	Artesia, CA	8 (15%)	7 (14%)	8 (15%)	7 (14%)	30 (14%)
7	Geoffrey Schwartz	Lansdale, PA	6 (11%)	6 (12%)	5 (9%)	8 (16%)	25 (12%)
8	Jeffrey Whitsett	Houston, TX	14 (26%)	12 (24%)	14 (26%)	10 (20%)	50 (24%)

Inclusion Criteria:

- Ability to provide informed consent for mode of topical anesthesia delivery
- Ability to verbally respond to pain
- Ability to return within 36 hours following application of study article
- At least 18 years of age
- Condition that requires ocular anesthesia

Exclusion Criteria

- Intravitreal injection within the past 14 days
- Recent ocular surgery requiring retrobulbar anesthesia within past 4 weeks
- Prior vitreous or retinal surgery within past 4 weeks
- Pre-existing diagnosis of ocular surface disease requiring punctal plug placement
- Evidence of any current ocular inflammation
- Any previous ocular condition (i.e. herpetic eye disease, presence of a corneal graft, etc.) that has permanently altered the native sensation of the ocular surface
- Use of exclusionary medications:
 - Topical Steroid Drops
 - Non-Steroid Drops
 - Any Anti-viral medications uses for herpes
 - More than one drop per day of any medication used to treat glaucoma
- Pregnant or nursing females
- Enrollment in another investigational drug or device study within 30 days prior to entry into this study
- Further planned eye procedures prior to completion of the final study evaluation

Study Schedule:

	Screening/Randomization Visit	Day 2
Procedures/ Examinations	Visit 1	Visit 2
Informed Consent	X	
Demographics/Medical History	X	
Vital Signs including brief Physical Exam	X	
Inclusion, Exclusion	X	
Ophthalmic Exam including Biomicroscopy	X	X
Study Drug Administration	X	
Pain Evaluation	X	
Fluorescein Corneal Staining	X	X
Assess and review concomitant medication/adverse events	X	X
End of Treatment Evaluation		X

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is acceptable: Akten is a local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures.

6.1.1 Methods

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

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

6.1.2 Demographics

Demographics of Clinical Trial 06AKO001 (ITT Population)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
Age				
Mean	40.3	38.9	40.5	37.4
Gender				
Male	15 (28%)	15 (29%)	18 (34%)	17 (33%)
Female	39 (72%)	36 (71%)	35 (66%)	34 (67%)
Race				
Asian	1 (2%)	2 (4%)	0	0
African American	7 (13%)	8 (16%)	4 (8%)	9 (18%)
Caucasian	46 (85%)	41 (80%)	49 (92%)	42 (82%)
Ethnicity				
Hispanic or Latino	19 (35%)	13 (25%)	17 (32%)	13 (25%)
Not Hispanic or Latino	35 (65%)	38 (75%)	36 (68%)	38 (75%)

6.1.3 Patient Disposition

Disposition of Subjects Clinical Trial 06AKO001

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
Safety Population	54	51	53	51
ITT Population	54	51	53	51
Per Protocol	54	51	52*	51

*NOTE: Patient 0172 had protocol deviation. 5 minute post-dose pain assessment was delayed to 6 minutes.

6.1.4 Analysis of Primary Endpoint(s)

Safety analyses were conducted for the ITT population (all subjects receiving study drug and having a determination of the presence or absence of pain at five minutes after study product application). Efficacy analyses were conducted for the ITT and PP populations. Subjects were eligible for the PP analysis if they completed the corneal fluorescein staining evaluation on Day 2 without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy).

Two-sided hypothesis testing was conducted for tests. Resulting p-values less than or equal to 0.05 were considered statistically significant. No interim analyses were planned or performed.

SAS software was used for all data analyses and tabulations. No imputations were performed for missing data, and none of the subjects withdrew from the study prematurely.

Akorn, Inc. Clinical Protocol

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.

Literature References Citing Lidocaine Gel Efficacy

In 7 of the 9 studies using topical lidocaine gel 2% patients achieved acceptable pain scores or anesthesia when compared to acceptable active controls. In these 7 studies 219 patients received topical lidocaine 2% gel. For further details regarding each study refer to section 5.1. To further support the efficacy of topical lidocaine 3 of the 5 studies using topical lidocaine solution 2-4% patients again achieved acceptable pain scores when compared to active controls. In these 3 studies 310 patients received topical lidocaine solution 2-4%. To further support the efficacy of lidocaine, there were multiple studies using intracameral lidocaine (see section 5.1).

6.1.5 Analysis of Secondary Endpoints(s)

The secondary outcome variables for Clinical Trial 06AKO001 were the determination of the time of onset of anesthesia, the duration of ocular surface anesthesia, and subject safety.

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

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
Mean Duration of Anesthesia (secs.)	171.2	614.3	823.1	801.8
Standard Deviation	433.5	458.5	1074.8	497.5
Mean Time to Anesthesia (secs.)	85.0	46.6	59.8	58.2
Standard Deviation	101.7	57.2	89.3	80.0

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
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.

(The mean value for the Akten 2.5% group was skewed by a duration value of 7192 seconds for Subject 06/0026. Therefore, the efficacy data were summarized without this outlier value to obtain a more accurate assessment of the relationship between Akten dose and duration of anesthesia.)

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.

Reviewer's Comments:

In the ITT Population, the proportion of subjects who achieved anesthesia in 5 minutes was comparable across the Akten dose groups. Anesthesia was achieved by 45 of 51 subjects (88%), 46 of 52 subjects (88%), and 47 of 51 subjects (92%), respectively, in the Akten 1.5%, 2.5%, and 3.5% groups. Only 12 of the 54 subjects (22%) in the sham group achieved anesthesia.

The mean time to anesthesia onset was not affected by Akten dose. Anesthesia onset times ranged from 20 seconds to 5 minutes, and the mean time to anesthesia onset was 85 seconds, 46.6 seconds, 60.6 seconds, and 58.2 seconds, respectively, for the sham and Akten 1.5%, 2.5%, and 3.5% groups.

Anesthesia duration was significantly longer ($p < 0.001$) in the Akten groups compared to the sham group. Duration of anesthesia demonstrated a clear pattern of increasing anesthesia duration with increasing dose. Among subjects who achieved anesthesia, mean anesthesia durations were 696 seconds (approximately 12 minutes), 792 seconds (approximately 13 minutes), and 870 seconds (approximately 15 minutes) for the Akten 1.5%, 2.5%, and 3.5% groups, respectively.

Overall, in clinical study 06AKO001 lidocaine 3.5% provided a statistically significant amount of anesthesia when compared to sham. The published studies discussed in section 6.1.3 further support the efficacy of lidocaine as an anesthetic for the use during ophthalmic procedures.

6.1.6 Other Endpoints

No other endpoints were examined.

6.1.7 Subpopulations

See Section 7.5.3

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable as this is for single use for intraocular surgical procedures, persistence and tolerance is not applicable.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 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): Subject safety was assessed through the monitoring and reporting of any adverse events (AEs) that occurred during the study. External eye exam and slit lamp eye examination (lids, lid margins, conjunctiva, anterior chamber, cornea and lens) were conducted before dosing and on Day 2 to assess for clinically significant changes.
- Literature references citing ophthalmic uses of lidocaine.

7.1.2 Adequacy of Data

Given the extensive history with the use of lidocaine, the clinical trial performed, and the literature references there was adequate data to establish safety.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable due to the limited number of events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Appropriate doses were given to the patients in the clinical trial and these patients represented the target population for this drug.

7.2.2 Explorations for Dose Response

The proposed dose of Akten Ophthalmic Gel 3.5% containing 35 mg/mL lidocaine hydrochloride is 2 drops applied to the ocular surface in the area of the planned procedure. In the clinical study of 3 concentrations of Akten (1.5%, 2.5%, and 3.5%), the 3.5% dose demonstrated a longer anesthesia duration and a safety profile comparable to that of the lower concentrations. This suggests the 3.5% dose will provide the highest level of anesthesia without an increased risk of adverse effects.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

No clinical laboratory testing was performed.

7.2.5 Metabolic, Clearance, and Interaction Workup

Since the drug product is topically applied to the site of action and has minimal systemic absorption no PK studies were performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 2.4.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during this study or in literature references.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events occurred during this study or in literature references.

7.3.3 Dropouts and/or Discontinuations

No dropouts and/or discontinuations occurred during this study.

7.3.4 Significant Adverse Events

No other significant serious adverse events occurred during this study or were mentioned in published literature when topical ophthalmic anesthetics are used as indicated. There is a potential for abuse with non-physician supervised use.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 30 treatment-emergent AEs were experienced by 24 of the 209 subjects (11%) in the safety population, with an AE incidence of 4% in the sham group, 16% in the Akten 1.5% group, 11% in the Akten 2.5% group, and 16% in the Akten 3.5% group.

Incidence of Treatment-Emergent Adverse Events (Safety Population)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
Subjects with at least one AE	2	8	6	8
Ocular	1	6	5	7
Conjunctival hemorrhage	0	3	1	3
Conjunctival hyperemia	1	4	4	4
Eye pain	0	0	0	1
Lacrimal disorders	0	0	0	1
Corneal staining	1	0	0	3
Nervous system disorders	0	1	1	1
Headache	0	1	1	1
Skin disorders	0	1	0	0
Hyperhidrosis	0	1	0	0

Overall Summary of Adverse Events (Safety Population)

	Sham (N=54)	Akten 1.5% (N=51)	Akten 2.5% (N=53)	Akten 3.5% (N=51)
Subjects with any treatment-emergent AE	2	8	6	8
Subjects with any serious treatment-emergent AE	0	0	0	0
Subjects who discontinued due to treatment-emergent AE	0	0	0	0

Reviewer's Comments:

The frequency of treatment-emergent AEs was low and did not appear to be related to Akten dose, with 14% in the Akten 1.5% group, 9% in the Akten 2.5% group, and 14% in the Akten 3.5% group. The most common treatment-emergent AEs reported were consistent with the known effects of the study drug and the study procedures and included conjunctival hyperemia (13 subjects [6%]) and corneal staining (4 subjects [2%]). Conjunctival hemorrhage another common AE was most likely a result of the pain assessments that included repeated pinching of the conjunctiva with a 0.3 forceps at periodic intervals throughout the study. The majority of AEs were reported as mild or moderate in severity and resolved without treatment within 24 hours. Four AEs of mild conjunctival hemorrhage and 1 AE of mild corneal staining were unresolved at the end of study visit on Day 2. Follow-up information from the sites revealed that all events had subsequently resolved when subjects returned for follow-up visits.

Only one event of corneal staining in a subject in the Akten 3.5% group was considered severe. Subject 03/0173 in the 3.5% group received study article at 7:06 p.m. At the time of study article application, the subject experienced mild conjunctival hyperemia, and 15 minutes following study article application (7:21 p.m.), the subject was reported to have severe corneal staining. No treatment was given for the events and they both resolved within 13 hours of onset.

No clinically significant changes from the baseline examination were noted in the results of the biomicroscopy, slit lamp lens, and visual acuity (VA) examinations. Sporadic increases and decreases in grading of corneal staining were observed for subjects across all treatment groups; however, few AEs of corneal staining were reported. Corneal staining was reported in 1 subject in the sham group (Subject 03/0160) and 3 subjects in the Akten 3.5% group (Subjects 03/0159, 03/0166, and 03/0173).

The above results of the clinical trial 06AKO001 along with a review of the published literature which did not reveal any deaths or significant AEs support the safety of lidocaine 3.5%.

7.4.2 Laboratory Findings

Clinical laboratory assessments were not performed in this study.

7.4.3 Vital Signs

Vital signs assessments and a brief physical exam were conducted at screening to assess subject eligibility. No clinically significant abnormalities precluding subject participation were noted.

7.4.4 Electrocardiograms (ECGs)

Not applicable. ECGs were not conducted during this study.

7.4.5 Special Safety Studies

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See section 7.4.1.

7.5.2 Time Dependency for Adverse Events

See section 7.4.1.

7.5.3 Drug-Demographic Interactions

Analysis of Treatment Effect by Gender-Male (ITT Population)

	Sham (N=15)	Akten 1.5% (N=15)	Akten 2.5% (N=18)	Akten 3.5% (N=17)
% Achieving Anesthesia Within 5 Minutes of Dosing	1 (7%)	14 (93%)	18 (100%)	16 (94%)
P value		0.001	0.001	<0.001
Duration of Anesthesia (Mean-seconds)	36.0	747.5	811.4	651.7
Time to Anesthesia (Mean-seconds)	60.0	55.6	59.1	31.3

Analysis of Treatment Effect by Gender-Female (ITT Population)

	Sham (N=39)	Akten 1.5% (N=36)	Akten 2.5% (N=35)	Akten 3.5% (N=34)
% Achieving Anesthesia Within 5 Minutes of Dosing	11 (28%)	31 (86%)	29 (83%)	31 (91%)
P value		<0.001	<0.001	<0.001
Duration of Anesthesia (Mean-seconds)	223.2	558.9	829.1	732.0
Time to Anesthesia (Mean-seconds)	87.3	42.6	60.2	72.1

Analysis of Treatment Effects by Age Group <65 Years Old (ITT Population)

	Sham (N=51)	Akten 1.5% (N=50)	Akten 2.5% (N=50)	Akten 3.5% (N=49)
% Achieving Anesthesia Within 5 Minutes of Dosing	12 (24%)	44 (88%)	44 (88%)	45 (92%)
P value		<0.001	<0.001	<0.001
Duration of Anesthesia (Mean-seconds)	181.3	620.6	692.6	791.7
Time to Anesthesia (Mean-seconds)	85.0	40.9	62.0	53.2

Analysis of Treatment Effects by Age Group ≥65 Years Old (ITT Population)

	Sham (N=3)	Akten 1.5% (N=1)	Akten 2.5% (N=3)	Akten 3.5% (N=2)
% Achieving Anesthesia Within 5 Minutes of Dosing	0	1 (100%)	3 (100%)	2 (100%)
P value		0.379	0.168	0.237
Duration of Anesthesia (Mean-seconds)	N/A	300	2997.3	1049
Time to Anesthesia (Mean-seconds)	N/A	301	26.7	169.5

Note: Subject 06/0026 was excluded in the Akten 2.5% group (>65) efficacy data in analysis in section 6.1.5 as this patient was an outlier. However, in this analysis since the number of subjects is so low (N=3) this patient was included.

Reviewer's Comments:

All three doses of Akten achieve statistical significance for the percentage of patients achieving anesthesia within 5 minutes in males and females.

Regarding the analysis of treatment effect in relation to age, it is difficult to make any useful conclusions since the group <65 had 149 patients in the active arm and the group ≥65 had only 6 patients in the active arm.

7.5.4 Drug-Disease Interactions

Not studied for this product.

7.5.5 Drug-Drug Interactions

Given its low potential for systemic absorption, no significant drug interactions are expected with the topical administration of Akten. Potential drug interactions cited in the labeling for Xylocaine are described as follows:

Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects are additive.

Lidocaine with epinephrine or other vasopressors should not be used concomitantly with ergot type oxytocic drugs, because a severe persistent hypertension may occur and cerebrovascular and cardiac accidents are possible. Likewise, lidocaine with epinephrine or another vasoconstrictor should be used with extreme caution in patients receiving MAO inhibitors or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

If sedatives are employed to reduce patient apprehension, they should be used in reduced doses, since local anesthetic agents, like sedatives, are CNS depressants which in combination may have an additive effect.

Solutions containing epinephrine should be used with caution in patients undergoing general anesthesia with inhalation agents such as halothane, due to the risk of serious cardiac arrhythmias.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Not applicable. The drugs used in this trial are not known to be genotoxic when dosed topically.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

This drug was not tested on a pediatric population. Height and weight data were not collected as part of this protocol.

A PubMed search was performed by the reviewer and when the terms topical, lidocaine, and children was entered 265 articles were found. There were a variety of articles supporting the efficacy of topical lidocaine in children. These studies studied children from 6 mos.-17 years old for a variety of indications such as in the treatment of: otitis media, anesthesia for strabismus surgery, anesthesia for nasoendoscopy, wound closure, myringotomy, tonsillectomy, anal fissures, and immunization pain. The articles were published between 2001-2008.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Akten gel is non-narcotic. There is no potential for withdrawal and rebound and therefore the effect of repeated administration of Akten gel was not studied.

7.7 Additional Submissions

On May 5, 2008 Akorn submitted 4 month safety update for the dates April 2007-present. The sponsor identified 5 pertinent citations in their search.

There is no new information provided to alter the conclusions regarding the safety or efficacy of the product.

Reference	Number of Patients	Number Treated With Lidocaine	Control Group	Outcome Measure	Was Outcome Measure Met?
DiDonato A Eur J of Anesth 2007; 24: 438-440. Double-blinded, prospective, single surgeon No long-term f/u; no significant differences for complication rates were noted.	203 patients undergoing cataract surgery	101-Topical lidocaine 4%	102-Topical levobupivacaine 0.75%	Mean time of onset	Lidocaine-1.6 min. +/- 24 secs Levobupivacaine-2.1 min. +/-20 secs. (P <0.01)
				Mean patient satisfaction (scale of 0-10)	Lidocaine-8.8 +/- 0.7 Levobupivacaine-9.0 +/- 0.7 (P <0.01)
				Mean surgeon satisfaction (scale of 0-10)	Lidocaine-8.2 +/- 0.7 Levobupivacaine-8.9 +/- 0.7 (P <0.01)
				Mean intraoperative pain score on 10 point visual analog scale	Lidocaine-1.6 Levobupivacaine-1.1 (P<0.01)
Borazan M Eye 2008;22: 425-429. Double-blinded, prospective, single surgeon No long-term f/u.	105 patients undergoing cataract surgery	35-Topical Lidocaine 2%	35-Topical levobupivacaine 0.75% 35-0.75% Topical ropivacaine 1%	Mean intraoperative score on 10 point visual analog scale	Incision-No significant difference between groups. Intraoperative-Mean VPS higher in the lidocaine group than other 2 groups (P=0.005). No difference in score between the other two groups. End of surgery-Mean VPS significantly higher in the lidocaine group than other 2 groups (P<0.01). 24 hours post-op-No significant difference among groups.
				Patient satisfaction (scale of 0-10)	Significantly better in both the levobupivacaine and ropivacaine groups as compared to the lidocaine groups (P<0.01). No

					significant difference between levobupivacaine and ropivacaine.
				Surgeon satisfaction (scale of 0-10)	Significantly better in both the levobupivacaine and ropivacaine groups as compared to the lidocaine groups (P<0.01). No significant difference between levobupivacaine and ropivacaine.
				Complications	Lidocaine-1 case of intraoperative miosis Levobupivacaine-none Ropivacaine-1 case of posterior capsule perforation
				Patients needing supplemental anesthesia	Lidocaine-2 Levobupivacaine-0 Ropivacaine-0 Difference not statistically significant.
Chuang L J Cat Refract Surg 2007;33: 293-296. Double-blind, prospective, single-surgeon Complications-1 patient in Group 1 had vitreous loss secondary to eye movement.	66 paired eyes undergoing cataract surgery	33- Non-preserved lidocaine 2% AND Intracameral BSS	33- Non-preserved lidocaine 2% AND Intracameral non-preserved lidocaine 0.5%	Mean endothelial cell loss	Group 1- 6.82% Group 2- 7.17% No statistically significant difference.
				BCVA	Both groups had significantly improved visual acuity.
				Mean intraoperative pain score on 10 point visual analog scale	Group 1- 1.52 Group 2- 0.64 (P=0.001)
Valimaki J Eur J Ophthalmol 2007;17: 332-335. Prospective, single-surgeon No intra-operative complications noted in any study patient.	96 patients undergoing cataract surgery	48- Topical non-preserved lidocaine 4% AND Intracameral BSS	48- Topical non-preserved lidocaine 4% AND Intracameral non-preserved lidocaine 1%	Mean intraoperative pain score (scale 0-3)	Group 1-0.73 Group-2-0.54 (P=0.21)
				Absence of corneal edema on POD #1	Group 1- 42% Group 2- 63% (P=0.07)
Perone JM Eur J Ophthalmol 2007;17: 171-	114 eyes undergoing cataract surgery	55- Topical tetracaine 1% and topical oxybuprocaine	59-Topical tetracaine 1% and topical oxybuprocaine	Mean intraoperative pain score on 10 point visual	Group 1- 1.1 +/- 6.8 Group 2- 1.3 +/- 4.6 (P=0.59)

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177. Un-blinded prospective, single-surgeon No intra-operative or immediate post-op complications noted.		0.4% AND VisThesia topical (lidocaine 2% and sodium hyaluronate 0.3%) and VisThesia intracameral (lidocaine 1% and sodium hyaluronate 1.5%)	0.4%	analog scale Mean endothelial cell loss at 30 day post-op	Group 1- 20.3% +/- 43.7 Group 2-8.8% +/- 59.6 (P<0.0001)
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The Office of Surveillance and Epidemiology (OSE) was also consulted on this application. Their comments for the applicant were:

1. Remove the triangular graphic near the 'A' of the proprietary name.

Reviewer's Comment: Agree.

2. Per 21 CFR 201.10(g)(2), ensure that the established name is the same font size as the dosage form and at least ½ the size of the proprietary name, and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

Reviewer's Comment: Agree.

3. Include the statement, "Discard unused portion" on the container label.

Reviewer's Comment: This statement is present on the carton.

4. Change the font color or increase the prominence of the statement "Sample Not for Sale" to distinguish the professional sample from the trade product.

Reviewer's Comment: Agree.

DMETS and DDMAC were also consulted for this application. Their comments were as follows:

1. DMETS does not recommend the use of the proprietary name, Akten.

Reviewer's Comments: We disagree. This medication will not be prescribed nor dispensed directly to the patient; it will be dispensed directly to the surgeon.

2. DMETS recommends implementation of the following labeling revisions in order to minimize potential errors with the use of this product:

1. Dosage and Administration

a. The dosage form of the proposed product is ophthalmic gel. However, the dose is expressed as "drops." Clarify how gel will be dispensed in drops. Would the amount of drug be consistent in each drop?

Reviewer's Comments: The product is a gel, not an ointment, and therefore can be dispensed as drops. The drop size is consistent.

b. Include a time to onset for anesthesia to take effect after the application of Akten.

Reviewer's Comments: Time to onset varies from patient to patient, and the surgeon's discretion.

c. Clarify the statement, "Additional anesthesia may be reapplied as needed." Clarify how to determine if reapplication is needed. Is it based on patient's pain threshold? Include quantifying/qualifying information such as how long after the first application, at what dose, maximum limit, etc.

Reviewer's Comments: This would be based on the surgeon's discretion; specific parameters are not necessary.

2. Dosage Forms and Strengths

The statement under this section should be consistent in Highlights and Full Prescribing Information.

Reviewer's Comments: The sections are consistent with each other.

3. How Supplied

Clarify what are "5 mL/10 cc plastic dropper bottles." The use of both units (mL and cc) in the same sentence is particularly confusing to the reader. We would prefer the use of mL unit.

Reviewer's Comments: Agree.

3. DDMAC finds the proprietary name, Akten, acceptable from a promotional perspective.

8 Post-marketing Experience

No post-marketing data available since this drug is not currently marketed.

9 Appendices

9.1 Literature Review/References

The reviewer performed a literature search and did not find any significant data regarding efficacy or safety that was not submitted to the NDA.

9.2 Labeling Recommendations

Included below is a summary of the major changes needed in the applicant's proposed label. Refer below for a line by line review.

5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

9.3 Advisory Committee Meeting

No Advisory Committee was necessary nor convened for this drug product.

Comments To Be Sent To the Applicant:

- 1. Revised Package Insert as found in Section 9.2*
- 2. The triangular graphic near the 'A' of the proprietary name should be removed.*
- 3. The prominence of the statement "Sample Not for Sale" should be increased.*

**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 11:31:51 PM
MEDICAL OFFICER
For Sonal Wadhwa

Wiley Chambers
6/2/2008 11:38:13 PM
MEDICAL OFFICER