CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-221

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(White Oak 22; Mail Stop 4447)

DATE RECEIVED: 8/1/2007 **DATE OF DOCUMENT:** 6/29/2007	**DESIRED COMPLETION DATE:** 11/15/2007 **PDUFA:** 5/2/08	**OSE REVIEW #:** 2007-1673

TO: Janice Soreth, MD
Director, Division of Anti-Infective and Ophthalmology Products, HFD-520

THROUGH: Kellie Taylor, PharmD, Team Leader
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Division of Medication Errors and Technical Support, HFD-420

FROM: Judy Park, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Akten™** (Lidocaine Hydrochloride) Ophthalmic Gel 3.5% **NDA #:** 22-221	**SPONSOR:** Akorn, Inc.

RECOMMENDATIONS:

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

2. DMETS recommends implementation of the labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

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

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Anne Crandall, OSE Project Manager, at 301-796-2282.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: February 28, 2008

NDA #: 22-221

NAME OF DRUG: **Akten™** (lidocaine hydrochloride)
Ophthalmic Gel 3.5%

NDA SPONSOR: Akorn, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Products for an assessment of the proprietary name, Akten, regarding potential name confusion with other proprietary or established drug names. Insert labeling submitted on June 29, 2007 was also provided for review and comment.

PRODUCT INFORMATION

Akten (Lidocaine Hydrochloride) is a topical, local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures. The recommended dose is 2 drops applied to the ocular surface in the area of the planned procedure. Akten is available as ophthalmic gel in a single strength of 3.5%, containing 35 mg/mL lidocaine hydrochloride. It is supplied for single-use in — plastic dropper bottles. b(4)

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Akten to a degree where

[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)

potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient orders) and one verbal prescription studies of the name, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Akten. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

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

2. The Expert Panel identified a total of 21 proprietary names that were thought to have potential for confusion with Akten.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Akten with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Inpatient order and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and prescription for Akten (see below). These

[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient order was recorded on voice mail. The voice mail message was then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription order, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Akten

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION 1
Outpatient RX: Akten #1 Instill 1 gtt into affected eye before procedure	Akten #1 Instill 1 drop into affected eye before procedure
Inpatient RX: Akten with 1 gtt into affected eye(s) before procedure	

2. Results for Akten:

   None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. However, 11 out of 12 respondents from a verbal study misinterpreted the proposed name as "Actin" which is the root name of Actin-N, which is a discontinued product (see discussion in Section II.C.1.c). See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name, 21 names were identified as having a similar appearance or sound to Akten. These names include AK-FLUOR[***], AK-CON, AK-TOB, Actin-N, Artane, Acthar, Oreton, Astelin, Actos, Axert, Akineton, Ceftin, Acticin, Actiq, Naftin, Adphen, Accutane, Axsain, Actonel, Actron, and Ativan. Additionally, the applicant's continued use of the prefix "AK" was identified as increasing the potential for confusion within the product line.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Akten could be confused with any of the aforementioned names. However, 11 out of 12 respondents from a verbal study misinterpreted the proposed name as "Actin" which is the root name of Actin-N, which is a discontinued product (see discussion in Section II.C.1.c). The negative findings in the studies are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Akten.

[***] This review contains proprietary and confidential information that should not be released to the public.

The following seventeen names: Artane, Acthar, Oreton, Astelin, Actos, Axert, Akineton, Ceftin, Acticin, Actiq, Naftin, Adphen, Accutane, Axsain, Actonel, Actron, and Ativan would not be considered further they lack significant look-alike and/or sound-alike similarities to Akten and do not share product commonalities such as indication of use, product strength, usual dose, route of administration, frequency of administration, and/or dosage form.

The remaining four names, AK-FLUOR***, AK-CON, AK-TOB, and Actin-N, warranted further review. These products are listed in Table 1 below along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for Akten

Product Name	Established name, Dosage form(s)	Usual adult dose	Other
Akten	Lidocaine Hydrochloride Ophthalmic Gel 3.5%	2 drops applied to ocular surface in the area of the planned procedure	
AK-FLUOR	Fluorescein Sodium Injectable: 10% (100 mg/mL); 25% (250 mg/mL)	Adults: 500 mg intravenously Pediatrics: 35 mg per 10 lb of body weight.	LA
AK-CON	Nephazoline Hydrochloride Ophthalmic Solution: 0.1%	1 or 2 drops into the affected eye(s) every 3 to 4 hours, up to 4 times daily	LA
AK-TOB	Tobramycin Ophthalmic Solution: 0.3%	1 or 2 drops into the affected eye(s) every 4 hours. In severe infections, instill 2 drops into the eye(s)hourly until improvement	LA/SA
Actin-N	Nitrofurazone Topical Dressing: 0.2%	Information not available	LA/SA

After further evaluation of AK-FLUOR***, it was determined to not pose an increased risk for name confusion with Akten because although they have orthographic similarity, they lack overlapping product characteristics such as product strength, indication of use, usual dose, and dosage form. Actin-N was evaluated further but found to be at low risk for confusion because the product is no longer marketed and generics are not available according to Drugs@FDA website. However, the active ingredient is available in a different dosage form in topical ointment.

DMETS believes AK-CON and AK-TOB pose a risk for confusion because they utilize the prefix AK which increase the visual similarity and overlap in product characteristics with Akten. These names are discussed below.

1. Use of Prefix "AK"

   When evaluating Akten, we noted the sponsor, Akorn Inc., has a history of using the prefix 'AK' in many of the proprietary names for their ophthalmic and injectable products. A review of the Akorn website reveals the following names as currently marketed: AK-CON, AK-DILATE, AK-FLUOR, AK-PENTOLATE, AK-POLY-BAC, AK-TOB, and AKWA TEARS. Additionally, DMETS has also identified the names, AKPRO, and AKBETA in the electronic Orange Book and Drugs@FDA websites. Most of these proprietary names were not reviewed by DMETS because they were approved prior to formation of DMETS (i.e. AK-PENTOLATE, AKBETA, AK-TOB,

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and AK-PRO) or because they are marketed without FDA approval (i.e. AK-CON, AK-DILATE, AK-POLY-BAC, AKWA TEARS). AK-FLUOR*** is the subject of a pending new drug application and is undergoing DMETS review although the product is already marketed.

Post-marketing experience has shown confusion and resulting medication errors due to proliferation of names with a common prefix. One example of such confusion has been seen with products having the prefix "APO", manufactured in Canada by Apotex. Consequently, DMETS has objected to inclusion of the prefix "APO" for proprietary names proposed in this country since this practice may result in the introduction of numerous sound-alike/look-alike names.

Although the prefix "AK" in the proposed name is not hyphenated like most of other Akorn products, DMETS is still concerned that the approval of names starting with "Ak" will lead to a proliferation of products with commonalties in nomenclature since practitioners can prescribe the product without the hyphen. Additionally, problems can occur with the approved proprietary names if the product later changes sponsors and is no longer marketed by Akorn. As it relates to this review, DMETS has identified several proprietary names that may be confused with Akten, in part due to the common "Ak" prefix. Two names appear particularly problematic, Aktob and Ak-CON.

2. AK-CON and AK-TOB Name Discussion

   a. AK-CON

      AK-CON was found to look alike to Akten. AK-CON and Akten are both ophthalmic products manufactured by Akorn Inc. AK-CON is a generic tradename for nephazoline hydrochloride ophthalmic solution. It is an ocular vasoconstrictor/ decongestant used for temporary relief of redness due to minor eye irritation, protection against further irritation, and temporary relief of burning and irritation due to dryness of the eye. AK-CON is available in 0.1% strength in 15 mL bottle. The recommended dose is 1 to 2 drops into the affected eye(s) every 3 to 4 hours, up to 4 times daily.

      The look-alike similarities stems from the fact that AK-CON and Akten both start with "AK-" and end in the letter "N". The second to last letter (-o- vs. -e-) look alike and can be mistaken for each other. The differentiating letter (-c- vs. -t-) may be easily overlooked when the rest of the letters in the name are the same or very similar looking. The other differentiating factor is that AK-CON is hyphenated and capitalized and Akten is not. Despite this difference, AK-CON may be prescribed without the hyphen or in mixed case letters which increase its visual resemblance to Akten.

Akon

Akten

*** This review contains proprietary and confidential information that should not be released to the public

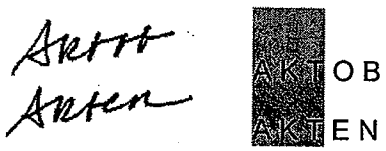
AK-CON and Akten have overlapping product characteristics which increase the potential for confusion. They have overlapping routes of administration (ophthalmic), single product strength availability, and usual dose (1 to 2 drops vs. 2 drops). Although the dosage form (solution vs. gel) is different, since both are ophthalmic products, this difference may not be significant enough in distinguishing the products. Although Akten will more likely be used directly by the ophthalmologist during the surgical procedure than dispensed in the outpatient pharmacy, there is still a risk of confusion between AK-CON and Akten since the both products can be ordered inpatient through requisition orders.

Due to concern of additional names in the market with the same prefix as discussed in II.C.1 in addition to look-alike similarities and overlapping product characteristics, DMETS believes there is a risk of confusion between Akten and AK-CON.

b. AK-TOB

AK-TOB and Akten were found to have look- and sound-alike similarities. They are both ophthalmic products manufactured by Akorn Inc. AK-TOB is a generic tradename for tobramycin ophthalmic solution. It is indicated for the treatment of superficial ocular infections and is available in 0.3% strength. The recommended dose for mild to moderate disease is 1 to 2 drops every 4 hours in the affected eye(s) and for severe infections is 2 drops every hour in the affected eye(s) until improvement is noted .

AK-TOB and Akten look and sound similar because both names start with the same letters in the same order (AKT-) and both contain two syllables. Additionally, the letter after "AKT" (-o- vs. -e-) can be easily mistaken for one another. The differentiating last letter (-b vs. -n) can be overlooked especially if the last letter is trailing. Although AK-TOB is hyphenated and capitalized according to the sponsor's website, it is presented without a hyphen on Drugs@FDA website (i.e. AKTOB). AK-TOB may be prescribed without the hypen or mixed case letters which increases its visual resemblance to Akten.



In addition to visual and phonetic similarities, AK-TOB and Akten have overlapping route of administration (ophthalmic), single product strength availability, and usual dose (1 to 2 drops vs. 2 drops). Although the dosage form (solution vs. gel) is different, since both are ophthalmic products, the difference may not be significant in distinguishing the products. Although Akten will more likely be used directly by the ophthalmologist during the surgical procedure than dispensed in the outpatient pharmacy, there is still a risk of confusion between AK-CON and Akten since the both products can be ordered inpatient through requisition orders.

Due to concern of additional names with the same prefix as discussed in II.C.2 in addition to look and sound alike similarities and overlapping product characteristics, DMETS believes there is a risk of confusion with AK-TOB and Akten.

III. COMMENTS TO THE SPONSOR

A. Akten Name Analysis

1. Use of Prefix "AK"

When evaluating Akten, we noted the sponsor, Akorn Inc., has a history of using the prefix 'AK' in many of the proprietary names for their ophthalmic and injectable products. A review of the Akorn website reveals the following names as currently marketed: AK-CON, AK-DILATE, AK-FLUOR, AK-PENTOLATE, AK-POLY-BAC, AK-TOB, and AKWA TEARS. Additionally, DMETS has also identified the names, AKPRO, and AKBETA in the electronic Orange Book and Drugs@FDA websites. Most of these proprietary names were not reviewed by DMETS because they were approved prior to formation of DMETS (i.e. AK-PENTOLATE, AKBETA, AK-TOB, and AK-PRO) or because they are marketed without FDA approval (i.e. AK-CON, AK-DILATE, AK-POLY-BAC, AKWA TEARS). AK-FLUOR*** is the subject of a pending new drug application and is undergoing DMETS review although the product is already marketed.

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Although the prefix "AK" in the proposed name is not hyphenated like most of other Akorn products, DMETS is still concerned that the approval of names starting with "Ak" will lead to a proliferation of products with commonalties in nomenclature since practitioners can prescribe the product without the hyphen. Additionally, problems can occur with the approved proprietary names if the product later changes sponsors and is no longer marketed by Akorn. As it relates to this review, DMETS has identified several proprietary names that may be confused with Akten, in part due to the common "Ak" prefix. Two names appear particularly problematic, Aktob and Ak-CON.

2. AK-CON and AK-TOB Name Discussion

a. AK-CON

AK-CON was found to look alike to Akten. AK-CON and Akten are both ophthalmic products manufactured by Akorn Inc. AK-CON is a generic tradename

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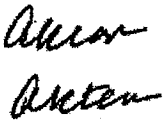
for nephazoline hydrochloride ophthalmic solution. It is an ocular vasoconstrictor/ decongestant used for temporary relief of redness due to minor eye irritation, protection against further irritation, and temporary relief of burning and irritation due to dryness of the eye. AK-CON is available in 0.1% strength in 15 mL bottle. The recommended dose is 1 to 2 drops into the affected eye(s) every 3 to 4 hours, up to 4 times daily.

The look-alike similarities stems from the fact that AK-CON and Akten both start with "AK-" and end in the letter "N". The second to last letter (-o- vs. -e-) look alike and can be mistaken for each other. The differentiating letter (-c- vs. -t-) may be easily overlooked when the rest of the letters in the name are the same or very similar looking. The other differentiating factor is that AK-CON is hyphenated and capitalized and Akten is not. Despite this difference, AK-CON may be prescribed without the hyphen or in mixed case letters which increase its visual resemblance to Akten.



AK-CON and Akten have overlapping product characteristics which increase the potential for confusion. They have overlapping routes of administration (ophthalmic), single product strength availability, and usual dose (1 to 2 drops vs. 2 drops). Although the dosage form (solution vs. gel) is different, since both are ophthalmic products, this difference may not be significant enough in distinguishing the products. Although Akten will more likely be used directly by the ophthalmologist during the surgical procedure than dispensed in the outpatient pharmacy, there is still a risk of confusion between AK-CON and Akten since the both products can be ordered inpatient through requisition orders.

Due to concern of additional names in the market with the same prefix as discussed in II.C.1 in addition to look-alike similarities and overlapping product characteristics, DMETS believes there is a risk of confusion between Akten and AK-CON.

b. AK-TOB

AK-TOB and Akten were found to have look- and sound-alike similarities. They are both ophthalmic products manufactured by Akorn Inc. AK-TOB is a generic tradename for tobramycin ophthalmic solution. It is indicated for the treatment of superficial ocular infections and is available in 0.3% strength. The recommended dose for mild to moderate disease is 1 to 2 drops every 4 hours in the affected eye(s) and for severe infections is 2 drops every hour in the affected eye(s) until improvement is noted .

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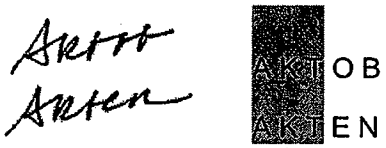

In addition to visual and phonetic similarities, AK-TOB and Akten have overlapping route of administration (ophthalmic), single product strength availability, and usual dose (1 to 2 drops vs. 2 drops). Although the dosage form (solution vs. gel) is different, since both are ophthalmic products, the difference may not be significant in distinguishing the products. Although Akten will more likely be used directly by the ophthalmologist during the surgical procedure than dispensed in the outpatient pharmacy, there is still a risk of confusion between AK-CON and Akten since the both products can be ordered inpatient through requisition orders.

Due to concern of additional names with the same prefix as discussed in II.C.2 in addition to look and sound alike similarities and overlapping product characteristics, DMETS believes there is a risk of confusion with AK-TOB and Akten.

B. Labeling Issues

In review of the proposed insert labeling of Akten, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement in the interest of minimizing user error and maximizing patient safety.

1. Dosage and Administration

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

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

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

2. Dosage Forms and Strengths

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

3. How Supplied

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

Appendix A

Akten Prescription Study Results

Written Inpatient	Written Outpatient	Voice
Aktia	Akten	Actin
Alcton	Ahten	Actin
Arctea	Autin	Actin
Aksta	Akten	Actin
Akten	Abten (Ahten)	Acton
Arten	Akten	Actin
Aktea	Ahten	Actin
Aktin	Astin	Actin
	Aktin	Actin
	Artin	Actin
	Anten	Actin
	Ahten	Actin

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/s/

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