CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-186

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-186**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**4/6/07**
PRODUCT:	**AK-FLUOR® 10 and 25% (Fluorescein Injection)**
INTENDED CLINICAL POPULATION:	**Dignostic fluorescein angiography or angioscopy of the fundus and of the iris vasculature**
SPONSOR:	**Akorn Inc.**
DOCUMENTS REVIEWED:	**Module 4: Nonclinical Summary**
REVIEW DIVISION:	**Division of Anti-Infective and Ophthalmology Products**
PHARM/TOX REVIEWER:	**María I. Rivera, Ph.D.**
PHARM/TOX SUPERVISOR:	**Wendelyn Schmidt Ph.D, Zhou Chen, M.D., Ph.D.**
DIVISION DIRECTOR:	**Janice Soreth, M.D.** **Acting: Katherine Laessig, M.D., Wiley Chambers, M.D.**
PROJECT MANAGER:	**Alison Rodgers**

Date of review submission to Division File System (DFS): December 19, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval is recommended.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: None

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No nonclinical studies were submitted. The sponsor is filing this NDA based on the summary basis of approval for NDA 21-980 (Fluorescite® Injection, approved March 28, 2006) and NDA 17-869 (Funduscein® Injection; approved November 10, 1976; discontinued). Single-dose nonclinical studies were submitted for NDA 17-869 and NDA 21-980. Overall, the LD_{50s} were ≥ 800 mg/kg IV in mice and dogs. No acute toxicity was seen at 10 mg/kg in mice and dogs (0.1- and 0.7-fold the human dose of 500 mg on a body surface area basis and using a 60 kg body weight).

In the review for NDA 21-980, the pharmacologist (Zhou Chen, M.D., Ph.D.) mentioned that since Fluorescite® is indicated for use as a diagnostic agent intended for single use, no repeated-dose toxicity, genotoxicity, reproductive toxicity, and carcinogenicity studies were conducted by the sponsor. A publication for a 28-day toxicity study in dogs was submitted for NDA-17-869. The pharmacologist (Georges W. James, Ph.D.) concluded that the toxic IV dose of fluorescein in dogs appeared to be greater than 100 mg/kg (7-fold the human dose of 500 mg on a body surface area basis and using a 60 kg body weight).

The fluorescein strength in NDA 21-980 is 10% (500 mg total dose) and 25% in NDA 17-869 (750 mg total dose, respectively). Akorn Inc. is seeking the approval to market similar fluorescein strengths of 10% (500 mg/5 mL) and 25% (500 mg/2 mL). The total dose of 500 mg is equivalent to the approved dose in Fluorescite®.

The clinical adverse effect profile of fluorescein is well known from the existent clinical experience for both the 10% and 25% concentration of fluorescein. There are no novel inactive ingredients in the AK-FLUOR®clinical formulation. Therefore, there are no specific nonclinical concerns regarding the approval of this NDA.

B. Pharmacologic activity

Sodium fluorescein is a water-soluble hydroxyxanthene dye with fluorescent properties. The drug responds to electromagnetic radiation or light between the wavelengths of 465-490 nm and emits yellowish-green light at wavelengths of 520-530 nm. Fluorescent dyes are useful in evaluating the clinical signs/lesions and treatment of ocular diseases in the anterior and posterior eye segments. As indicated in the product label, following intravenous injection of fluorescein sodium, the fluorescein can be excited with a blue light flash from a fundus camera as it circulates through the ocular vasculature, and the yellowish green fluorescence of the dye is captured by the camera. In the fundus, the fluorescence of the dye demarcates the retinal and/or choroidal vasculature under observation, distinguishing it from adjacent areas/structures.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

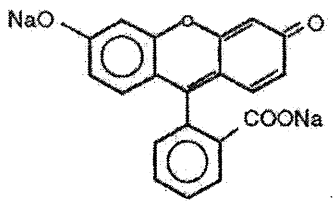
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-186
Sequence number/date/type of submission: 000/April 5, 2007/Initial NDA; 000/Apr 26, 2007/BL, PW
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Akorn Inc., Buffalo Grove, IL 60089
Manufacturer for drug substance: Akorn Inc., Buffalo Grove, IL 60089

Reviewer name: María I. Rivera, Ph.D.
Division name: Anti-infective and Ophthalmology Products
Review completion date: August 1, 2007

Drug:

Trade name: AK-Fluor® 10% or 25%
Generic name: Fluorescein sodium
Chemical name: Spiro[isobenzofuran-1 (3H), 9'-[9H]xanthene]-3-one, 3'6'-dihydroxy, disodium salt
CAS registry number: 2321-07-5 for fluorescein; 518-47-8 for fluorescein sodium
Molecular formula/molecular weight: $C_{20}H_{10}O_5.2Na/376.28$
Structure:



Relevant INDs/NDAs/DMFs: NDA 17-869 (Funduscein® 25% Injection), NDA 21-980 (Fluorescite® 10%)

Drug class: Diagnostic agent, angiographic agent

Intended clinical population: Subjects needing diagnostic fluorescein angiography or angioscopy of the fundus and of the iris vasculature

Clinical formulation: The formulation consists of 100 mg/mL (AF-Fluor® 10%) or 250 mg/mL (AF-Fluor® 25%) active ingredient and sodium hydroxide and/or hydrochloric acid and water as excipients.

Route of administration: Intravenous

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-186 are owned by Akorn Inc. or are data for which Akorn Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-186 that Akorn Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Akorn Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-186.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

No Pharmacology studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Neither study reports nor tabulated summary was provided by the sponsor.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

No PK studies were submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Neither study reports nor tabulated summary was provided by the sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No studies were submitted. The sponsor is filing this NDA based on the summary basis of approval for NDAs 17-869 and 21-980.

Single-dose nonclinical studies were submitted for NDA 17-869 and NDA 21-980. Overall, the LD_{50s} were ≥ 800 mg/kg IV in mice and dogs. No acute toxicity was seen at 10 mg/kg in mice and dogs (0.1- and 0.7-fold, respectively, the human dose of 500 mg on a body surface area basis and using a 60 kg body weight). Refer to the pharmacologist's review for each application for further details on each study.

In the review for NDA 21-980, the pharmacologist mentioned that since Fluorescite® is indicated for use as a diagnostic agent intended for single use, no repeated-dose toxicity, genotoxicity, reproductive toxicity, and carcinogenicity studies were conducted by the sponsor. A publication for a 28-day toxicity study in dogs was submitted for NDA-17-869. The pharmacologist concluded that the toxic IV dose of fluorescein in dogs appeared to be greater than 100 mg/kg (7-fold the human dose of 500 mg on a body surface area basis and using a 60 kg body weight).

Genetic toxicology: No genetic toxicology studies or literature reports were submitted. Genetic toxicology studies were not conducted for approval of NDAs 17-869 and 21-980.

Carcinogenicity: The carcinogenic potential of fluorescein has not been evaluated. Given the short term use (single administration) and relatively rapid elimination (complete clearance by 48-72 hrs after administration of 500 mg fluorescein), carcinogenicity studies are not considered necessary.

Reproductive toxicology: Animal reproductive studies have not been conducted with AK-FLUOR®. Reproductive toxicity studies were not conducted for approval of NDA 17-869. For NDA 21-980, the sponsor submitted two publications for reproductive studies in rats and rabbits to address the toxicological and teratogenic potential of the drug. As summarized by the pharmacology reviewer of NDA 21-980, administration of fluorescein at the IV dose of 140 mg/animal (about 31 mg/kg) in rabbits and 500 mg/kg in rats during different time periods (gestation Days 6 to 8 and 13 to 16 for rabbits and gestation Day 1, 6, 12, or 18 for rats) caused no teratogenic effects. However, the pharmacology reviewer of NDA 21-980 concluded that these studies were not adequate regarding animal numbers, dosage, or measured parameters (e.g., no skeletal examinations) when compared to guidelines within ICH documents.

The sponsor has assigned a Pregnancy Category C for teratogenic effects in the AK-FLUOR® label. Adequate cautions (same as in the label for Fluorescite® Injection) were placed in the AK-FLUOR® label to avoid angiography during pregnancy, unless clearly needed.

Special toxicology: No special toxicology studies were conducted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Neither study reports nor tabulated summary was provided by the sponsor.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: No nonclinical studies were submitted. The sponsor is filing this NDA based on the summary basis of approval for NDAs 17-869 and 21-980. Given the existent

clinical experience for both 10% and 25% concentration of fluorescein (for a total dose of 500 or 750 mg, respectively) and the use of common inactive ingredients in the clinical formulation, there are no nonclinical specific concerns regarding the approval of this NDA.

Unresolved toxicology issues: None

Recommendations: Approval is recommended.

Suggested labeling: No carcinogenicity, mutagenicity, impairment of fertility, or reproductive toxicity studies have been conducted with AK-FLUOR®. The nonclinical information in the AK-FLUOR® label is the same as that used in the Fluorecite® Injection label. No changes are suggested.

Signatures:

Reviewer's Signature _____
María I. Rivera, Ph.D.

Supervisor's Signature_____ Concurrence Yes ___ No ___
Wendelyn Schmidt, Ph.D.

Supervisor's Signature_____ Concurrence Yes ___ No ___
Zhou Chen, M.D., Ph.D.

cc list:

A. Rodgers/PM
R. Lloyd/MO

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

/s/

Maria I. Rivera
12/19/2007 04:55:57 PM
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Wendelyn Schmidt
1/2/2008 08:43:43 AM
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