# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-186**

# PROPRIETARY NAME REVIEW(S)

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**
**OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY**
**(DMETS; HFD-420)**

| **DATE RECEIVED:** | **DESIRED COMPLETION DATE:** | **OSE CONSULT #:** 2007-1226 |
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| May 31, 2007 | October 17, 2007 | |
| **DATE OF DOCUMENT:** | **PDUFA:** | |
| April 5, 2007 | February 6, 2008 | |

**TO:** Janice Soreth, M.D., Director
Division of Anti-infective and Ophthalmology Products

**THROUGH:** Kellie Taylor, Pharm.D., M.P.H., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

**FROM:** Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

| **PRODUCT NAME:** | **NDA SPONSOR:** Akorn, Inc. |
|---|---|
| **AK-FLUOR**<br>(Fluorescein Injection, USP)<br>100 mg/mL in a 5 mL vial<br>250 mg/mL in a 2 mL vial<br><br>**NDA #:** 22-186 | |

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, AK-FLUOR. DMETS believes that approving the current proprietary name is appropriate as there have not been any documented cases of name confusion within the Akorn product line with AK-FLUOR as outweighed by the unknown risk of name confusion that may be associated with an alternate name. This recommendation is based on our current understanding of medication errors associated with the AK-FLUOR product and is limited to the current proposed proprietary name, AK-FLUOR. This conclusion should not be taken or used to imply allowances for any other product with the 'AK-' prefix. This is considered a final decision. However, if approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

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

3. DDMAC finds the proprietary name, AK-FLUOR, 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 communications forwarded to the Sponsor regarding this review. If you have further questions or need clarifications, please contact Anne Crandall, Project Manager, at 301-796-2282.

**Division of Medication Errors and Technical Support (DMETS)**
**Office of Surveillance and Epidemiology**
**HFD-420; WO 22; Mail Stop 4447**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME, LABEL AND LABELING REVIEW**

**DATE OF REVIEW:** July 27, 2007

**NDA #:** 22-186

**NAME OF DRUG:** **AK-FLUOR**
(Fluorescein Injection, USP)
100 mg/mL in a 5 mL vial
250 mg/mL in a 2 mL vial

**NDA HOLDER:** Akorn, Inc.

## I. INTRODUCTION:

This review was written in response to a request from the Division of Anti-infective and Ophthalmology Products, for assessment of the proprietary name, AK-FLUOR, regarding potential name confusion with other proprietary or established drug names. AK-FLUOR Injection is a currently marketed drug from Akorn, Incorporated that does not have NDA approval. Akorn has now submitted a NDA for approval. Container labels, carton, and insert labeling submitted on April 5, 2007, were provided for review and comment.

PRODUCT INFORMATION

AK-FLUOR Injection is Fluorescein Injection, an imaging agent used in ophthalmologic procedures. AK-FLUOR is indicated for use in diagnostic angiography or angioscopy of the fundus and of the iris vasculature. The recommended adult dose of AK-FLUOR is 500 mg intravenously. For pediatric patients the dose should be calculated on the basis of 35 mg for each ten pounds of body weight.

AK-FLUOR should be inspected visually for particulate matter and discoloration, and filtered through a —— sterile filter prior to use. Fluorescein is injected rapidly into the antecubital vein, *after taking precautions to avoid extravasation.* A scalp (butterfly) needle attached to a small syringe is ideal for administration. A syringe, filled with fluorescein, is attached to transparent tubing and a — gauge scalp vein needle for injection. Insert the needle and draw the patient's blood to the hub of the syringe so that a small air bubble separates the patient's blood in the tubing from the fluorescein. With the room lights on, slowly inject the blood back into the vein while watching the skin over the needle tip. If the needle has extravasated, the patient's blood will be seen to bulge the skin and the injection should be stopped before any fluorescein is injected. When assured that extravasation has not occurred, the room light may be turned off and the fluorescein injection completed. Luminescence appears in the retina and choroidal vessels in —to 14 seconds and can be observed by standard viewing equipment.

(4)

b(4)

If potential allergy is suspected, an intradermal skin test may be performed prior to intravenous administration, i.e., 0.05 mL injection intradermally to be evaluated 30 to 60 minutes following injection.

AK-FLUOR is available in two strengths: 10% (100 mg/mL) in a 5 mL single dose vial and 25% (250 mg/mL) in a 2 mL single dose vial. The vials are supplied in carton packaging of twelve vials. AK-FLUOR should be stored at controlled room temperature (20 to 25 degrees Celsius).

## 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 AK-FLUOR to a degree where 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.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name AK-FLUOR. Potential concerns regarding drug marketing and promotion related to the proposed name(s) 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, AK-FLUOR, acceptable from a promotional perspective.

2. The Expert Panel identified the following three proprietary names that were thought to have the potential for confusion with AK-FLUOR: Acular, Acthar, Fluor-op, and the "AK-" product line from Akorn, Inc.

### B. AERS SEARCH

Since AK-FLUOR Injection is already marketed in the United States, the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports concerning medication errors associated with use of the product. The search was conducted using the high level terms "maladministrations", "medication monitoring errors", "medication errors due to accidental exposure", and "medication errors NEC" and the preferred terms "overdose", "accidental

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[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 98-04, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[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

overdose", "accidental exposure", "multiple drug overdose", "multiple drug overdose accidental," and "pharmaceutical product complaint", as well as the active ingredient "fluorescein" and the verbatim term "AK-FLUOR". The search did not identify any medication error cases associated with the use of AK-FLUOR Injection in the AERS database.

C. MEDMARX SEARCH

Since AK-FLUOR Injection is already marketed in the United States, the United States Pharmacopeia's (USP) MEDMARX database was searched for medication errors associated with the use of the product. The MEDMARX database includes medication errors voluntarily reported by participating hospitals and health systems nationwide. The search did not identify any medication error cases associated with the proprietary name, AK-FLUOR, or the labels, labeling, and packaging of AK-FLUOR in the MEDMARX database.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, three names were identified as having the potential to look and sound similar to AK-FLUOR: Acular, Acthar, Fluor-op, and the "AK-" product line from Akorn.

Upon initial analysis of the aforementioned names, it was determined three names Acular, Acthar, and Fluor-op lacked convincing look-alike and sound-alike similarities with AK-FLUOR in addition to the following:

- Acular lacks product commonalities such as product strength, dosage formulation, frequency of administration, route of administration, indication for use, and duration of therapy.
- Acthar is no longer marketed as a brand of corticotropin injection. The only remaining corticotropin product in the U.S. market is "HP Acthar Gel". HP Acthar Gel lacks product commonalities such as product strength, frequency of administration, indication for use, and duration of therapy. Additionally, HP Acthar Gel is only available through a specialty pharmacy distribution program.
- Fluor-Op is no longer marketed as a brand of fluorometholone ophthalmic suspension 0.1%. However, fluorometholone ophthalmic suspension 0.1% is still marketed under the proprietary names "FML" and "Flarex". The names FML and Flarex lack product commonalities such as product strength, dosage formulation, frequency of administration, route of administration, indication for use, and duration of therapy.

Additionally, no cases of name confusion concerning AK-FLUOR and any of these three names were found in the AERS and MEDMARX searches. Because of the many product differences, market status, and no reports of current error, these names will not be considered further. The remaining list of names in Akorn's 'AK-' product line warranted further evaluation.

Akorn's use of the prefix 'AK-' in their product line

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 AK-SPORE, AKPRO, and AKBETA in the electronic Orange Book and Drugs@FDA websites.

DMETS' typically recommends against the use of part or all of the Sponsor's name (e.g., 'AK-' for Akorn) in proposed proprietary names. The use of a common prefix increases the risk of name confusion, and post-marketing experience with other manufacturers products has shown that this practice results in medication error. Additionally, problems with the approved proprietary name can occur if the product later changes Sponsors and is no longer marketed by Akorn.

DMETS acknowledges that the name AK-FLUOR could be problematic due to the aforementioned reasons and would likely object to the name if this was a traditional pre-market assessment. However, the situation for AK-FLUOR is somewhat different because AK-FLUOR is already marketed in the Unites States by Akorn. Our post-marketing database searches have not revealed any medication error cases associated with the use of the current name, AK-FLUOR Injection. In this particular situation, DMETS' believes that continued use of the current proprietary name is appropriate as there have not been any documented cases of name confusion within the Akorn product line with AK-FLUOR. Moreover, DMETS does not believe that AK-FLUOR will be confused with the existing 'AK-' products due to differentiating product characteristics such as clinical setting of use, strength, and route of administration. This recommendation is based on our current understanding of medication errors associated with the AK-FLUOR product and is limited to the current proposed proprietary name, AK-FLUOR. This conclusion should not be taken or used to imply allowances for any other product with the 'AK-' prefix. Therefore, for this product only, DMETS' has no objections to the proposed proprietary name, AK-FLUOR.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS reviewed the labels and labeling from a safety perspective. DMETS acknowledges that no errors have been identified or attributed to the product packaging but we have identified the following areas of improvement, to minimize user error and maximize patient safety.

### A. GENERAL COMMENTS

1. The proposed labels and labeling express the strength of AK-FLUOR in two ways: as a percentage, and in terms of milligram per one milliliter of injection. The percentage expression of strength can make it confusing for health care practitioners to calculate the volume of drug to administer when AK-FLUOR is ordered on a milligram basis. The percentage expression of strength also makes it difficult for health care practitioners to determine how much drug (in milligrams) is contained in each vial. DMETS notes that the other FDA approved fluorescein injection product, Fluorescite is currently labeled in terms of milligram per milliliter and as a percentage. However, based on, DMETS' postmarketing experience with similar products, for safety reasons, we recommend that the product strength for AK-FLUOR should be also expressed in terms of milligrams and total drug content (i.e., 500 mg fluorescein per 5 mL) to minimize potential confusion. The total drug content (mg/total mL) and drug concentration (mg/mL) should be added to the principal display panel of the container label and carton labeling in order to prevent medication errors as follows:

AK-FLUOR 25%
(Fluorescein Injection, USP)
500 mg/2 mL
(250 mg/mL)
For intravenous injection

and

AK-FLUOR 10%
(Fluorescein Injection, USP)
500 mg/5 mL
(100 mg/mL)
For intravenous injection

2. Please note that DMETS recommends that the abbreviation "IV" for "intravenous" be spelled out to decrease the potential of misinterpretation of this abbreviation and resulting medication errors.

3. DMETS questions why two strengths of AK-FLUOR are marketed. Although the concentrations are different, (250 mg/mL vs. 100 mg/mL), the total vial contents is the same (500 mg/vial). The recommended adult dose of AK-FLUOR is 500 mg intravenously, with smaller milligram doses recommended for pediatrics or patients receiving dialysis. However, it is not apparent why two strengths or concentrations need to be marketed, and having two strengths of AK-FLUOR can increase the potential for medication error if the wrong product is selected and administered.

4. In the proposed labels and labeling, it appears that the proprietary names are "AK-FLUOR 10%" and "AK-FLUOR 25%". The proposed proprietary name for both strengths of this product is "AK-FLUOR" and therefore this name should be communicated with no modifier or name extension. All labels and labeling should be revised to reflect this name. Additionally, DMETS recommends that the name, AK-FLUOR, be printed in a combination of upper and lower case letters rather than printed in all capital letters (e.g., AK-Fluor) to increase readability. Printing the name in all capital letters reduces readability and may lead to medication errors.

5. The labels and carton labeling for both strengths of AK-FLUOR are orange in color. Although the labels and carton labeling for the 100 mg/mL strength is light orange, and the labels and carton labeling for the 250 mg/mL strength is a darker orange, these colors are too similar to be helpful in differentiating between the strengths. DMETS recommends that an alternate color (e.g., not orange) be used to differentiate one of the strengths and to decrease the potential for confusion between the two strengths. Additionally, DMETS' notes that the orange font on orange background for some of the text on the vial labels (e.g., 2 mL and 5 mL) is very difficult to read and therefore recommends that an alternate colored font be used for this text.

B. CONTAINER LABELS (100 mg/mL and 250 mg/mL vials)

1. Refer to General Comments A1-A5.

2. The product strength (e.g., 250 mg/mL and 100 mg/mL) should be relocated to immediately follow the total drug content to increase readability. Refer to A1 for the recommended display format. Additionally, DMETS notes that the proprietary and established names should be the most prominent text on the principal display panel.

C. CARTON LABELING (100 mg/mL and 250 mg/mL: 12 vials per carton)

1. Refer to General Comments A1-A5.

2. The prominence of the product strength (in mg/mL) should be increased on the principal display panel to improve readability. Additionally, the total drug content (mg/total mL) and the statement "For intravenous injection" should be added to the principal display panel. Refer to A1 for the recommended display format.

D. FULL PRESCRIBING INFORMATION LABELING

1. Refer to General Comments A1 and A4.

2. The statement " [redacted] " is used throughout the insert labeling which is false and may lead to administration errors. DMETS notes that AK-FLUOR is for intravenous injection through the antecubital vein which is in the arm, not the eye. Although AK-FLUOR injection circulates to the ophthalmic vasculature for imaging, use of the statement " [redacted] " implies that AK-FLUOR may be applied or injected into the eyes. Significant harm and ocular damage could result should this statement be misinterpreted and result in the erroneous administration of AK-FLUOR. The correct route of administration should read, "for intravenous use only" to convey the actual route of administration. b(4)

3. Section 2 DOSAGE AND ADMINISTRATION

For the recommended pediatric dosage, we recommend that the dose be calculated on a milligram per kilogram of body weight basis, rather than milligram per ten pounds of body weight. Most hospitals now require that patient weights be recorded and reported in kilograms, therefore, recommending a dose based on pounds introduces one more unnecessary calculation when body weight is converted from kilograms to pounds that increases the potential for error. Additionally, basing the dose on milligrams per *ten* pounds of body weight is a second unnecessary calculation that further increases the potential for error. Please revise the dosage recommendation to read "For pediatric patients, the dose should be calculated on the basis of 7.7 milligrams per kilogram of body weight" (which equals 35 milligrams per 10 pounds of body weight).

4. Section 5.3 PRECAUTIONS: General

a. DMETS notes that the term ' [redacted] ' is not a term that is commonly recognized by health care practitioners. Refer to 21 CFR 201.57 for the terminology to use such as "adverse reactions". b(4)

b. The sentence " [redacted] b(4)

[redacted] ' is confusing given that section 2.4 Administration discusses that an intradermal fluorescein test may be performed if potential allergy (to flurorescein) may be suspected. If the intent is to state that the [redacted] b(4)

[redacted], please state that. DMETS recommends that this statement be worded to provide clarification on testing for these particular allergies, and state that the flurorescein test is only of value in detecting flurorescein allergies.

c. All references to the European drug name '[redacted] should be changed b(4) to " [redacted] ', the accepted term and established name for this neurotransmitter hormone in the United States.

d. DMETS notes that the abbreviation "cf.", the abbreviation for the latin word "confer", meaning to "compare" or "consult", should not be used as it could be misinterpreted. DMETS recommends that use of all abbreviations be avoided in labels and labeling to decrease the potential for misinterpretation and resulting errors.

5. Section 5.4 SPECIAL PRECAUTIONS FOR USE:

DMETS recommends that all doses be expressed on a milligram basis and not in milliliters, especially given that there are two concentrations available for AK-FLUOR (100 mg/mL and 250 mg/mL). Therefore, the statement " [redacted] b(4)

[redacted] to decrease the potential for misinterpretation and dosing errors.

b(4)

Additionally, the statement "[redacted]

[redacted]. Administration of AK-FLUOR is already complex with the extravasation precautions, needle placement check, and timing of the dose to obtain useful luminescence in the retina and choroidal vessels within 9 to 14 seconds of injection. Therefore, providing a time reference for slow injection (e.g., over [redacted] seconds) is important. Revise accordingly. b(4

6. Section 11 DESCRIPTION

The established name for this product is Fluorescein Injection, USP and not Fluorescein Sodium as stated in this section. The correct established name should be used consistently throughout all labels and labeling. Revise accordingly.

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