CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 040433Orig1s000

Name: Lidocaine Hydrochloride Jelly USP 2% (5 mL and 30 mL)

Sponsor: Akorn, Inc.

Approval Date: February 12, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

APPROVAL LETTER

ANDA 40-433

FEB 12 2003

Akorn, Inc.
Attention: Ambareen Sheriff
1222 West Grand Street
Decatur, IL 62522

Dear Madam:

This is in reference to your abbreviated new drug application dated March 9, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lidocaine Hydrochloride Jelly USP, 2% (5 mL and 30 mL).

Reference is also made to your amendments dated August 10, 2001; and August 12, September 27, November 13, and December 11, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Lidocaine Hydrochloride Jelly USP, 2% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Xylocaine® Jelly, 2% of AstraZeneca LP).
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 2/12/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-433
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-645/R.Rajagopalan/ R. Rajagopalan 2/4/03
HFD-645/B.Arnwine/1/30/03 2/7/03
HFD-617/N.Park/ 2/4/03
HFD-600/M.Stevens-Riley/ Maria Stevens-Riley 2/5/03
HFD-600/N.Sweeney/ N Sweeney 2/5/03
HFD-613/~~K.Lee~~ G Park/ 2/5/03
HFD-613/L.Golson 2/5/03

v:/firmsam/akorn/ltrs&rev/40433ap.doc
F/T by: EW 1/31/03

APPROVAL

Robert Lee Let
2/12/2003

cmc satisfactory
2/11/03.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

LABELING

DOSAGE AND ADMINISTRATION
When Lidocaine HCl 2% Jelly is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

The dosage varies and depends upon the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered. Dosages should be reduced for children and elderly and debilitated patients. Although the incidence of adverse effects with Lidocaine HCl 2% Jelly is quite low, caution should be exercised, particularly when employing large amounts, since the incidence of adverse effects is directly proportional to the total dose of local anesthetic agent administered.

For Surface Anesthesia of the Male Adult Urethra: The plastic cone is sterilized for 5 minutes in boiling water, cooled and attached to the tube. The cone may be gas sterilized or cold sterilized, as preferred. Slowly instill approximately 15 mL (300 mg of lidocaine HCl) into the urethra or until the patient has a feeling of tension. A penile clamp is then applied for several minutes at the corona. An additional dose of not more than 15 mL (300 mg) can be instilled for adequate anesthesia.

Prior to sounding or cystoscopy, a penile clamp should be applied for 5 to10 minutes to obtain adequate anesthesia. A total dose of 30 mL (600 mg) is usually required to fill and dilate the male urethra. Prior to catheterization, smaller volumes of 5 to 10 mL (100 to 200 mg) are usually adequate for lubrication.

For Surface Anesthesia of the Female Adult Urethra: When using Lidocaine HCl 2% Jelly 30 mL tubes, the plastic cone is sterilized for 5 minutes in boiling water, cooled and attached to the tube. The cone may be gas sterilized or cold sterilized, as preferred. Slowly instill 3 to 5 mL (60 to 100 mg of lidocaine HCl) of the jelly into the urethra. If desired, some jelly may be deposited on a cotton swab and introduced into the urethra. In order to obtain adequate anesthesia, several minutes should be allowed prior to performing urological procedures.

Lubrication for Endotracheal Intubation: Apply a moderate amount of jelly to the external surface of the endotracheal tube shortly before use. Care should be taken to avoid introducing the product into the lumen of the tube. Do not use the jelly to lubricate endotracheal stylettes. See WARNINGS and ADVERSE REACTIONS concerning rare reports of inner lumen occlusion. It is also recommended that use of endotracheal tubes with dried jelly on the external surface be avoided for lack of lubricating effect.

MAXIMUM DOSAGE
No more than 600 mg of lidocaine HCl should be given in any 12 hour period.

Children: It is difficult to recommend a maximum dosage of any drug for children since this varies as a function of age and weight. For children less than ten years who have a normal lean body mass and a normal lean body development, the maximum dose may be determined by the application of one of the standard pediatric drug formulas (e.g., Clark's rule). For example, in a child of five years weighing 50 lbs., the dose of lidocaine hydrochloride should not exceed 75 to 100 mg when calculated according to Clark's rule. In any case, the maximum amount of Lidocaine HCl administered should not exceed 4.5 mg/kg (2 mg/lb) of body weight.

HOW SUPPLIED
Lidocaine HCl Jelly USP, 2%, is supplied in 5 mL and 30 mL aluminum tubes in individual cartons.

A detachable applicator cone and a key for expressing the contents are included in the 30 mL tube carton.

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP].

AKORN, INC.
Buffalo Grove, IL 60089

Iss. 09/02

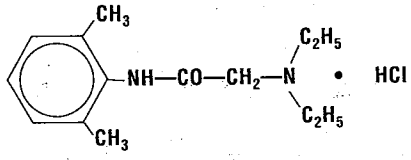
Lidocaine Hydrochloride Jelly USP, 2%

Iss. 09/02

℞ only.

DESCRIPTION
Lidocaine HCl 2% Jelly is a sterile, aqueous product that contains a local anesthetic agent and is administered topically. (See INDICATIONS AND USAGE for specific uses.)

Lidocaine HCl 2% Jelly contains lidocaine HCl which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride and has the following structural formula:



Its molecular formula is $C_{14}H_{22}N_2O \cdot HCl$ and its molecular weight is 270.80.

Lidocaine HCl 2% Jelly also contains hydroxypropylmethylcellulose, and the resulting mixture maximizes contact with mucosa and provides lubrication for instrumentation. The unused portion should be discarded after initial use.

Composition of Lidocaine HCl 2% Jelly. Each mL contains 20 mg of lidocaine HCl. The formulation also contains methylparaben, propylparaben, hydroxypropylmethylcellulose, and sodium hydroxide and/or hydrochloric acid to adjust pH between 6.0 and 7.0.

CLINICAL PHARMACOLOGY
Mechanism of Action: Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

Onset of Action: The onset of action is 3 to 5 minutes. It is ineffective when applied to intact skin.

Hemodynamics: Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. These changes may be attributable to a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system.

Pharmacokinetics and Metabolism: Lidocaine may be absorbed following topical administration to mucous membranes, its rate and extent of absorption depending upon concentration and total dose administered, the specific site of application, and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application occurs most rapidly after intratracheal administration. Lidocaine is also well-absorbed from the gastrointestinal tract, but little intact drug may appear in the circulation because of biotransformation in the liver.

Lidocaine is metabolized rapidly by the liver and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine.

Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Studies of lidocaine metabolism following intravenous bolus injections have shown that the elimination half-life of this agent is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that effects liver function may alter lidocaine kinetics. The half-life may be prolonged twofold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 mcg free base per mL. In the rhesus monkey arterial blood levels of 18 to 21 mcg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE
Lidocaine HCl 2% Jelly is indicated for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

CONTRAINDICATIONS
Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components of Lidocaine HCl 2% Jelly.

WARNINGS
EXCESSIVE DOSAGE, OR SHORT INTERVALS BETWEEN DOSES, CAN RESULT IN HIGH PLASMA LEVELS AND SERIOUS ADVERSE EFFECTS. PATIENTS SHOULD BE INSTRUCTED TO STRICTLY ADHERE TO THE RECOMMENDED DOSAGE AND ADMINISTRATION GUIDELINES AS SET FORTH IN THIS PACKAGE INSERT. THE MANAGEMENT OF SERIOUS ADVERSE REACTIONS MAY REQUIRE THE USE OF RESUSCITATIVE EQUIPMENT, OXYGEN AND OTHER RESUSCITATIVE DRUGS.

Lidocaine HCl 2% Jelly should be used in extreme caution in the presence of sepsis or severely traumatized mucosa in the area of application, since under such conditions there is the potential for rapid systemic absorption.

When used for endotracheal tube lubrication care should be taken to avoid introducing the product into the lumen of the tube. Do not use the jelly to lubricate the endotracheal stylettes. If allowed into the inner lumen, the jelly may dry on the inner surface leaving a residue which tends to clump with flexion, narrowing the lumen. There have been rare reports in which this residue has caused the lumen to occlude. (See also ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

PRECAUTIONS
General: The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. (See WARNINGS and ADVERSE REACTIONS.) The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine should also be used with caution in patients with severe shock or heart block.

Lidocaine HCl 2% Jelly should be used with caution in patients with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not know whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Information for Patients: When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. For this reason, food should not be ingested for 60 minutes following use of local anesthetic preparations in the mouth or throat area. This is particularly important in children because of their frequency of eating.

Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food or chewing gum should not be taken while the mouth or throat area is anesthetized.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Use in Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Labor and Delivery: Lidocaine is not contraindicated in labor and delivery. Should Xylocaine 2% Jelly be used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric Use: Dosages in pediatric patients should be reduced commensurate with age, body weight, and physical condition. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS
Adverse experiences following the administration of lidocaine are similar in nature to those observed in other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy, or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:

There have been rare reports of endotracheal tube occlusion associated with the presence of dried jelly residue in the inner lumen of the tube. (See also WARNINGS and DOSAGE AND ADMINISTRATION.)

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by light headedness, nervousness, apprehension, euphoria; confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respitory depression, and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to the local anesthetic agent or other components in the formulation. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

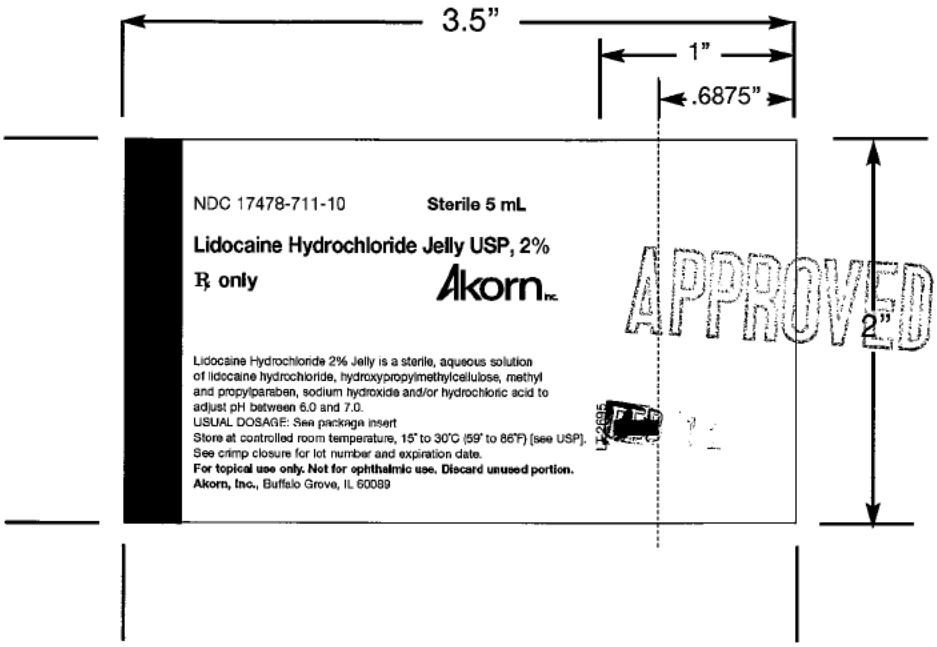
OVERDOSAGE
Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic administration. At the first sign of change, oxygen should be administered.

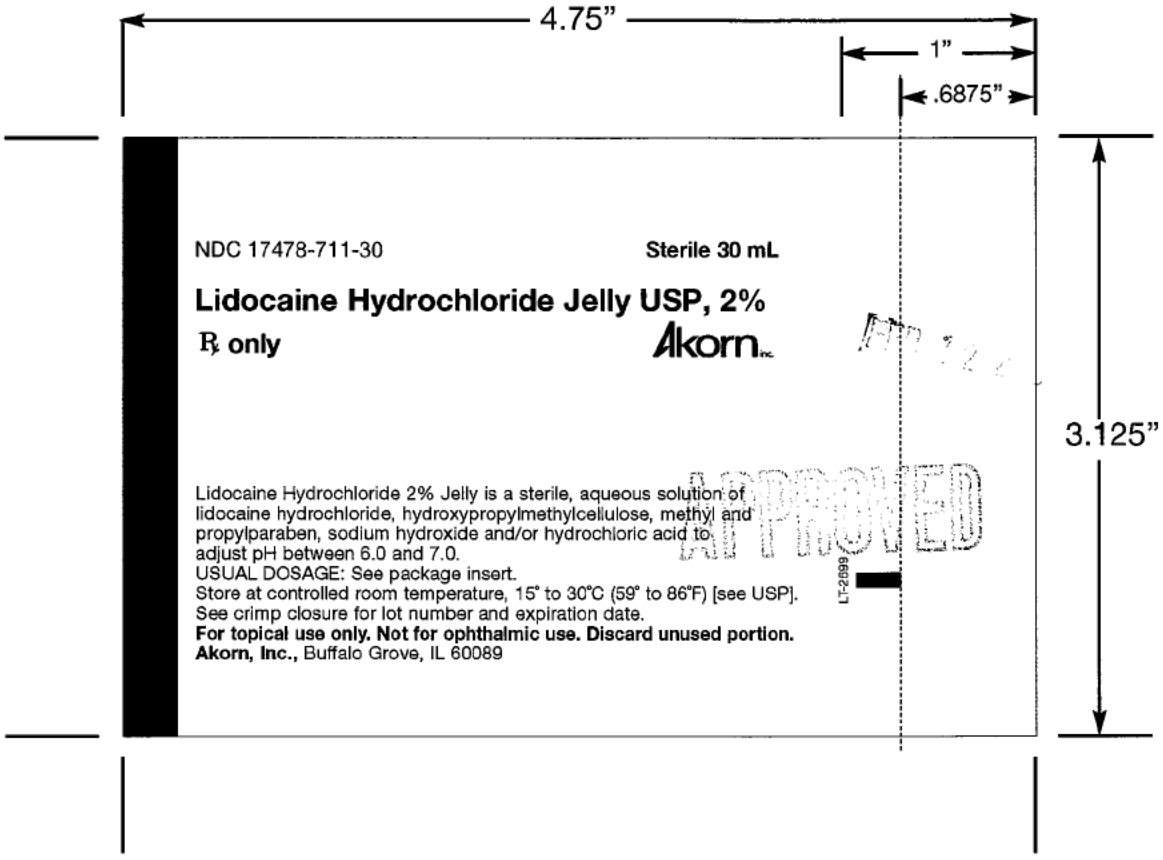
The first step in the management of convulsions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias, and cardiac arrest. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted. Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

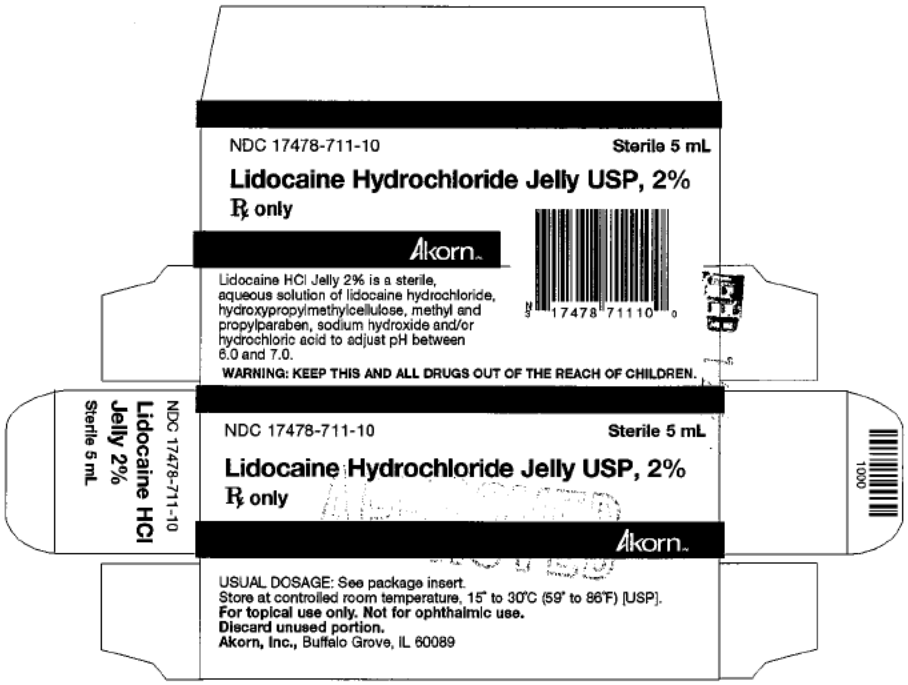
The oral LD_{50} of lidocaine HCl in non-fasted female rats is 459 (346 to 773) mg/kg (as the salt) and 214 (159 to 324) mg/kg (as the salt) in fasted female rats.


3.5”
1”
.6875”
NDC 17478-711-10
Sterile 5 mL
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Akorn Inc.
Lidocaine Hydrochloride 2% Jelly is a sterile, aqueous solution of lidocaine hydrochloride, hydroxypropylmethylcellulose, methyl and propylparaben, sodium hydroxide and/or hydrochloric acid to adjust pH between 6.0 and 7.0.
USUAL DOSAGE: See package insert
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
See crimp closure for lot number and expiration date.
For topical use only. Not for ophthalmic use. Discard unused portion.
Akorn, Inc., Buffalo Grove, IL 60089
APPROVED
2”
LT2695

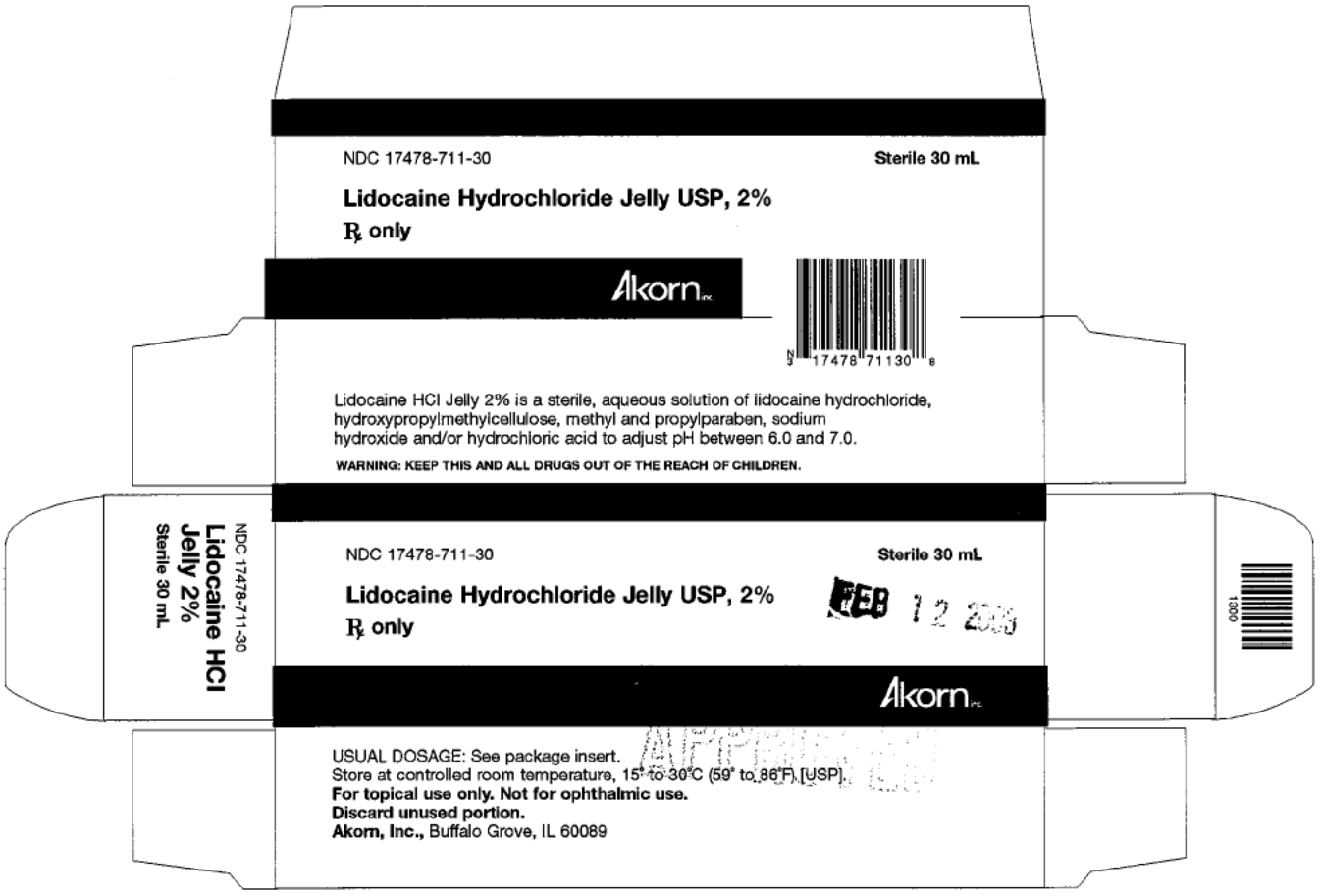
(b) (4)


4.75"
1"
.6875"
3.125"
NDC 17478-711-30
Sterile 30 mL
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Akorn Inc.
APPROVED
LT-2899
Lidocaine Hydrochloride 2% Jelly is a sterile, aqueous solution of lidocaine hydrochloride, hydroxypropylmethylcellulose, methyl and propylparaben, sodium hydroxide and/or hydrochloric acid to adjust pH between 6.0 and 7.0.
USUAL DOSAGE: See package insert.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [see USP].
See crimp closure for lot number and expiration date.
For topical use only. Not for ophthalmic use. Discard unused portion.
Akorn, Inc., Buffalo Grove, IL 60089


(b) (4)


NDC 17478-711-10
Sterile 5 mL
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Akorn
Lidocaine HCl Jelly 2% is a sterile, aqueous solution of lidocaine hydrochloride, hydroxypropylmethylcellulose, methyl and propylparaben, sodium hydroxide and/or hydrochloric acid to adjust pH between 6.0 and 7.0.
WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
NDC 17478-711-10
Lidocaine HCl Jelly 2%
Sterile 5 mL
NDC 17478-711-10
Sterile 5 mL
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Akorn
USUAL DOSAGE: See package insert.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [USP].
For topical use only. Not for ophthalmic use.
Discard unused portion.
Akorn, Inc., Buffalo Grove, IL 60089

(b) (4)


NDC 17478-711-30
Sterile 30 mL
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
Akorn Inc.
17478 71130
Lidocaine HCl Jelly 2% is a sterile, aqueous solution of lidocaine hydrochloride, hydroxypropylmethylcellulose, methyl and propylparaben, sodium hydroxide and/or hydrochloric acid to adjust pH between 6.0 and 7.0.
WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
NDC 17478-711-30
Lidocaine HCl
Jelly 2%
Sterile 30 mL
NDC 17478-711-30
Sterile 30 mL
Lidocaine Hydrochloride Jelly USP, 2%
℞ only
FEB 12 2009
Akorn Inc.
1300
USUAL DOSAGE: See package insert.
Store at controlled room temperature, 15° to 30°C (59° to 86°F) [USP].
For topical use only. Not for ophthalmic use.
Discard unused portion.
Akorn, Inc., Buffalo Grove, IL 60089

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-433 Date of Submission: March 9, 2001

Applicant's Name: Akorn, Inc.

Established Name: Lidocaine Hydrochloride Jelly USP, 2%

Labeling Deficiencies:

1. CONTAINER – 5 mL, [redacted] (b) (4) & 30 mL

   a. "propylparaben" rather than "propylparabens" [singular]

   b. Include "sodium hydroxide" and "hydrochloric acid" in the listing of inactive ingredients as appearing in the DESCRIPTION section of the package insert labeling and/or comment.

   c. Revise the statement "Consult package...information." to read "USUAL DOSAGE: See package insert.".

   d. Revise the storage temperature statement to read "Store at controlled room temperature, 15° to 30°C (59° to 86°F). [see USP]".

   e. We ask that you include the route of administration "For topical use only". In addition, we encourage the inclusion of the text "Not for ophthalmic use".

   f. We encourage the inclusion of the text "Discard unused portion.". We refer you to the statement "The unused portion should be discarded after initial use." found in your DESCRIPTION section of the package insert labeling.

   g. The reference listed drug has packaging configurations, which **cannot** be reused (syringes). Your product must be the same in this regard. Please explain what measures you intend to take to ensure that your drug product is not reused.

   h. We note that the address of the manufacturer (Baffalo Grove) is different from the one appearing in your description of manufacturing/testing facilities statements. Please revise and/or comment.

2. CARTON – 1s (5 mL, [redacted] (b) (4) & 30 mL)

   a. See comments above under CONTAINER except comment (a).

   b. Please ensure that the conditions of 21 CFR 201.15(a)(2) are met for your carton labeling.

   c. Revise to read "...and propylparaben.". [no space after "propyl"]

   d. Describe the name and place of business as required per 21 CFR 201.1.

   e. Include the net quantity (how many tubes) if more than one tube is contained in the carton.

3. INSERT

a. GENERAL

i. Please be advised that the review was done using the innovator's last approved insert labeling for Xylocaine® 2% Jelly (approved April 7, 1998)

ii. It is preferable to use the term "mcg" rather than "μg".

iii. It is preferable use the term "to" rather than a hyphen when expressing a range.

iv. Delete the terminal zeros when referencing an amount. [e.g., "6 mcg" rather than "6.0 μg"]

b. TITLE

We encourage the inclusion of the phrase "Rx only".

c. DESCRIPTION

i. First paragraph:

..."(See INDICATIONS AND USAGE for...)"

ii. Include the route of administration per 21 CFR 201.57(a)(ii).

iii. We encourage the inclusion of molecular formula and weight.

iv. It is not necessary to list the package sizes in this section.

v. We note that there are formatting problems in this section and throughout the draft insert labeling (e.g., incorrect spacing in your listing of package sizes). Please check formatting carefully when submitting final printed labeling.

d. CLINICAL PHARMACOLOGY – Let the sentence third to the last begin as the new last paragraph as follows:

...of metabolites.

Factors such as acidosis...

e. PRECAUTIONS

i. General

A) Last paragraph, penultimate sentence:

...tachycardia, tachypnea, labile blood pressure... [add "tachypnea"]

B) Last paragraph, last sentence:

Successful outcome is dependent... [spelling]

Successful outcome is dependent... [spelling]

ii. Pediatric Use

...in pediatric patients should be... [rather than "children"]

f. ADVERSE REACTIONS (Central Nervous System) – First sentence:

...characterized by lightheadedness, nervousness,...

g. OVERDOSAGE – Management of Local Anesthetic Emergencies:

i. Let the third sentence "The first step..." begin a new second paragraph.

ii. Let the penultimate sentence of the first paragraph "If not treated..." begin a new third paragraph.

h. DOSAGE AND ADMINISTRATION

i. For Surface Anesthesia of the Male Adult Urethra

A) Revise the first paragraph to read:

The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube. The cone may be gas sterilized or cold sterilized, as preferred. Slowly...

B) Let the last sentence "Prior to catherization..." be the new last paragraph.

ii. For Surface Anesthesia of the Female Adult Urethra - Revise the first two sentences to read as follows:

The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube. The cone may be gas sterilized or cold sterilized, as preferred. Slowly...

i. HOW SUPPLIED

i. First sentence – Revise to read as follows:

Lidocaine HCl Jelly USP, 2% is...

ii. Include information on how your product will be packaged. (e.g., individually packaged in carton)

iii. We note that a detachable applicator cone and a key for expressing the contents are listed in this section for your 30 mL tube package size. However, you did not submit data to support this statement in the container/closure section. Please submit the data/or explain. What provisions do you propose for other package sizes so that your products meet the conditions of use approved for the reference listed drug? See also the comment (g) under CONTAINER.

iv. [redacted] (b) (4)

(b) (4)

v. (b) (4)

vi. See comment (d) under CONTAINER.

vii. We encourage the inclusion of the date of issuance of the insert labeling.

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST:

1. **Do you concur the comment (b) under CONTAINER?**

   Concurred by the chemist

2. **The sponsor claims that a detachable applicator cone and a key for expressing the contents are included in the 30 mL tube. Has the sponsor submitted data supporting this claim in the container/closure section?**

   Answer; ANDA 40-433 does utilize collapsible aluminum tubes for all sizes (b) (4) (b) (4). The tubes have a nozzle (tip) with a (b) (4) cap, and the nozzle can be sealed after filling. The container closure section mentions nothing about using a dispensing detachable cone or a key for any of the (b) (4) (especially the 30 mL) sizes. The diagrams are provided for in the container section (volume 1.2) if you wish to see them. I have also questioned them in the CMC deficiencies about the dispensing cone/key.

   Radhika

3. **Please refer to the comments (iii), (iv), & (v) under HOW SUPPLIED section and make comment in your chemistry review, if deemed necessary.**

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	

Are there any other safety concerns?			
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

FOR THE RECORD:

1. MODEL LABELING – Xylocaine 2% Jelly (AstraZeneca, approved July 11, 1984). This is NDA 08816/SLR- 013.

2. This drug product is the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 132 (Volume 1.1). However, see the comment (b) under CONTAINER.

4. The concentrations of the inactive ingredients, [redacted] (b) (4) and [redacted] (b) (4) are [redacted] (b) (4) of those found in the formulation of Xylocaine 2% jelly. However, these concentrations were found acceptable by OGD as these concentrations were allowed for other generic products in the past.

5. Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: CRT

7. PACKAGING CONFIGURATIONS

   RLD: 30 mL aluminum tube & 5 mL plastic tube. 10 mL & 20 mL polypropylene syringe

   ANDA: 5 mL [redacted] (b) (4) 30 mL (all collapsible aluminum tube)

8. CONTAINER/CLOSURE (p.480, vol.1.2)

   Aluminum tube with an nozzle and a white [redacted] (b) (4) cap. See comment (b) under NOTE/QUESTION TO CHEMIST.

9. Akorn, Inc is the sole manufacturer of this drug product. (p.207, vol.1.1)

10. I spoke with Lisa DeLuca of AstraZeneca on 5/25/01) regarding the packaging configuration of Xylocaine 2% Jelly and how this drug product is being used in the clinical settings. The 30 mL aluminum tube comes with the detachable cone, but not the 5 mL tube. In addition, she sated that the syringe may be accompanied with the catheter attached, but she is not sure. She said she would mail me the sample of these different packaging configurations.

11. We have received in mail the sample of these different packaging configurations from the innovator. The innovator's syringe of 10 mL & 20mL has a narrow-tube like extension of about 5 mm at the tip of the syringe, which may be used for a catheter.

Date of Review: May 25, 2001 **Date of Submission: March 9, 2001**

Primary Reviewer: Chan Park **Date:** 6/8/01

Team Leader: **Date:** 6/7/01

cc:

ANDA: 40-433
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-433 Date of Submission: February 12, 2002 & August 12, 2002

Applicant's Name: Akorn, Inc.

Established Name: Lidocaine Hydrochloride Jelly USP, 2%

Labeling Deficiencies:

1. CONTAINER – 5 mL, & 30 mL

   a. GENERAL

      We note your statement that you have submitted 12 representations of all final printed labels and labeling in your submission of February 12, 2002. However, we find only side-by-side comparisons without the actual final printed labeling included in your submission. Please submit.

   b. Please assure that the statements "For topical use only", "Not for ophthalmic use", and "Discard unused portion." appears sufficiently prominent.

   c. We acknowledge in your amendment of August 12, 2002, that you have decided to [redacted] (b) (4)

2. CARTON – 1s (5 mL and 30 mL)

   a. See comments under CONTAINER.

   b. We believe that 21 CFR 201.15(a)(2) requires the established name, strength and the net quantity of your drug product be printed on more than one panel. Please revise accordingly.

3. INSERT

   a. DESCRIPTION

      It is preferable to retain the statement "The unused portion...initial use." rather than ""Discard unused portion." to be in accordance with the innovator's labeling.

   b. CLINICAL PHARMACOLOGY

      As stated in the last deficiency letter, it is preferable to use the term "to" rather than a hyphen when expressing a range.

   c. DOSAGE AND ADMINISTRATION

      i. For Surface Anesthesia of the Male Adult Urethra - Revise the first sentence to read as follows:

         ...cooled and attached to...

ii. For Surface Anesthesia of the Female Adult Urethra - Revise the first sentence to read as follows.

The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube. The cone ...

d. HOW SUPPLIED

i. First sentence – Revise to read as follows:

Lidocaine HCl Jelly USP, 2% is...

ii. Include information on how your product will be packaged. (e.g., individually packaged in carton)

iii. Please refer to the comment 1(c) above. Revise this section accordingly.

iv. We acknowledge that you have included a proposal for a detachable applicator cone and a key for expressing the contents included in your 30 mL tube package size. We ask you to revise the statement regarding this to read "... are included in 30 mL tube" and/or comment. [add "in 30 mL tube"]

Please revise your labels and labeling, as instructed above, and submit in final print, or in draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST: (Sent via e-mail on 9/12/02)

1. The sponsor submitted (labeling amendment dated 8/14/02) a proposal for applicator cone and a key for expressing the contents included in the 30 mL tube. This is included in vol.2.1. Is the firm's proposal acceptable? When you have a chance, please take a look and let me know whether this is acceptable or not. Thanks

2. The sponsor [redacted] (b) (4).

FOR THE RECORD:

1. MODEL LABELING – Xylocaine 2% Jelly (AstraZeneca, approved April 7, 1998). This is NDA 08-816/SCP-028. SCP-031 was approved on June 2, 2000 and this was for a change in the tube sealant. The labeling supplement was last approved on July 11, 1884 (SLR-013). However, I was told by the new drug PM to use the labeling approved in SCP-028 as a model for the generics.

2. This drug product is the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 132 (Volume 1.1).
4. The concentrations of the inactive ingredients, [redacted] (b) (4) and [redacted] (b) (4) are [redacted] (b) (4) of those found in the formulation of Xylocaine 2% jelly. However, these concentrations were found acceptable by OGD as these concentrations were allowed for other generic products in the past.
5. Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   Both RLD and the ANDA: CRT

7. PACKAGING CONFIGURATIONS

   RLD: 30 mL aluminum tube & 5 mL plastic tube. 10 mL & 20 mL polypropylene syringe (Cone is a part of the syringe), 30 mL comes with a detachable cone. See below for detail.

   ANDA: 5 mL & 30 mL (all collapsible aluminum tube); one tube contained in carton. The sponsor [redacted] (b) (4) in the amendment of August 12, 2002.

8. CONTAINER/CLOSURE (p.480, vol.1.2)

   Aluminum tube with an nozzle and a white [redacted] (b) (4) cap. ANDA 40-433 does utilize collapsible aluminum tubes for all sizes (5 through 30 mL). The tubes have a nozzle (tip) with a [redacted] (b) (4) cap, and the nozzle can be sealed after filling according to Chemist. See comment (1) under NOTE/QUESTION TO CHEMIST.

9. Akorn, Inc is the sole manufacturer of this drug product. (p.207, vol.1.1)

10. Regarding the innovator's packaging system, I have received the following e-mail form PM, Michael Theodorakis on May 23, 01.

The cone is part of the syringe container. It is used to instill the jelly into urethra. The jelly prefilled syringes are not packaged with catheters. The jelly can also be applied directly on the catheter w/o using the cone. The jelly is also package with aluminum 30 mL tubes. If you need more information as to how the drug product is used by clinicians, please contact Lisa DeLuka, Director of Regulatory Affairs of AstraZeneca at 302-886-5594.

11. I spoke with Lisa DeLuca of AstraZeneca on 5/25/01) regarding the packaging configuration of Xylocaine 2% Jelly and how this drug product is being used in the clinical settings. The 30 mL aluminum tube comes with the detachable cone, but not the 5 mL tube. In addition, she sated that the syringe may be accompanied with the catheter attached, but she is not sure. She said she would mail me the sample of these different packaging configurations.

12. We have received in mail the sample of these different packaging configurations from the innovator. The innovator's syringe of 10 mL & 20mL has a narrow-tube like extension of about 5 mm at the tip of the syringe, which may be used for a catheter. there was no catheter attached.

13. The sponsor prefers to have the corporate address on its entire product labeling, rather than the address for the actual manufacturing site. We find this acceptable.

Date of Review: Sep 12, 02 **Date of Submission: Feb 12, 2002 & Aug12, 2002**

Primary Reviewer: Chan Park **Date:** 9/18/02

Acting Team Leader: Lillie Golson **Date:** 9/18/02

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ANDA: 40-433
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Review

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-433 Date of Submission: September 27, 2002

Applicant's Name: Akorn, Inc.

Established Name: Lidocaine Hydrochloride Jelly USP, 2%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS - 5 mL & 30 mL

Satisfactory in FPL as of 9/27/02 submission (vol.21. Attachment B)

CARTON LABELING - 1s (5 mL & 30 mL)

Satisfactory in FPL as of 9/27/02 submission (vol.21. Attachment B)

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 9/27/02 submission (vol. 2.1, Attachment B; Code # 0600; Iss. 09/02)

REVISIONS NEEDED POST-APPROVAL: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Xylocaine® Jelly, 2%

NDA Drug Name: Xylocaine® Jelly, 2%

NDA Firm: AstraZeneca

Date of Approval of NDA Insert and supplement #:
08-816/SCP-028, approved April 7, 1998

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison

Basis of Approval for the Carton Labeling: Side-by-side comparison

9. Akorn, Inc is the sole manufacturer of this drug product. (p.207, vol.1.1)

10. Regarding the innovator's packaging system, I have received the following e-mail form PM, Michael Theodorakis on May 23, 01.

    The cone is part of the syringe container. It is used to instill the jelly into urethra. The jelly prefilled syringes are not packaged with catheters. The jelly can also be applied directly on the catheter w/o using the cone. The jelly is also package with aluminum 30 mL tubes. If you need more information as to how the drug product is used by clinicians, please contact Lisa DeLuka, Director of Regulatory Affairs of AstraZeneca at 302-886-5594.

11. I spoke with Lisa DeLuca of AstraZeneca on 5/25/01) regarding the packaging configuration of Xylocaine 2% Jelly and how this drug product is being used in the clinical settings. The 30 mL aluminum tube comes with the detachable cone, but not the 5 mL tube. In addition, she stated that the syringe may be accompanied with the catheter attached, but she is not sure. She said she would mail me the sample of these different packaging configurations.

12. We have received in mail the sample of these different packaging configurations from the innovator. The innovator's syringe of 10 mL & 20mL has a narrow-tube like extension of about 5 mm at the tip of the syringe, which may be used for a catheter. there was no catheter attached.

13. The sponsor prefers to have the corporate address on its entire product labeling, rather than the address for the actual manufacturing site. We find this acceptable.

Date of Review: October 1, 2002 **Date of Submission: September 27, 2002**

Primary Reviewer: Chan Park **Date:** 10/2/02

Acting Team Leader: Lillie Golson **Date:** 10/3/02

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ANDA: 40-433
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433 Orig1s000

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # **40-433**

3. NAME AND ADDRESS OF APPLICANT
Akorn, Inc
Attention: James G. Baumann, Jr.,
1222 West Grand Avenue
Decatur, IL 62522

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Xylocaine 2% Jelly
Innovator Company: Astrazeneca, Inc.
Marketing exclusivity is not applicable to the product. There are no patents covering this product also.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Lidocaine USP 2% Jelly

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
Firm
Original submission: 3/9/01
Telephone amendment: 4/12/01

FDA
Date accepted for filing: 3/13/01
Phone call for revised certificates: 4/11/01

10. PHARMACOLOGICAL CATEGORY
Topical anesthetic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Type II [redacted] (b)(4) DMF
NDA 08-816

DMF number	DMF type	DMF holder
(b) (4)	II: (b) (4) (b) (4)	(b) (4)
	III: (b) (4)	
	III: (b) (4)	

13. DOSAGE FORM
Jelly

14. POTENCY
2%

15. CHEMICAL NAME AND STRUCTURE
2-(diethylamino)N-(2,6-dimehtylphenyl)-monohydrochloride
$C_{14}H_{23}N_2OCl$

16. RECORDS AND REPORTS
DS and DP have USP Monographs.

17. COMMENTS
Deficiencies are documented throughout the review.

18. CONCLUSIONS AND RECOMMENDATIONS
Minor amendment is recommended.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

Radhika Rajagopalan

DATE COMPLETED:
5/18/01

6/18/01

Following this page, 8 pages withheld in full (b)(4)

[redacted] (b) (4)

30. CONTROL NUMBERS
NA

31. SAMPLES AND RESULTS
Both drug substance and product are compendial items. Hence validation by a field lab will be not be initiated.

32. LABELING
Review is inadequate. See labeling review dated 6/8/01.

33. ESTABLISHMENT INSPECTION
EER requested. Pending results.

34. BIOEQUIVALENCY STATUS
Pending waiver review.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSIONS:
Exclusion request is provided on page 812.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.
X Yes
☐ No
If no, explain reasons(s) below:

37. **DMF Checklist for ANDA/AADA # 40-433 REVIEW # 1**

DMF # DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT REVIEW	DATE OF REVIEW
[redacted] II: [redacted]	1	Inadequate	5/11/01
Comments:			
[redacted] III: [redacted]	1	Adequate	7/10/00
Comments: [redacted]			
[redacted] III: [redacted]	1/3	Ade	
Comments: [redacted]			
[redacted] III: [redacted]	3	Ade	
Comments:			

ACTION CODES:

(1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
Type 1 DMF;
(2) Reviewed previously and no revision since last review;
(3) Sufficient information in application;
(4) Authority to reference not granted;
(5) DMF not available;
(6) Other (explain under "Comments").;

Page 1 of 1

Raedhika Rajagopalan 6/18/01

Reviewer signature Date

38. Chemistry comments to be provided to the Applicant

ANDA: 40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride Jelly USP, 2%

The deficiencies presented below represent Minor deficiencies.

Deficiencies:

1. We recommend that you identify [redacted] (b) (4)

2. Please include information regarding the function of each ingredient in the formulation under Components and Composition.

3. Please provide a copy of [redacted] (b) (4)

4. Please provide a validated method for the quantitation of [redacted] (b) (4).

5. We notice that [redacted] (b) (4)

6. On page 238, [redacted] (b) (4)

7. On page 320, you have indicated [redacted] (b) (4)

8. Page 326 indicates that [redacted] (b) (4)

9. Please clarify your statement on page 309 regarding, [redacted] (b) (4)

10. Please clarify if tubes are [redacted] (b) (4)

11. The DMF holder [redacted] (b) (4) letter on page 482 indicates that the Aluminum tubes are [redacted] (b) (4)

12. Please provide composition information on the [redacted] (b) (4).

13. We notice your statement that the tube and cap are one integral unit. Are they sterilized as a unit together? Are any glues used for crimping?

14. We notice that a detachable applicator cone and a key for expressing the contents are included in the 30 mL tube label section. However, there is no supporting composition, test data, COA and manufacturer/DMF information provided

in the ANDA under Container/Closure section. Please address this issue. Also, address how the other packages will deliver the dose without an applicator cone.

15. Please provide a listing of known degradation products of Lidocaine Hydrochloride. Also, include copies of chromatograms (initial and selected stability test stations) where degradants are observed for review.

16. In case of dispute the USP method will be deemed as the regulatory method even though the proposed methodology is quantitating Lidocaine from its degradants and excipients. Please provide an acknowledgement regarding this.

17. We request that you modify [redacted] (b) (4)

18. Please update the ambient stability data available for the past 3 months, for all configurations.

Chemistry Comments:

1. Please compare the RLD stability data with that of the ANDA product, as per your methods.

2. DMF [redacted] (b) (4) is inadequate. Deficiencies in the DMF would have to be corrected prior to ANDA approval.

Sincerely yours,

6/26/01

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-433
ANDA DUP
DIV FILE
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Endorsements:
HFD-645/RRajagopalan/5/18/01 R. Rajagopalan 6/18/01
HFD-645/BTArnwine/6/8/01 B Arnwine 6/18/01
HFD-617/KSherrod/6/11/01 K Sherrod 6/25/01

F/T by cll/6/14/01
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CHEMISTRY REVIEW - MINOR DEFICIENCY

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-433

3. NAME AND ADDRESS OF APPLICANT
Akorn, Inc
Attention: Shahid Ahmed
1222 West Grand Street
Decatur, IL 62522

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Xylocaine 2% Jelly
Innovator Company: Astrazeneca, Inc.
Marketing exclusivity is not applicable to the product. There are no patents covering this product also.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Lidocaine USP 2% Jelly

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
Firm
Original submission: 3/9/01
Minor amendment: 2/12/02
Telephone amendment: 4/12/01
Chemistry amendment: 5/6/02
Micro amendment: 6/6/02

FDA
Date accepted for filing: 3/13/01
Phone call for revised certificates: 4/11/01
Bio NA waiver: 4/12/01
First Minor amendment request: 6/27/01 (CMC, label)
Bio waiver granted: 10/19/01
Phone call on 4/16/02, but could not issue deficiencies due to lack of personnel at IL facility

10. PHARMACOLOGICAL CATEGORY
Topical anesthetic

11. Rx or OTC
Rx

2. RELATED IND/NDA/DMF(s)
Type II (b)(4) DMF
NDA 08-816

DMF number	DMF type	DMF holder
(b)(4)	II: (b)(4)	(b)(4)
	III: (b)(4)	
	III: (b)(4)	
	III: (b)(4)	
	III: (b)(4)	

13. DOSAGE FORM
Jelly

14. POTENCY
2% filled in 5 mL, (b)(4) 30 mL tubes

15. CHEMICAL NAME AND STRUCTURE
2-(diethylamino)N-(2,6-dimehtylphenyl)-monohydrochloride
$C_{14}H_{23}N_2OCl$

16. RECORDS AND REPORTS
DS and DP have USP Monographs.

17. COMMENTS
Awaiting micro review

18. CONCLUSIONS AND RECOMMENDATIONS
Labeling response requested. See item 38.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
7/10/02

Radhika Rajagopalan 7/17/02

Following this page, 12 pages withheld in full (b)(4)

30. CONTROL NUMBERS
NA

31. SAMPLES AND RESULTS
Both drug substance and product are compendial items. Hence validation by a field lab will be not be initiated.

32. LABELING
Review is inadequate. See labeling review dated 6/8/01. Second review is also inadequate. Firm's response is pending. To be conveyed to them under item 38.

33. ESTABLISHMENT INSPECTION
EER requested. Acceptable as of 7/10/02.

34. BIOEQUIVALENCY STATUS
Review dated adequate is filed in volume 1.1 (dated 10/19/01).

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSIONS:
Exclusion request is provided on page 812.

36. ORDER OF REVIEW
The application submission(s) covered by this review as taken in the date order of receipt.
X Yes
☐ No
If no, explain reasons(s) below:

37. **DMF Checklist for ANDA/AADA # 40-433 REVIEW # 2**

DMF # DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT REVIEW	DATE OF REVIEW
(b) (4) II: (b) (4)	1	adequate	4/8/02
Comments:			
(b) (4) III: (b) (4)	1	Adequate	7/10/00
Comments: (b) (4)			
(b) (4) III: (b) (4)	1/3	Ade	
Comments: (b) (4)			
(b) (4) III: (b) (4)	3	Ade	
Comments:			
(b) (4) III: (b) (4)	1	Ade	12/13/99
Comments:			

ACTION CODES:

(1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
Type 1 DMF;
(2) Reviewed previously and no revision since last review;
(3) Sufficient information in application;
(4) Authority to reference not granted;
(5) DMF not available;
(6) Other (explain under "Comments").;

Andrew Rajpal 7-17-02

Reviewer signature Date

38. Chemistry comments to be provided to the Applicant

ANDA: 40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride USP 2% Jelly

The deficiency presented below represents a Minor deficiency.

Deficiency:

We await a response to the labeling deficiencies conveyed on April 3, 2002 by telephone.

Sincerely yours,

U.V. Venkataram 7/23/02

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-433
DIV FILE
Field Copy

Endorsements:
HFD-645/RRajagopalan/7/10/02 R. Rajagopalan 7/17/02
HFD-645/BTArnwine/7/16/02 BT (amicine) 7/23/02
HFD-617/NPark/7/16/02 NPark 7/23/02

F/T by rad7/17/02
V:\firmsam\akorn\ltrs&rev\40433r2.d.doc

CHEMISTRY REVIEW - ADEQUATE; Label amendment requested

1. CHEMISTRY REVIEW NO. 3

2. ANDA # **40-433**

3. NAME AND ADDRESS OF APPLICANT
Akorn, Inc
Attention: Ambareen Sheriff
1222 West Grand Street
Decatur, IL 62522

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Xylocaine 2% Jelly
Innovator Company: Astrazeneca, Inc.
Marketing exclusivity is not applicable to the product. There are no patents covering this product also.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Lidocaine USP 2% Jelly

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Firm

Original submission: 3/9/01
Minor amendment: 2/12/02
Telephone amendment: 4/12/01
Chemistry amendment: 5/6/02
Micro amendment: 6/6/02
Label amendment: 8/12/02
Label amendment: 9/27/02
Micro amendment: 11/13/02 and 12/11/02

FDA

Date accepted for filing: 3/13/01
Phone call for revised certificates: 4/11/01
Bio NA waiver: 4/12/01
First Minor amendment request: 6/27/01 (CMC, label)
Bio waiver granted: 10/19/01
Phone call on 4/16/02, but could not issue deficiencies due to lack of personnel at IL facility
Label review: 9/18/02
Label review: 10/3/02

Micro review: 11/25/02 and 12/30/02

10. PHARMACOLOGICAL CATEGORY
Topical anesthetic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
Type II (b)(4) DMF
NDA 08-816

DMF number	DMF type	DMF holder
(b)(4)	II: (b)(4)	(b)(4)
	III: (b)(4)	
	III: (b)(4)	
	III: (b)(4)	
	III: (b)(4)	

13. DOSAGE FORM
Jelly

14. POTENCY
2% filled in 5 mL, and 30 mL tubes. (b)(4)
(b)(4)

15. CHEMICAL NAME AND STRUCTURE
2-(diethylamino)N-(2,6-dimehtylphenyl)-monohydrochloride
$C_{14}H_{23}N_2OCl$

16. RECORDS AND REPORTS
DS and DP have USP Monographs.
Micro and label review satisfactory.

17. COMMENTS
None.

18. CONCLUSIONS AND RECOMMENDATIONS
ANDA recommended for approval.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
1/10/03

Radhika Rajagopalan 2/4/03

Following this page, 12 pages withheld in full (b)(4)

30. CONTROL NUMBERS
NA

31. SAMPLES AND RESULTS
Both drug substance and product are compendial items. Hence validation by a field lab will be not be initiated.

32. LABELING
Review satisfactory as of 10/3/02.

33. ESTABLISHMENT INSPECTION
EER requested. Acceptable as of 7/10/02.

34. BIOEQUIVALENCY STATUS
Review is adequate and is filed in volume 1.1 (dated 10/19/01).

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSIONS:
Exclusion request is provided on page 812.

36. ORDER OF REVIEW

The application submission(s) covered by this review as taken in the date order of receipt.

X Yes

☐ No

If no, explain reasons(s) below:

37. **DMF Checklist for ANDA/AADA # 40-433 REVIEW # 3**

DMF # DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT REVIEW	DATE OF REVIEW
[redacted] II: [redacted]	1	adequate	4/8/02
Comments:			
[redacted] III: [redacted]	1	Adequate	7/10/00
Comments: [redacted]			
[redacted] III: [redacted]	1/3	Ade	
Comments: [redacted]			
[redacted] III: [redacted]	3	Ade	
Comments:			
[redacted] III: [redacted]	1	Ade	12/13/99
Comments:			

ACTION CODES:

(1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:
Type 1 DMF;
(2) Reviewed previously and no revision since last review;
(3) Sufficient information in application;
(4) Authority to reference not granted;
(5) DMF not available;
(6) Other (explain under "Comments").;

Page 1 of 1

Radhika Rajagopalan 2/4/03

Reviewer signature Date

cc: ANDA 40-433
DIV FILE
Field Copy

Endorsements:
HFD-645/RRajagopalan/1/10/03 R. Rajagopalan 2/4/03
HFD-645/BTArnwine/1/30/03 BT Arnwine 2/7/03
HFD-617/NPark/1/29/03

F/T by: EW 1/31/03
V:\firmsam\akorn\ltrs&rev\40433r3.d.doc

CHEMISTRY REVIEW - ADEQUATE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

BIOEQUIVALENCE REVIEWS

Lidocaine Hydrochloride 2% Jelly, USP
ANDA #40-433
Reviewer: Carol Y. Kim
v:\firmsam\akorn\ltrs&rev\40433w.401

Akorn, Inc.
Decatur, IL
Submission Date:
~~April 12~~, 2001
march 9

REVIEW OF A WAIVER REQUEST

I. Background

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its proposed product, Lidocaine Hydrochloride 2% Jelly, USP. The reference listed drug is Xylocaine^{R} (lidocaine hydrochloride) 2% Jelly, NDA# 008816, manufactured by AstraZeneca.

2. The RLD, Xylocaine^{R} 2% Jelly, is a DESI effective drug product and is coded "AT" in the Orange Book (2001). See the attached e-mail dated 5/1/01.

3. Lidocaine HCl 2% Jelly is an aqueous non-solution product. It is used as a topical anesthetic for urological procedures and lubrication of endotracheal tubes.

4. The test and reference products are both for topical use. The RLD is supplied in the following dosage forms: 30 ml aluminum tube, 5 ml plastic tube, 10 ml polypropylene syringe, and 20 ml polypropylene syringe (PDR, 2001). The firm's proposed test product's tube sizes are 5 ml, (b) (4) and 30 ml.

II. Formulation comparison

The test and reference formulations are compared as shown below.

Ingredients	^Reference: Xylocaine^{R} 2% Jelly, per ml	Test: Lidocaine HCl 2% Jelly, USP, per ml
Lidocaine hydrochloride	20 mg	20 mg
Methylparaben	(b) (4)	(b) (4)
Propylparaben		
Hydroxypropyl methylcellulose		
Sodium hydroxide	Adjust pH to 6.0-7.0	Adjust pH to 6.0-7.0
Hydrochloric acid	Adjust pH to 6.0-7.0	Adjust pH to 6.0-7.0
(b) (4)		

^COMIS database

III. History of Submissions

The DBE granted a waiver of *in vivo* testing for Copley Pharmaceutical Inc.'s Lidocaine HCl 2% Topical Jelly based on the qualitative comparison of the formulation (ANDA #81-318, 10/25/90). Subsequently, the application was approved by the Agency on April 29, 1993. However, the conditions under which waivers of *in vivo* bioequivalence can be granted for topical products were changed after 21 CFR was modified in 1992. At present, 21 CFR 320.22 (b) (3) states that waivers can only be granted for topical products which are solutions.

IV. Comments

1. A waiver cannot be granted for topical jelly (non-solution) products under 21 CFR 320.22.

2. A bioequivalence study is currently requested, as per recommendation of Dr. Mary Fanning, OGD Associate Director for Medical Affairs. See attached Medical Officer Review, dated 7/6/01.

3. Dr. Fanning concluded that a standard bioequivalence (pharmacokinetic) study should be conducted to evaluate the generic drug product's bioequivalence to the reference listed drug.

4. Dr. Fanning also recommends that, due to the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products should be evaluated. This can be accomplished during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

5. Similar recommendations were communicated to [redacted] (b) (4) and Hi-Tech Pharmacal, respectively, for combination lidocaine/prilocaine topical products. (see OGD#00-236 and P #00-022).

V. Recommendations

1. The Division of Bioequivalence does not agree that the information submitted by Akorn Inc. demonstrates that Lidocaine Hydrochloride 2% Jelly, USP, 5 ml, [redacted] (b) (4) [redacted] (b) (4) and 30 ml tubes, falls under 21 CFR section 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations.

2. The Division of Bioequivalence requests that the firm conduct an *in vivo* bioequivalence study based on pharmacokinetic endpoints to compare their proposed product to the reference listed drug, Xylocaine^{R} 2% Jelly.

3. Due to the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products should also be evaluated. This can be accomplished during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

4. The firm should submit a study protocol prior to the initiation of the study.

The firm should be informed of the above recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT

Date: 7/13/01

Concur:

Date: 7/24/2001

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: #40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride 2% Jelly, USP

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

1. A waiver cannot be granted for non-solution topical products under 21 CFR 320.22.

2. Please conduct an *in vivo* bioequivalence study based on pharmacokinetic endpoints to compare your proposed product to the reference listed drug, Xylocaine^{R} 2% Jelly.

3. Due to the high rate of local skin reactions, the comparability of local skin reactions for the reference and your products should be evaluated. This can be accomplished during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

4. It is recommended that you submit your proposed protocols to the Office of Generic Drugs for review prior to study initiation.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #40433
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

v:\FIRMSam\akorn\ltrs&rev\40433w.401

Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 7/13/01
HFD-658/ Bio team Leader B. Davit 7/13/01
HFD-650/ S. Mazzella
HFD-650/ D. Conner for 7/24/2001

BIOEQUIVALENCY -UNACCEPTABLE Submission date: ~~4/12~~ 3/9/01

1. WAIVERS (WAI) **Strengths: 2%**

Outcome: UC

Outcome Decisions: **UC** - Unacceptable

WinBio Comments: A waiver is not granted

Attachment

-----Original Message-----
From: Hare, Donald B
Sent: Tuesday, May 01, 2001 4:16 PM
To: Kim, Carol Y
Subject: RE: Is lidocaine DESI drug?

Carol:

Lidocaine Jelly NDA 8861, is a DESI effective drug product.

Don

MEDICAL OFFICER REVIEW
July 6, 2001

ANDA 40-433
Drug Product: Lidocaine HCl 2% Jelly
Sponsor: Akorn, Inc.

The Division of Bioequivalence has reviewed a protocol for a bioequivalence study based on pharmacokinetic measurements. They have enquired whether this will suffice for the bioequivalence assessment or if a bioequivalence study with clinical endpoints is required.

The final review for two related products containing lidocaine and applied topically is appended. The final recommendation is that a standard bioequivalence study should be relied on to demonstrate bioequivalence of the generic drug product to the reference listed drug. In addition, because of the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products could be evaluated during the standard bioequivalence study. The following parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

Mary Fanning, MD, PhD
Associate Director for Medical Affairs
Office of Generic Drugs

MEDICAL OFFICER REVIEW
October 10, 2000

CD #00-236
Drug Product: Lidocaine and Prilocaine
Sponsor: (b) (4)
Reference Listed Drug: EMLA ® cream and patch

And

Protocol 00-022
Drug Product: Lidocaine 2.5% and Prilocaine 2.5%
Sponsor: HiTech Pharma
Reference Listed Drug: EMLA ® cream and patch

HFD-170 was consulted about these two inquiries on bioequivalence studies for the generic equivalent of EMLA ® cream and patch. The Division concluded that a standard bioequivalence study of the 60 mg dose could be used to determine bioequivalence of the generic drug product. In addition, they indicated that the proposed clinical endpoint study submitted by (b) (4) was acceptable if OGD decided that a clinical endpoint study was necessary. Should we make that recommendation, they suggested that the sponsor should submit a protocol for review prior to undertaking the study. The Division did not address the question on the skin irritation evaluation.

Recommendation: The Sponsors should be informed that a standard bioequivalence (pharmacokinetic) study should be conducted using the 60 mg dose in order to evaluate the generic drug product's bioequivalence to the reference listed drug. Because of the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products could be evaluated during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

Mary M. Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Bio Management Meeting
June 7, 2001

Dale Conner, Rabindra Patnaik, Yi-Chain Huang, Shriniwas Nerurkar, Barbara Davit, Lizzie Sanchez

1. (b) (4)

2.

3. **Lidocaine 2% Jelly:** Carol is reviewing an ANDA for this protocol A waiver of in-vivo testing was requested. The product is not Q2 the same. Jelly is not considered a solution. A product by Copley was waived in 1990. A medical consult should also be requested for this product. The history of the EMLA product should be considered. The clinical division agreed that a PK study would be sufficient to establish BE.

4. (b) (4)

5.

6.

7.

8. 

Drafted: L. Sanchez 6/13/01

Lidocaine Hydrochloride 2% Jelly, USP
ANDA #40-433
Reviewer: Carol Y. Kim
v:\firmsam\akorn\ltrs&rev\40433sta.801

Akorn, Inc.
Decatur, IL
Submission Date:
August 10, 2001

REVIEW OF AN AMENDMENT

I. Objective

1. In this amendment, the firm asks the DBE to reconsider the request for an *in vivo* bioeqiuivalence study for Lidocaine Hydrochloride 2% Jelly, USP.

2. The firm argues that their product is an aqueous solution for the following reasons:

   a. The approved RLD label claims that Lidocaine Hydrochloride Jelly, 2%, USP, is a sterile, aqueous solution of lidocaine hydrochloride.

   b. This product contains the active and inactive ingredients, which are soluble in water.

   c. Although the product is somewhat viscous, by definition it is still an aqueous solution and imparts the physicochemical properties of a solution. The active ingredient and (b) (4) methyl and propylparaben, are (b) (4) and (b) (4) (b) (4)

II. Background

1. In the original application submitted on April 12, 2001, the firm requested a waiver of *in vivo* BE study requirements for Lidocaine Hydrochloride 2% Jelly, USP. However, on July 30, 2001, the DBE denied the waiver request and asked the firm to conduct *in vivo* BE study because a waiver cannot be granted for non-solution topical products under 21 CFR 320.22.

2. Dr. Mary Fanning, OGD Associate Director for Medical Affairs, concluded that a standard bioequivalence (pharmacokinetic) study should be conducted to evaluate the generic drug product's bioequivalence to the reference listed drug. (see Medical Officer Review, dated 7/6/01)

3. Akorn proposed tube sizes in 5 ml, [redacted] and 30 ml. The RLD is supplied in the following dosage forms: 30 ml aluminum tube, 5 ml plastic tube, 10 ml and 20 ml polypropylene syringes (no preservatives)

4. Lidocaine Hydrochloride 2% Jelly is a DESI-effective (pre-1962) non-solution topical product. Under the current regulations, a waiver cannot be granted for any non-solution topical drug products. On 9/18/01, OGD management decided to treat newly submitted applications for pre-1962 non-solution topical drug products on a case-by-case basis. Since waivers of in vivo testing do not apply to non-solution topical products, the regulation 21 CFR 320.24 (b) (6) should be cited for the determination of bioequivalence for pre-62 non-solution topical products. See attached OGD Division Director (DBE) meeting minutes for details (Attachment 4).

5. This reviewer noted that the formulation of RLD listed in COMIS database is incorrect. Based on the current Annual Report (January 4, 2001) submitted to NDA # 8816, the correct components and compositions of the RLD formulation are shown below:

Ingredients	^Reference: Xylocaine^R 2% Jelly, per ml (tubes)	Test: Lidocaine HCl 2% Jelly, USP, per ml (tubes)
Lidocaine hydrochloride	20 mg	20 mg
Methylparaben	[redacted]	[redacted]
Propylparaben		
Hydroxypropyl methylcellulose		
Sodium hydroxide	Adjust pH to 6.0-7.0	Adjust pH to 6.0-7.0
Hydrochloric acid	Adjust pH to 6.0-7.0	Adjust pH to 6.0-7.0
[redacted]		

^NDA # 8816 Annual Report, 5 ml and 30 ml tubes

The test product is qualitatively and quantitatively the same as the RLD.

III. Comments

1. The approved RLD label states Xylocaine^R 2% Jelly as "a sterile aqueous product". The OGD Chemistry Team Leader, Division II, confirmed that this product is not a solution. Therefore, the firm cannot claim that this product is an aqueous solution based on the RLD label without any further supportive information.

2. Based on the OGD management decision of 9/18/01, the DBE deems this DESI effective non-solution topical product, Lidocaine Hydrochloride 2% Jelly, USP, bioequivalent to Xylocaine^R 2% Jelly under 21 CFR 320.24 (b) (6).

IV. Recommendations

1. The Division of Bioequivalence does not agree that the information submitted by Akorn Inc. demonstrates that Lidocaine Hydrochloride 2% Jelly, USP, 5 ml, (b) (4) (b) (4) and 30 ml tubes, falls under 21 CFR section 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations.

2. The Division of Bioequivalence deems that the DESI-effective non-solution topical product, Lidocaine Hydrochloride 2% Jelly, USP, bioequivalent to Xylocaine^{R} 2% Jelly under 21 CFR section 320.24 (b) (6). It is not necessary that the firm conduct an *in vivo* bioequivalence study as previously suggested in the Agency's response dated July 30, 2001 at this time.

The firm should be informed of the above recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT
for FT INITIALLED BY BDAVIT

Date:_____

Concur:

Date: 11/16/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride 2% Jelly, USP

The Division of Bioequivalence has completed its review and has the following comments.

The Division of Bioequivalence has determined that your product is bioequivalent to Xylocaine^{R} 2% Jelly under 21 CFR section 320.24 (b) (6) since it is a DESI-effective product. Therefore, it is not necessary to conduct an *in vivo* bioequivalence study as previously suggested in the Agency's response dated July 30, 2001.

The Division has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #40433
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim CK 10/19/01
for HFD-658/ Bio team Leader B. Davit MHM
HFD-650/ S. Mazzella
HFD-650/ D. Conner DTC 11/16/01

BIOEQUIVALENCY -ACCEPTABLE Submission date: 8/10/01

1. Study Amendment (STA) **Strengths: 2%**

Outcome: AC

Outcome Decisions: **AC** - Acceptable

Attachment #1

-----Original Message-----
From: Hare, Donald B
Sent: Tuesday, May 01, 2001 4:16 PM
To: Kim, Carol Y
Subject: RE: Is lidocaine DESI drug?

Carol:

Lidocaine Jelly NDA 8861, is a DESI effective drug product.

Don

Attachment #2

Bio Management Meeting
June 7, 2001

Dale Conner, Rabindra Patnaik, Yi-Chain Huang, Shriniwas Nerurkar, Barbara Davit, Lizzie Sanchez

1.

(b) (4)

2.

3. **Lidocaine 2% Jelly:** Carol is reviewing an ANDA for this protocol A waiver of in-vivo testing was requested. The product is not Q2 the same. Jelly is not considered a solution. A product by Copley was waived in 1990. A medical consult should also be requested for this product. The history of the EMLA product should be considered. The clinical division agreed that a PK study would be sufficient to establish BE.

4.

(b) (4)

5.

6.

7.

8. (b) (4) [redacted]

Drafted: L. Sanchez 6/13/01

Attachment #3

MEDICAL OFFICER REVIEW

July 6, 2001

ANDA 40-433
Drug Product: Lidocaine HCl 2% Jelly
Sponsor: Akorn, Inc.

The Division of Bioequivalence has reviewed a protocol for a bioequivalence study based on pharmacokinetic measurements. They have enquired whether this will suffice for the bioequivalence assessment or if a bioequivalence study with clinical endpoints is required.

The final review for two related products containing lidocaine and applied topically is appended. The final recommendation is that a standard bioequivalence study should be relied on to demonstrate bioequivalence of the generic drug product to the reference listed drug. In addition, because of the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products could be evaluated during the standard bioequivalence study. The following parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

Mary Fanning, MD, PhD
Associate Director for Medical Affairs
Office of Generic Drugs

MEDICAL OFFICER REVIEW

October 10, 2000

CD #00-236

Drug Product: Lidocaine and Prilocaine
Sponsor: (b) (4)
Reference Listed Drug: EMLA ® cream and patch

And

Protocol 00-022

Drug Product: Lidocaine 2.5% and Prilocaine 2.5%
Sponsor: HiTech Pharma
Reference Listed Drug: EMLA ® cream and patch

HFD-170 was consulted about these two inquiries on bioequivalence studies for the generic equivalent of EMLA ® cream and patch. The Division concluded that a standard bioequivalence study of the 60 mg dose could be used to determine bioequivalence of the generic drug product. In addition, they indicated that the proposed clinical endpoint study submitted by (b) (4) was acceptable if OGD decided that a clinical endpoint study was necessary. Should we make that recommendation, they suggested that the sponsor should submit a protocol for review prior to undertaking the study. The Division did not address the question on the skin irritation evaluation.

Recommendation: The Sponsors should be informed that a standard bioequivalence (pharmacokinetic) study should be conducted using the 60 mg dose in order to evaluate the generic drug product's bioequivalence to the reference listed drug. Because of the high rate of local skin reactions, the comparability of local skin reactions for the reference and generic products could be evaluated during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

Mary M. Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Attachment #4

Division of Bioequivalence Director's Meeting

September 18, 2001

Attending: G. Buehler, Bob West D. Conner, R. Patnaik, Lizzie Sanchez, Cecelia Parise, Donald Hare, Barbara Davit, Carol Kim

1. (b) (4)

2. Lidocaine Topical Jelly, 2%. This is a DESI drug and is rated AT. This means that in vivo bioequivalence studies were waived for pre-62 topical drug products. Should a waiver of in vivo bioequivalence continue to be granted for non-solution pre-1962 topical products? A gel is not a solution and does not "fit" under the current waiver regulations. Bioequivalence for topical lidocaine can be demonstrated through a pharmacokinetic study.

   All Pre 1962 topical drugs products were eligible for waivers of in vivo bioequivalence. The regulations in place at the time indicated that the Agency shall grant a waiver for these topical products. Post 1962 non- solution topical drugs are not eligible for waivers of in vivo studies. If OGD and the Division of Bioequivalence decide that pre 1962 topical products require bioequivalence studies, then it will have to request bioequivalence studies for all pre 1962 non-solution topical products that have been approved. This would be a major undertaking, and would most likely require some type of notice to industry. The present product under discussion is qualitatively the same and has some minor quantitative differences in (b) (4). However, these differences are not believed to impact bioequivlence. If an inactive ingredient such as propylene glycol were sufficiently different, such that it may impact absorption of the active ingredient, then the product may need an in vivo study or would have to be reformulated. If the agency believes that there is good reason to require a bioequivalence study for a product that normally would be eligible for a waiver of in vivo studies it can invoke 21 CFR 320.22(f).

   The decision was made to treat newly submitted applications for pre-1962 topical drug products on a case-by-case basis. The regulation 21 CFR 320.24(b)(6) should be cited for the determination of bioequivalence when reviewing pre-62 topical products, since topical products that are not solutions cannot be "waived" under the current regulations. A waiver under 21 CFR 320.22(e) is not appropriate since there is no public health need for this product.

   A similar situation exists for Erythromycin 2% topical Gel. This product is not a pre-1962 drug product, but is an antibiotic that was formerly regulated under section 507 of the Act and was approved prior to the implementation of the Waxman-Hatch regulations. This product is rated AT also. It was also determined that since agency did not require an in vivo bioequivalence studies for this product in the past, this practice will continue. The same regulation should be cited for the determination of bioequivalence for this product since it does not fall under the "waiver" provisions (21 CFR 320.24(b)(6)). In addition, if the Division of Bioequivalence believes that there are sufficient reasons not to approve this product without in vivo studies the Division may request that the firm submit an in vivo bioequivalence study, or reformulate the product, whichever is the more suitable option.

3.

4.

5.

6.

7.

q:\division\meet\01-09-18
CParise 10/15/01

Please file in NDA 40-433 4.1 - Medical

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 40-433 (Amendment) SPONSOR : Akorn, Inc.

DRUG AND DOSAGE FORM : Lidocaine Hydrochloride 2% Jelly, USP

STRENGTH(S) : 2%

TYPES OF STUDIES : STF SSTP STM OTHER X

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: N/A

Formulation is acceptable.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : CYK DATE : 10/19/01

TEAM LEADER : Barbara M. Davit BRANCH : 3

for INITIAL : mHm DATE : 10/19/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 11/16/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-640

20 March 2002

ANDA: 40-433

Drug Product Name
Proprietary: N/A
Non-proprietary: Lidocaine HCl 2% jelly, USP
Drug Product Classification: Anesthetic

Review Number: 1

Subject of this Review
Submission Date: 3-9-01
Receipt Date: 3-13-01
Consult Date: N/A
Date Assigned for Review: February 28, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Akorn, Inc.
Address: 1222 West Grand Ave.
Decatur, IL 62522
Representative: James G. Baumann, Jr.
Telephone: 217-423-9715

Name of Reviewer: Marla Stevens-Riley

Conclusion: Not Recommended

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR: N/A**

3. **MANUFACTURING SITE:** Akorn, Inc.
72-6 Veronica Avenue
Somerset, NJ 08873

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lidocaine HCl is a jelly packaged in an aluminum tube at a concentration of 2% and applied topically.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** anesthetic for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:**
The subject drug product Lidocaine HCl jelly 2% USP is manufactured in Somerset, NJ. The subject drug product is sterilized by (b) (4) (b) (4).

filename: microrev\40-433.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - not recommended

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The subject drug product is sterilized by [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies - In-process validation is not complete.

C. Assessment of Risk Due to Microbiology Deficiencies -minor

III. Administrative

A. Reviewer's Signature Maila Stevens-Riley

B. Endorsement Block

M. Stevens-Riley, Ph.D. 3/29/02
L. Ensor, Ph.D. L Ensor 4/2/02

C. CC Block

cc:
Original ANDA 40-433
HFD- 600 v:microrev\40-433.doc

Following this page, 17 pages withheld in full (b)(4)

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA:40-433 APPLICANT: Akorn

DRUG PRODUCT: Lidocaine HCl Jelly 2% USP

A. Microbiology Deficiencies:

1. Please briefly describe the airflow, pressure differentials, and personnel flow within the manufacturing facility.

2. Please indicate the maximum production sterilization cycle parameters for [redacted] (b) (4)

3. Please clarify your maximum sterile [redacted] (b) (4)

4. With regard to validation of the [redacted] (b) (4) (b) (4):

   a. [redacted] (b) (4)

   b.

   c.

   d.

   e.

f. (b) (4)

g.

h.

5. With regard to validation of the sterilization of the (b) (4) (b) (4)

a. (b) (4)

b.

c.

d.

e.

f.

g. (b) (4)

h.

6. With regard to validation of sterilization of (b) (4)

a. (b) (4)

b.

c.

7. With regard to the sterilization of the container-closure system:

a. (b) (4)

b.

8. With regard to the media fills:

a. (b) (4)

b. (b) (4)

c.

d.

e.

9. Please state the (b) (4)

10. With regard to the container/closure integrity testing: please indicate the sensitivity of (b) (4) and describe how the sensitivity was measured.

11. Please explain the difference between SOP 73-073-00 (referenced for the sterility test in the stability protocol Vol. 1.2, p. 741) and SOP 72-073-00 (referenced for the sterility test in the "Sterility Testing Methods and Release Criteria Vol. 1.3, p. 316).

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You should consider incubating both the bulk bioburden sample of the Active phase of the subject drug product and the media filled units under aerobic conditions due to the composition of the product as a gel.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Farming, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

Product Quality Microbiology Review
Review for HFD-640

5 August 2002

ANDA: 40-433

Drug Product Name
Proprietary: Xylocaine 2%
Non-proprietary: Lidocaine HCl 2% jelly, USP
Drug Product Classification: N/A

Review Number: 2

Subject of this Review
Submission Date: June 6, 2002
Receipt Date: June 14, 2002
Consult Date: N/A
Date Assigned for Review: July 31, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): March 9, 2002
Date(s) of Previous Micro Review(s): March 20, 2002

Applicant/Sponsor
Name: Akorn, Inc.
Address: 1222 West Grand Ave.
Decatur, IL 62522
Representative: James G. Baumann, Jr.
Telephone: 217-423-9715

Name of Reviewer: Marla Stevens-Riley

Conclusion: Not recommended for approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR: N/A**

3. **MANUFACTURING SITE:** Akorn, Inc.
72-6 Veronica Avenue
Somerset, NJ 08873

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lidocaine HCl is a jelly packaged in an aluminum tube at a concentration of 2% and applied topically.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** anesthetic for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The subject amendment provides responses to the Microbiology deficiencies in the letter dated April 3, 2002.

filename: microrev\40-433a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –Not recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –Incomplete responses to microbiology deficiencies.

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with these deficiencies is low.

III. Administrative

A. Reviewer's Signature M. Stevens-Riley

B. Endorsement Block

M. Stevens-Riley, Ph.D. 8/16/02
N. Sweeney, Ph.D.
Neal Sweeney
8/22/02

C. CC Block

cc:
Original ANDA 40-433
Division file
Field Copy

Following this page, 13 pages withheld in full (b)(4)

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA:40-433 APPLICANT: Akorn

DRUG PRODUCT: Lidocaine HCl Jelly 2% USP

A. Microbiology Deficiencies:

1. Please provide the most recent requalification data for the (b) (4) (b) (4)

2. Please clarify if the parameters that were established in 1993 are those currently used for the requalification of the (b) (4) (b) (4)

3. Please indicate if the same lot of BI was used for the 90 minute and 180 minute (b) (4)

4. Please clarify the response to deficiency 5d and provide document PD00-010. In addition, please indicate (b) (4)

5. Please provide the most recent revalidation data of the sterilization cycle for (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please note that (b) (4)

2. Please note that the contact time of the drug product with (b) (4)

3. Please note that the spore population and D-value should be confirmed prior to use.

4. Please consider including in the media fill requalifications an increase in the duration of at least one run to last for the maximum production duration or consider performing the media fills immediately after a production run without cleaning or sterilization of the filling equipment.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

Product Quality Microbiology Review
Review for HFD-640

25 November 2002

ANDA: 40-433

Drug Product Name
Proprietary: Xylocaine 2%
Non-proprietary: Lidocaine HCl 2% jelly, USP
Drug Product Classification: N/A

Review Number: 3

Subject of this Review
Submission Date: November 13, 2002
Receipt Date: November 14, 2002
Consult Date: N/A
Date Assigned for Review: November 19, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): March 9 and June 6, 2002
Date(s) of Previous Micro Review(s): March 20 and August 5, 2002

Applicant/Sponsor
Name: Akorn, Inc.
Address: 1222 West Grand Street
Decatur, IL 62522
Representative: Ambareen Sheriff
Telephone: 847-353-4929

Name of Reviewer: Marla Stevens-Riley

Conclusion: Not recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: N/A

2. SUPPLEMENT PROVIDES FOR: N/A

3. MANUFACTURING SITE: Akorn, Inc.
72-6 Veronica Avenue
Somerset, NJ 08873

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lidocaine HCl is a jelly packaged in an aluminum tube at a concentration of 2% and applied topically.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: anesthetic for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The subject amendment provides responses to the Microbiology deficiencies in the letter dated November 7, 2002.

filename: microrev\40-433a2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –Not recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –Incomplete responses to microbiology deficiencies.

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with these deficiencies is low.

III. Administrative

A. Reviewer's Signature Maila Stevens-Riley

B. Endorsement Block

M. Stevens-Riley, Ph.D. 12/3/02
N. Sweeney, Ph.D. Neal J. Sweeney 12/3/02

C. CC Block

cc:
Original ANDA 40-433
Division file
Field Copy

Following this page, 4 pages withheld in full (b)(4)

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA:40-433 APPLICANT: Akorn

DRUG PRODUCT: Lidocaine HCl Jelly 2% USP

A. Microbiology Deficiencies:

1. Please explain why [redacted] (b) (4)

2. Please indicate the [redacted] (b) (4)

3. Please indicate the [redacted] (b) (4)

4. Please provide complete BI information for the most recent sterilization revalidation of the [redacted] (b) (4). The information should include the manufacturer, lot number, and expiry.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please clarify the response. In the June 6, 2002 amendment, it is stated that there are currently [redacted] (b) (4) running to fill the entire batch. In addition, it was indicated that the duration of the media fill runs was between [redacted] (b) (4).

2. For future applications, please provide complete BI information. This would include the manufacturer, the lot number, the expiry, the D-value,

the population, confirmation of the population, and confirmation of the D-value when the BI is in suspension.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Neal J. Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

Product Quality Microbiology Review
Review for HFD-640

30 December 2002

ANDA: 40-433

Drug Product Name
Proprietary: Xylocaine 2%
Non-proprietary: Lidocaine HCl 2% jelly, USP
Drug Product Classification: N/A

Review Number: 4

Subject of this Review
Submission Date: December 11, 2002
Receipt Date: December 12, 2002
Consult Date: N/A
Date Assigned for Review: December 17, 2002

Submission History (for amendments only)
Date(s) of Previous Submission(s): March 9, 2002, June 6, 2002, and November 13, 2002
Date(s) of Previous Micro Review(s): March 20, 2002, August 5, 2002, and November 25, 2002

Applicant/Sponsor
Name: Akorn, Inc.
Address: 1222 West Grand Street
Decatur, IL 62522
Representative: Ambareen Sheriff
Telephone: 847-353-4929

Name of Reviewer: Marla Stevens-Riley

Conclusion: Recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: N/A

2. SUPPLEMENT PROVIDES FOR: N/A

3. MANUFACTURING SITE: Akorn, Inc.
72-6 Veronica Avenue
Somerset, NJ 08873

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lidocaine HCl is a jelly packaged in an aluminum tube at a concentration of 2% and applied topically.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: anesthetic for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The subject amendment provides responses to the Microbiology deficiencies in the letter dated December 11, 2002.

filename: microrev\40-433a3.doc

Executive Summary

I. Recommendations

B.)m c 2/14/03

A. Recommendation on Approvability –~~Not~~ recommended for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies –none

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with this product is minimal.

III. Administrative

A. Reviewer's Signature Marla Stevens-Riley

B. Endorsement Block
M. Stevens-Riley, Ph.D. 12/31/02
N. Sweeney, Ph.D.
Mad Sweeney
12/31/02

C. CC Block
cc:
Original ANDA 40-433
Division file
Field Copy

Following this page, 4 pages withheld in full (b)(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040433Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Akorn inc.
Ophthalmic and Parenteral Health Care

0 S. Wyckles Road • Decatur, IL 62522
Grand Avenue Facility
217-423-9715 • Fax: 217-428-8514

505(b)(2)(A) OK
20-APR-2001

March 9, 2001

Office of Generic Drugs, CDER, FDA
Metro Park North II, **HFD-600**
7500 Standish Place
Rockville, MD 20855-2773

RE: ABBREVIATED NEW DRUG APPLICATION
LIDOCAINE HYDROCHLORIDE 2% JELLY USP

Dear Ladies and Gentlemen:

In accordance with 21 CFR § 314.92 (a)(1), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Abbreviated New Drug Application for Lidocaine Hydrochloride 2% Jelly USP, a prescription drug product indicated for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal). The reference listed drug (RLD) is Xylocaine® 2% Jelly, NDA 8-816 and is held by Astra USA, Inc. The suitability of the ANDA is documented in the submission.

To support this ANDA one (1) [(b) (4)] batch ***(batch # PD00010)*** was compounded and split-filled into [(b) (4)] aluminum tube sizes (5 mL, [(b) (4)] and 30 mL). All operations during the manufacture of the Lidocaine Hydrochloride 2% Jelly USP stability batch were performed by production personnel according to established cGMPs and were monitored by Quality Assurance (QA) personnel, using established production equipment. All material used was released by the Quality Control (QC) laboratory according to established specifications and procedures. The stability study for Lidocaine Hydrochloride 2% Jelly USP was performed in the marketed container/closure systems.

The formulation ingredients, both active and inactive, are the same for Lidocaine Hydrochloride 2% Jelly USP and the reference listed drug (RLD), Xylocaine® 2% Jelly and, therefore, meet the criteria for wavier of evidence of in vivo bioavailability or bioequivalence as per 21 CFR § 320.22 (b)(3)(i), (ii), and (iii). In addition, the inactive ingredient concentrations for Lidocaine Hydrochloride 2% Jelly USP were optimized during development to be the same (± 5%) as those for the RLD, in order to qualify the subject product for the ANDA interim and bioequivalence waiver per the Interim Inactive Ingredient policy issued by Doug Sporn, OGD, in a memo dated November 17, 1994.

This ANDA for Lidocaine Hydrochloride 2% Jelly USP is contained in three (3) volumes and is organized in the manner recommended by the Office of Generic Drugs in its Policy and Procedure Guide 30-91 and the "Guidance for Industry" document on the organization of an ANDA and ANDA issued by OGD in April, 1997. **At this time, Akorn requests approval for Lidocaine Hydrochloride 2% Jelly USP manufactured according to the attached documentation, using Lidocaine Hydrochloride manufactured by** [redacted] (b) (4) **and packaging components manufactured by** [redacted] (b) (4) **. An expiration dating period of twenty four months is requested, based on three months acceptable stability data from stability batches stored at accelerated stability conditions.**

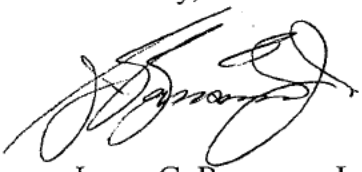
This submission contains sterility assurance data. Akorn, Inc. is providing sterility assurance information, including documentation for the validation for Lidocaine Hydrochloride 2% Jelly USP *Volume 3* of this application. The sterility assurance information is organized according to the directives presented in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (November, 1994).

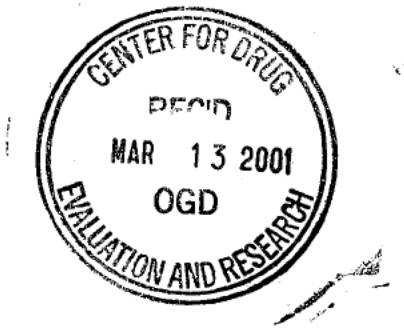
Akorn is filing an archival copy (in blue folders) of the ANDA, a technical review copy (in red folders), and a field copy (in maroon folders) sent to the FDA Newark District Office. The technical review and field copies are identical to the archival copy and a certification attesting to this is provided with the field copy.

In accordance with 21 CFR § 314.94 (d)(5), and by reference 314.50 (k)(3), Akorn, Inc. certifies that a true copy of this Abbreviated Drug Application for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office. A copy of this certification with an original signature is provided with this application.

Should additional information be required, please feel free to contact me at (217) 423-9715 or FAX (217) 423-5206.

Sincerely,





James G. Baumann, Jr.
Manager, Regulatory Submissions

cc: Lou Fraser (Akorn, Inc.)

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

ANDA# 40-433 FIRM NAME Akorn Inc

RELATED APPLICATION(S) N/A

DRUG NAME: Lidocaine HCl

DOSAGE FORM: Jelly USP, 2%

FIRST GENERIC? N/A

Electronic Submission (Chem) ✓ E-mail notification sent ✓

Team Leader Glen Smith

Labeling Reviewer Chan Park 6/1/A

Random Assignment RN9

Micro Reviewer MICRO yes

Pharmacodynamic study (Dr. Fanning) N/A

Letter Date 3/9/2001 Received Date 3/13/2001

		YES	NO
	Comments EC1 ✓ On Cards ✓ Therapeutic Code 6040400 anesthetic/Topical	✓	
	Methods Validation Package (3 copies) NO (Required for Non-USP drugs)		✓
	Archival, and Review copies Field copy certification (original signature) ✓	✓	
	Cover Letter ✓	✓	
	Table of Contents ✓	✓	

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status)	✓	
Sec. II	**Basis for Submission** NDA 8-816 RLD x Xylocaine Firm astra USA, ✓ Inc Is an ANDA suitability petition required? No If yes, consult needed for pediatric study requirement.	✓	
Sec. III	**Patent Certification** 1. Paragraph? I ✓ 2. Expiration of Patent N/A A. Pediatric Exclusivity Submitted? N/A B. Pediatric Exclusivity Tracking System checked? N/A	✓	
	Exclusivity Statement ✓	✓	
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	✓	
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓	✓	
Sec. VI	**Bioavailability/Bioequivalence** 1. Financial certification (Form FDA 3454)_____ and Disclosure statement (Form 3455)_____ (for BE studies only!) 2. In Vivo Study Protocol(s)_____ 3. In Vivo Study(ies)_____ 4. Computer Disk Submitted_____ 5. Request for Waiver of In Vivo Study(ies) ✓✓ (pg 130) 6. In Vitro Dissolution Data_____ 7. Formulation Data Same? (Comparison of all Strengths)_____ (b) (4) (Ophthalmics, Otics, Externals, Parenterals) 8. Paragraph IV bio study acceptable for filing N/A 9. Lot numbers of products used in Bio-study_____ 10. DSI inspection request needed?_____ 1st Generic_____ 1st study for site_____ Other_____ E-mail notification to bio PMs sent_____		

~~Will Bio waiver be O.K. b/c use~~ (b) (4) ~~mat of~~ (b) (4)

Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate ✓ Alkaid uses (b) (4) the amount of (b) (4) as the RLD. These Amnts justify in comrs for topical route of admin	✓	
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis DMF (b) (4) ✓ c. Certificate(s) of analysis specifications and test results from drug substance manufacturer(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers_____ 2. **Inactive Ingredients** a. Source of inactive ingredients identified ✓ (pg 154) b. Testing specifications (including identification and characterization) ✓ (missing specs for HCl & NaOH) c. Suppliers' certificates of analysis (specifications and test results) ✓ d. Applicant certificate of analysis ✓	✓	
Sec. IX	**Description of Manufacturing Facility** 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing ✓ 2. CGMP Certification ✓ (pg 212) 3. CFN numbers_____	✓	
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ✓ 4. CFN numbers_____ (No CGMP from (b) (4) however this firm is solely sterilizing the opthalmic tray tubes)	✓	
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with Equipment Specified ✓ (mfg setup (b) (4) on page 233) 3. If sterile product: (b) (4) (b) (4) 5. Reprocessing Statement ✓ (pg 309) (b) (4) Sampling (b) (4) from top, middle, & bottom of tray (b) (4)	✓	

Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓	✓	
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and supplier's address ✓	✓	
Sec. XIV	**Controls for the Finished Dosage Form** 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. Certificate of Analysis for Finished Dosage Form ✓	✓	
Sec. XV	**Stability of Finished Dosage Form** (this is an aqueous soln ∴ humidity not reqd for stability testing. Also see pg 742 = cartons stored in impermeable containers) 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on Stability records the same as the test batch ✓ (test batch split into lots for stability) All accelerated stability test performed in both vertical & horizontal position	✓	
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	✓	
Sec. XVII	**Environmental Impact Analysis Statement** PD00010	✓	

(b) (4)

Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) _____ 2. Debarment Certification (original signature) ✓ 3. List of Convictions statement (original signature) ✓	✓	

Reviewing CSO/CST MARTIN SHINNER Date _____

Recommendation: (FILE) REFUSE to FILE

Supervisory Concurrence/Date [signature] 20-APR-2001

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD _____ for consult

Type of consult:

Comments regarding the ANDA: (http://forms.psc.gov), FDA, 356h

J.K. 356h should read ~~AUTHORIZATION~~ & should be most recent revision of 356h

OK MWS Revise Debarment statement to certify that this application for Withdrawal; current statement lists application as being for Bacitracin Ophthalmic Ointment (incorrect).

- (b) (4) O.K. / MARIA PILAR STEVENS 4-9-01

See Chemistry review 81-246 this contains a comprehensive review of this ANDA

4-9-01

This is classified as a topical Aqueous product that must be qualitatively the same as the RLD according to 21CFR 314.94

However this product is not required to be quantitatively the same. The applicant makes a statement on pg 130

that the applicant product utilizes the same concentration of inactive ingredients ~~(or experimentally determined)~~ as the RLD Kyloceine. This is not the case according to Comis. The conc of both (b) (4) used in the Applicants product are (b) (4) than the RLD. These concentrations of (b) (4) do justify in COMIS though.

Akorn inc.
Ophthalmic and Parenteral Health Care

30 S. Wyckles Road • Decatur, IL 62522
Grand Avenue Facility
217-423-9715 • Fax: 217-428-8514

Amber Scherff -
1-847-353-4926

NEW CORRESP

April 12, 2001

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TELEPHONE AMENDMENT TO ANDA 40-433
Lidocaine Hydrochloride 2% Jelly USP

Dear Ladies and Gentlemen:

In accordance with 21 CFR § 314.96 (a)(1), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Telephone Amendment to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP.

This amendment is in response to the teleconference on April 10 and 11, 2001 between FDA and Akorn regarding two (2) items submitted in the original application requiring correction as follows:

- **The copy of the Generic Drug Enforcement Act: Certification Statement contained reference to "Bacitracin Ophthalmic Ointment USP" instead of the subject drug product "Lidocaine Hydrochloride 2% Jelly USP."**

  Akorn has noted the typographical error in the drug product name and is providing a revised signed copy ***(appended)*** of the **Generic Drug Enforcement Act: Certification Statement** containing the correct name of the subject drug product.

- **The correct referenced listed drug (RLD) for the subject drug product is "Astrazeneca" and not "Astra USA, Inc." This should be revised on the Form FDA 356h for this product.**

  As requested, Akorn has corrected the RLD on the 356h form ***(appended)*** to reflect the name "Astrazeneca Pharmaceuticals" in lieu of the name "Astra USA, Inc."

Akorn is filing an archival copy *(original)* of this amendment and a technical review copy *(duplicate)* which is identical to the archival copy. An additional certified field copy was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Telephone Amendment to our Abbreviated New Drug Application for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment ***(appended).***

Should additional information be required regarding this amendment, please feel free to contact me at (217) 423-9715 or FAX (217) 423-5206.

Sincerely,

James G. Baumann, Jr.
Manager, Regulatory Submissions

cc: Lou Fraser (Akorn)

ANDA 40-433

Akorn, Inc.
Attention: James G. Baumann, Jr.
1222 West Grand Avenue
Decatur, IL 62522

APR 24 2001

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated April 11, 2001 and your correspondence dated April 12, 2001.

NAME OF DRUG: Lidocaine Hydrochloride Jelly USP, 2%

DATE OF APPLICATION: March 9, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 13, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

Gregory D. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40433
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB _____ date 20-APR-2001
HFD-615/MShimer, CSO _____ date 4/19/01
Word File V:\Firmsam\Akorn\ltrs&rev\40433.ack
F/T EEH 04/19/01
ANDA Acknowledgment Letter!

MINOR AMENDMENT

ANDA 40-433

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 27 2001

TO: APPLICANT: Akorn, Inc. TEL: 217-423-9715

ATTN: James G. Baumann, Jr. FAX: 217-423-5206

FROM: Kassandra Sherrod PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 9, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Hydorchloride Jelly USP, 2%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (7 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry and labeling deficiencies

JUN 27 2001

38. Chemistry comments to be provided to the Applicant

ANDA: 40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride Jelly USP, 2%

The deficiencies presented below represent Minor deficiencies.

Deficiencies:

1. We recommend that you identify [redacted] (b) (4)

2. Please include information regarding the function of each ingredient in the formulation under Components and Composition.

3. Please provide a copy of [redacted] (b) (4)

4. Please provide a validated method for the quantitation of [redacted] (b) (4).

5. We notice that a [redacted] (b) (4)

6. On page 238, [redacted] (b) (4)

7. On page 320, you have indicated [redacted] (b) (4)

8. Page 326 indicates that [redacted] (b) (4)

9. Please clarify your statement on page 309 regarding, [redacted] (b) (4)

10. Please clarify if tubes are [redacted] (b) (4)

11. The DMF holder [redacted] (b) (4) letter on page 482 indicates that the Aluminum tubes are [redacted] (b) (4)

12. Please provide composition information on the [redacted] (b) (4).

13. We notice your statement that the tube and cap are one integral unit. Are they sterilized as a unit together? Are any glues used for crimping?

14. We notice that a detachable applicator cone and a key for expressing the contents are included in the 30 mL tube label section. However, there is no supporting composition, test data, COA and manufacturer/DMF information provided

in the ANDA under Container/Closure section. Please address this issue. Also, address how the other packages will deliver the dose without an applicator cone.

15. Please provide a listing of known degradation products of Lidocaine Hydrochloride. Also, include copies of chromatograms (initial and selected stability test stations) where degradants are observed for review.

16. In case of dispute the USP method will be deemed as the regulatory method even though the proposed methodology is quantitating Lidocaine from its degradants and excipients. Please provide an acknowledgement regarding this.

17. We request that you modify the [redacted] (b)(4)

18. Please update the ambient stability data available for the past 3 months, for all configurations.

Chemistry Comments:

1. Please compare the RLD stability data with that of the ANDA product, as per your methods.

2. DMF [redacted] (b)(4) is inadequate. Deficiencies in the DMF would have to be corrected prior to ANDA approval.

Sincerely yours,

for Vilayat Sayed

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

ANDA 40-433

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

30 2001

TO: APPLICANT: Akorn, Inc. TEL: 217-423-9715

ATTN: James G. Baumann, Jr. FAX: 217-423-5206

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 9, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Hydrochloride Jelly USP, 2%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

C YR

A.1

JUL 30 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: #40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride 2% Jelly, USP

The Division of Bioequivalence has completed its review. The following deficiencies have been identified:

1. A waiver cannot be granted for non-solution topical products under 21 CFR 320.22.

2. Please conduct an *in vivo* bioequivalence study based on pharmacokinetic endpoints to compare your proposed product to the reference listed drug, Xylocaine® 2% Jelly.

3. Due to the high rate of local skin reactions, the comparability of local skin reactions for the reference and your products should be evaluated. This can be accomplished during the standard bioequivalence study. The following skin parameters should be compared: pallor or blanching, erythema, alteration in temperature sensation, edema, and skin rash for intensity and time to resolution.

4. It is recommended that you submit your proposed protocols to the Office of Generic Drugs for review prior to study initiation.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Akorn inc.
Ophthalmic and Parenteral Health Care

50 S. Wyckles Road • Decatur, IL 62522
217-428-1100 • Fax: 217-422-9048

August 10, 2001

N/AB

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: BIOEQUIVALENCY AMENDMENT TO ANDA 40-433
Lidocaine Hydrochloride Jelly USP 2%

Dear Ladies and Gentlemen:

We wish to amend our pending application ANDA 40-433 in response to the Agency letter, dated July 30, 2001 ***(see Attachment A)*** regarding the request for an *in-vivo* bioequivalence study.

Akorn would like to make the following comments in regards to the initial request for a wavier of a bioequivalence study as permitted by 21 CFR § 320.22.

Please note that Lidocaine Hydrochloride Jelly USP 2% is defined in the proposed labeling, per the RLD ***(see Attachment B)*** as a sterile, aqueous solution of lidocaine hydrochloride, hydroxpropylmethylcellulose, methyl- and propylparaben. The product is filled in various packaging sizes and the contents are defined in mL as indicated in the attached labeling. The drug product contains the active and inactive ingredients, which are soluble in water. Additionally, per the inactive ingredient guide, hydroxypropylmethylcellulose is listed as an inactive ingredient approved for a topical solution. Although the product is somewhat viscous, by definition it is still an aqueous solution and imparts the physicochemical properties of a solution. The active ingredient, lidocaine hydrochloride, and (b) (4) methyl- and propylparaben are (b) (4) (b) (4)

Since the above referenced drug product is a topically applied aqueous solution intended for local therapeutic effect and contains both qualitatively and quantitatively the identical active and inactive ingredients as the reference listed drug product Xylocaine 2% Jelly, manufactured by Astra, we are of the opinion that the proposed drug product meets the requirements of ***21 CFR § 320.22(b)(3)(i)(ii)(iv)*** and that the in vivo bioequivalency

study may be simply unnecessary for the drug product in order to achieve its intended purpose.

Additionally, Lidocaine Hydrochloride Jelly USP 2% is considered therapeutically equivalent, therefore, it is coded AT in the Orange Book ***(see Attachment C).***

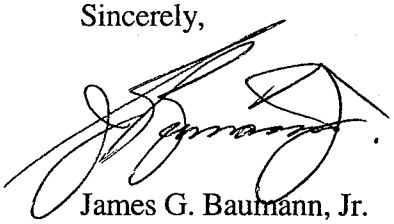
Based on the foregoing, Akorn Inc. is hereby requesting that the requirement to demonstrate bioequivalency be waived for Lidocaine Hydrochloride Jelly USP 2%.

Akorn is filing an archival copy *(original)* of the amendment, a technical review copy *(duplicate),* and a field copy sent to the FDA Newark District Office. The technical review and field copies are identical to the archival copy and a certification attesting to this is provided with the field copy.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Bioequivalency Amendment to our Abbreviated Drug Application for Lidocaine Hydrochloride Jelly USP 2% has been provided to the FDA Newark District Office. A copy of this certification with an original signature is provided as ***Attachment D.***

Should additional information be required, please feel free to contact me at (217) 423-9715 or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

cc: Shahid Ahmed (Akorn, Inc., Decatur, IL
Abu Alam (Akorn, Inc., Buffalo Grove, IL)

Akorn inc.
Ophthalmic and Parenteral Health Care

0 S. Wyckles Road • Decatur, IL 62522
.and Avenue Facility
217-423-9715 • Fax: 217-428-8514

initial 2/25/02

February 12, 2002

Chemistry/Labeling

ORIG AMENDMENT
N/A M.

The Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MINOR AMENDMENT TO ANDA 40-433
Lidocaine Hydrochloride 2% Jelly, USP

Dear Sir:

In accordance with 21 CFR § 314.96 (a), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits response to the Minor Amendment to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP.

Form 356h is provided in **Attachment 1.**

Attached is a written response to the deficiency items listed in the FDA Minor Amendment dated June 27, 2001.

Additionally, in accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Minor Amendment to our Abbreviated Drug Application for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office.

Should additional information be required, please feel free to contact me at (217) 423-9715, ext 173, or via FAX at (217) 423-5206.

Sincerely,

Shahid Ahmed
Vice President, Regulatory Affairs, QA, QC

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 15 2002

RECORD OF TELEPHONE CONVERSATION

The sponsor submitted an amendment to this original application on 2/12/02. However, we note that the sponsor did not make point to point responses to the labeling comments. The sponsor has proposed (b) (4) [redacted]. I called the firm and asked that they make response to our labeling comments, regarding the packaging configuration in particular and submit as an amendment. Mr. Ahmend stated that they would do as directed.

Chan

V:\FIRMSAM\AKORN\TELECONS\40433April.2002.doc

DATE April 3, 2002

ANDA 40-433

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR X FDA

MADE X BY TELE. _ IN PERSON

PRODUCT NAME
Lidocaine HCL Jelly, 2%

FIRM NAME
Akorn

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Shahid Ahmed

TELEPHONE NUMBER
217-423-9715

SIGNATURE
Chan

I called Mr. Ahmed again on 7/11/02 reminely that we have not received the revised amendment as of 7/11/02. Chan
July 11, 02

Akorn inc.
Ophthalmic and Parenteral Health Care

2 West Grand Avenue • Decatur, IL 62522
217-423-9715 • Fax: 217-428-5206

June 06, 2002

MICROBIOLOGY

The Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AS

RE: MICROBIOLOGY AMENDMENT TO ANDA 40-433
Lidocaine Hydrochloride 2% Jelly, USP

Dear Sir:

In accordance with 21 CFR § 314.96 (a), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits response to the Microbiology Amendment to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP.

Form 356h is provided in **Attachment A.**

Attached is a written response to the deficiency items listed in the FDA Microbiology Amendment dated April 03, 2002.

Additionally, in accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Microbiology Amendment to our Abbreviated Drug Application for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office.

Should additional information be required, please feel free to contact me at (217) 423-9715, ext 173, or via FAX at (217) 423-5206.

Sincerely,

Shahid Ahmed
Vice President, Regulatory Affairs, QA, QC

RECEIVED
JUN 14 2002
OGD / CDER

MINOR AMENDMENT

ANDA 40-433

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 24 2002

TO: APPLICANT: Akorn Inc.

TEL: 217-423-9715

ATTN: Shahid Ahmed

FAX: 217-423-5206

FROM: Nicole Park

PROJECT MANAGER: 301-827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 9, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Hydrochloride USP 2% Jelly.

Reference is also made to your amendment(s) dated: February 12 and May 6, 2002, 6/6/02 Mamt 8/28/02.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Mamt

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #40-433 APPLICANT: Akorn, Inc.

DRUG PRODUCT: Lidocaine Hydrochloride 2% Jelly, USP

The Division of Bioequivalence has completed its review and has the following comments.

The Division of Bioequivalence has determined that your product is bioequivalent to Xylocaine^{R} 2% Jelly under 21 CFR section 320.24 (b) (6) since it is a DESI-effective product. Therefore, it is not necessary to conduct an *in vivo* bioequivalence study as previously suggested in the Agency's response dated July 30, 2001.

The Division has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Akorn inc.
Ophthalmic and Parenteral Health Care

[illegible]0 Millbrook Drive • Buffalo Grove, IL 60089-4694
847-279-6100 • Fax: 847-279-6123

August 12, 2002

Labeling

The Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/Am

RE: MINOR AMENDMENT TO ANDA 40-433
Lidocaine Hydrochloride 2% Jelly, USP

Dear Sir:

In accordance with 21 CFR § 314.96 (a), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a response to the remaining deficiency items listed in the Minor Amendment dated July 24th, 2002 to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP.

In accordance with 21 CFR § 314.92 Akorn, Inc., hereby requests withdrawal of (b) (4) (b) (4) from this Abbreviated New Drug Application for Lidocaine Hydrochloride 2% Jelly USP, a prescription drug product indicated for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

Form 356h is provided in **Attachment - A.**

Additionally, in accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Minor Amendment to our Abbreviated Drug Application for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office.

Should additional information be required regarding this response, please feel free to contact me at (847) 353-4929, or FAX at (847) 279-6196.

Sincerely,

Ambareen Sheriff
Manager, Regulatory Affairs

RECEIVED
AUG 1 3 2002
OGD / CDER

Akorn inc.
Ophthalmic and Parenteral Health Care

2500 Millbrook Drive • Buffalo Grove, IL 60089-4694
847-279-6100 • Fax: 847-279-6123

September 27, 2002

Labeling

The Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NAF

FPL

RE: FAX AMENDMENT TO ANDA 40-433
Lidocaine Hydrochloride 2% Jelly, USP

Dear Sir:

In accordance with 21 CFR § 314.96 (a), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a response to the labeling deficiency listed in the Fax Amendment dated September 18th, 2002, to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP.

Form 356h is provided in **Attachment – A.**

Labeling Deficiencies:

Following are the responses to the labeling deficiencies along with a representation of all final printed labels and labeling copies (12) for Lidocaine Hydrochloride Jelly USP, 2% that are provided in **Attachment – B**. Provided in **Attachment – C** for each of the submitted labeling is a side-by-side comparison of the final printed labeling and the labeling provided in the previous submission with all the differences annotated and explained in accordance with 21 CFR § 314.94 (a)(8)(iv).

1. **CONTAINER: -5 mL and 30 mL**

   a. **GENERAL:**
   We note your statement that you have submitted 12 representations of all final printed labels and labeling in your submission of February 12, 2002. However, we find only side-by-side comparisons without the actual final printed labeling included in your submission. Please submit.

   A representation of all final printed labels and labeling copies (12) for Lidocaine Hydrochloride Jelly USP, 2% as requested are provided in **Attachment - B.**

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b. Please assure that the statements "For topical use only". "Not for ophthalmic use" and "Discard unused portion" appears sufficiently prominent.

The statements, **"For topical use only", "Not for ophthalmic use" and "Discard unused portion"** have been bolded on the container labels for both the 5 mL and 30 mL fill sizes so that they are prominent.

c. We acknowledge in your amendment of August 12, 2002, that you have decided to (b) (4).

Yes, Akorn, Inc. has decided to (b) (4).

2. CARTON: -5 mL and 30 mL

a. See comments under CONTAINERS.

The statements, **"For topical use only", "Not for ophthalmic use" and "Discard unused portion"** have been bolded on carton labels for both the fill sizes 5 mL and 30 mL. The representations of final printed labels are provided in **Attachment - B**.

b. We believe that CFR 201.15(a)(2) requires the established name, strength and the net quantity of your product be printed on more than one panel. Please revise accordingly.

Akorn has added the established name and strength on the more than one panel as per conditions stated in CFR 201.15(a)(2) for carton labeling.

3. INSERT:

a. DESCRIPTION:
It is preferable to retain the statement "The unused portion…..initial use." Rather than "Discard unused portion." to be in accordance with the innovators labeling.

The changes have been made

b. CLINICAL PHARMACOLOGY
As stated in the last deficiency letter, it is preferable to use the term "to" rather than a hyphen when expressing a range.

The changes have been made. To have consistency in the labels the container labels, carton labels have also been revised along with the package insert and the hyphen has been replaced by "to".

c. **DOSAGE AND ADMINISTRATION**

i. **For Surface Anesthesia of the Male Adult Urethra – Revise the first sentence to read as follows:**
....cooled and attached to ....

The sentence has been revised to read as follows, "The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube."

ii. **For Surface Anesthesia of the Female Adult Urethra – Revise the first sentence to read as follows:**
The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube. The cone.....

The sentence has been revised to read as follows, "The plastic cone is sterilized for 5 minutes in boiling water, cooled, and attached to the tube."

d. **HOW SUPPLIED**

i. **First sentence – Revise to read as follows:**

Lidocaine HCl Jelly USP, 2% is

The sentence has been revised to read as follows, "Lidocaine HCl Jelly USP, 2% is supplied in 5mL, and 30mL aluminum tubes in individual carton."

ii. **Include information on how your product will be packaged. (e.g., individually packaged in carton).**

The information has been included to read as follows, "Lidocaine HCl Jelly USP, 2% is supplied in 5mL, and 30mL aluminum tubes in individual carton."

iii. **Please refer to the comment 1(c) above. Revise this section accordingly.**

The section has been revised to read as follows, "Lidocaine HCl Jelly USP, 2% is supplied in 5mL, and 30mL aluminum tubes in individual carton."

iv. **We acknowledge that you have included a proposal for a detectable applicator cone and a key for expressing the contents included in your 30 mL tube package size. We ask you to revise the statement regarding this to read, "...are included in 30mL tube" and/or comment.**
[add "in 30 mL tube"]

The statement has been revised to read as follows, "A detachable applicator cone and a key for expressing the contents are included in 30 mL tube carton."

Additionally, in accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Faxed Amendment to our Abbreviated Drug Application for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office.

Should additional information be required regarding this response, please feel free to contact me at (847) 353-4929, or FAX at (847) 279-6196.

Sincerely,

Ambareen Sheriff
Manager, Regulatory Affairs

Akorn inc.
Ophthalmic and Parenteral Health Care

2500 Millbrook Drive • Buffalo Grove, IL 60089-4694
847-279-6100 • Fax: 847-279-6123

November 13, 2002

MICROBIOLOGY
ORIG AMENDMENT
N/AS

The Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: RESPONSE TO MICROBIOLOGY DEFICIENCIES TO ANDA 40-433
Microbiology Amendment for Lidocaine Hydrochloride 2% Jelly, USP

Dear Sir:

In accordance with 21 CFR § 314.96 (a), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits response to the Microbiology Amendment to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP.

Form 356h is provided in **Attachment A.**

Following are the responses to the microbiology deficiency items listed in the FDA facsimile 'Microbiology Deficiencies and Comments' dated November 07, 2002 for Lidocaine Hydrochloride Jelly USP, 2%.

A. Microbiology Deficiencies:

1. **Please provide the most recent requalification data for the** (b) (4) (b) (4)

(b) (4)

2. **Please clarify if the parameters that were established in 1993 are those currently used for the requalification of the** (b) (4).

(b) (4)

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Following this page, 2 pages withheld in full (b)(4)

Akorn is filing an archival copy (original) of this minor amendment to ANDA 40-433 and a technical review copy (duplicate), which is identical to the archival copy. An additional certified field copy was sent to the Newark District Office.

Additionally, in accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Microbiology Amendment to our Abbreviated Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office.

Should additional information be required, please feel free to contact me at (847) 353-4929, or via FAX at (847) 279-6196.

Sincerely,

Ambareen Sheriff

Ambareen Sheriff
Manager, Regulatory Affairs

Akorn inc.
Ophthalmic and Parenteral Health Care

Veronica Avenue • Somerset, NJ 08873
732-846-8066 • Fax: 732-846-7952

December 11, 2002

MICROBIOLOGY

The Director
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AS

RE: RESPONSES TO MICROBIOLOGY DEFICIENCIES TO ANDA 40-433
Microbiology Amendment for Lidocaine Hydrochloride Jelly, USP, 2%

Dear Sir:

In accordance with 21 CFR § 314.96 (a), and by reference § 314.60 (a), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products, hereby submits response to the Microbiology Amendment to our Abbreviated New Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly, USP.

Form 356h is provided in **Attachment A.**

Following are the responses to the microbiology deficiency items listed in the FDA facsimile "Microbiology Deficiencies ad Comments" dated December 4, 2002 for Lidocaine Hydrochloride Jelly USP, 2%.

A. Microbiology Deficiencies:

1. **Please explain why** [redacted] (b) (4)

[redacted] (b) (4)

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Following this page, 1 page withheld in full (b)(4)

A. Microbiology Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please clarify the response. In the June 6, 2002 amendment, it is stated that there are currently (b) (4) running to fill the entire batch. In addition, it was indicated that the duration of the media fill runs was between (b) (4).

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

2. For future applications, please provide complete BI information. This would include the manufacturer, the lot number, the expiry, the D-value, the population, and confirmation of the D-value when the BI is in suspension.

Response: All future applications will include complete biological indicator in formation used in the validation of sterilization processes.

Akorn is filing an archival copy (original) of this minor amendment to ANDA 40-433 and a technical review copy (duplicate), which is identical to the archival copy. An additional certified field copy was sent to the Newark District Office.

Additionally, in accordance with 21 CFR § 314.96 (b) and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Microbiology Amendment to our Abbreviated Drug Application 40-433 for Lidocaine Hydrochloride 2% Jelly USP has been provided to the FDA Newark District Office.

Should additional information be required, please feel free to contact me at (847) 353-4929, or via FAX at (847) 279-6196.

Sincerely,

for Ambareen Sheriff
Manager, Regulatory Affairs

AM/SA/ra
Enclosures
Via Overnight Mail

cc: FDA – North Brunswick District Office (w/encls)

DIVISION APPROVAL SUMMARY

ANDA:

40-433

DRUG PRODUCT:

Lidocaine Hydrochloride Jelly USP 2%

FIRM:

Akorn, Inc.,

DOSAGE FORM:

Jelly

CGMP:

Acceptable 1/29/03

BIO:

Bio review acceptable, 10/19/01.

VALIDATION - *(Description of dosage form same as firm's):*

NA - compendial product.

STABILITY:

Containers in the stability studies are identical to those in the container section.

LABELING:

Acceptable review is dated 10/3/02.

STERILIZATION VALIDATION *(If applicable)*:

Acceptable review is dated 12/30/02.

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:

DMF [redacted] (b) (4) is adequate.

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?):*

Stability batch size was [redacted] (b) (4) which is essentially similar to the proposed batch [redacted] (b) (4)

PROPOSED PRODUCTION BATCH – MANUFACTURING PROCESS THE SAME?:

The proposed production size is [redacted] (b) (4)

Signature of Chemist/Date: R Rajagopalan 2/4/03

Signature of Team Leader/Date: BY 2/7/03

OGD APPROVAL ROUTING SUMMARY

ANDA # 40-433 Applicant Akorn, Inc.
Drug Lidocaine HCl Jelly USP Strength 2%

PROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Project Manager, Team Review Support Br — MPatil (17)

DRAFT Package Date 1/28/03 Initials MP

FINAL Package Date 2/7/03 Initials

Application Summary:

Original Rec'd date 3-9-01
Date Acceptable for Filing 3-13-01 J
Patent Certification (type) I
Date Patent/Exclus.expires NA
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked NA NDA# NA
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☒ Acceptable ☒ OAI ☐
Date of EER Status 1-29-03
Date of Office Bio Review 10-19-01
Date of Labeling Approv. Sum 10-3-02
Date of Sterility Assur. App. 12-30-02
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

Gregg Davis PPIV ANDAs Only
Supv., Reg. Support Branch

Date 2/12/03 Initials RW J
Date 2/12/03 Initials RW for

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled: N/A
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD = ☒ Xylocaine Jelly 2% NDA 8-814 AstraZeneca LP

Comments: There are no unexpired patents or exclusivity listed in the Orange Book for this drug product.

3. Div. Dir./Deputy Dir. Chemistry Div. I or II — 2/10/03 OS
Comments:

Date 2/11/03 Initials

CMC satisfactory.

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Date _____
Initials _____
Comments: (First generic drug review)

N/A. There are 2 ANDAs listed in the Orange Book for this drug product (Cpdex, IMS).

5. Peter Rickman
Acting Director, DLPS
Date 2/12/03
Initials PR (Left/fax)
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 1/29/03 (received 2/12/03). No OAI. Objects noted - Bioequivalence waiver granted under 320.24(b)(6). Office-level bio found acceptable 12/31/02. CMC-found acceptable 2/7/03. Methods validation is not required - the API and drug product are compendial. This product will be supplied in 5mL and 30mL tubes. The formulation is "Q1Q" to the RLD (per DBE review).

5. Robert L. West
Acting Deputy Director, OGD
Date 2/12/2003
Initials RLW (Left/fax)
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments:

This application is recommended for approval.

6. Gary Buehler
Director, OGD
Date 2/12/03
Initials GB
Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Nicole Park
Review Support Branch
Date 2/12/03
Initials NP

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1:45pm Time notified of approval by phone 1:50 Time approval letter faxed

FDA Notification:
2/12/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/12/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

":\reports\approval\approvrou2.doc