CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-186

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-186
Submission Date	April 5, 2007
Brand Name	AK-Fluor®
Generic Name	Fluorescein Sodium Injection, USP
Primary Reviewer	Sarah Robertson, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Akorn, Inc.
Submission Type; Code	505(b)(2)
Formulation; Strength	Injection, 10% (500 mg/5 mL vial) and 25% (500 mg/2 mL vial)
Indication(s)	Diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature

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1. EXECUTIVE SUMMARY

Akorn, Inc. submitted an NDA under 505(b)(2) for AK-Fluor Injection (fluorescein sodium injection), 10% and 25%. Fluorescein Injection, USP 10% (5 mL) and 25% (2 mL) are classified as DESI-2 drugs. The Sponsor has marketed AK-Fluor 10% and 25% in the U.S. for several years under "grandfather" status. The drug is also marketed in Europe by Novartis. This NDA was submitted based on the approval of Funduscein-25 by Novartis (NDA 17-869), which has been discontinued, and Fluorescite® 10% Injection by Alcon (NDA 21-980), approved March 28, 2006. The proposed indication is for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. The total dose of both proposed strengths is equivalent to the approved adult dose of 500 mg.

The Sponsor has not submitted any clinical pharmacology studies in the NDA. A waiver of *in vivo* bioavailability is requested under 21 CFR 320.22. This is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA.

1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 4 (OCP/DCP 4) has reviewed this submission and determined it is acceptable from a clinical pharmacology perspective.

Changes to the Sponsor's proposed label should be forwarded to the Sponsor.

1.2. Phase IV Commitments

No Phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The Sponsor did not submit any clinical pharmacology studies in the NDA. However, several literature articles describing the pharmacokinetics of intravenous fluorescein were submitted in support of NDA 21-980 for Fluorescite® 10% Injection.

The time from injection of fluorescein to its appearance in the retina ranges from 7.5 to 13.5 seconds. Fluorescein is metabolized to fluorescein monoglucuronide, which is 1/3 to 1/34 as fluorescent as fluorescein. At 60 minutes after administration, approximately 80% of the fluorescein in plasma is converted to the glucuronide conjugate. As angiography is typically performed within minutes of IV administration, the effect of glucuronidation on ocular fluorescence as a diagnostic tool is minimal. Fluorescein and its metabolites are excreted in the urine, which remains slightly fluorescent for 24 to 36 hours. The systemic clearance of fluorescein is complete by 48 to 72 hours after administration of a 500 mg dose. The terminal elimination half-life of intravenous fluorescein is approximately 3 hours.

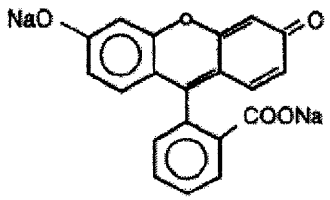
2. QUESTION-BASED REVIEW

2.1. General attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Fluorescein sodium is a sterile solution in water for use intravenously as a diagnostic aid. Its chemical name is Spiro[isobenzofuran-1(3H),9'-[9H]xanthene]-3-one,3'6'-dihydroxy,disodium salt. The molecular weight is 376.28. The chemical structure is shown below in Figure 1.

Figure 1. Chemical Structure of Fluorescein Sodium Salt



The 10% formulation contains 500 mg fluorescein sodium per 5 mL vial, while the 25% formulation contains 500 mg fluorescein sodium per 2 mL vial. The inactive ingredients consist of sodium hydroxide and/or hydrochloric acid (to adjust pH to [redacted] - 9.8) and purified water. b(4)

2.1.2. What is the proposed mechanism of action and therapeutic indication?

The yellowish-green fluorescence of the product allows for demarcation of the vascular area under observation, distinguishing it from adjacent areas. The proposed indication is for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

2.1.3. What is the proposed dosage and route of administration?

The adult dose of fluorescein sodium, 10% or 25%, is a single 500 mg dose by [redacted] intravenous injection. b(4)

2.2. General clinical pharmacology

2.2.5. What are the PK characteristics of the drug and its major metabolite?

The time from injection of fluorescein to its appearance in the retina ranges from 7.5 to 13.5 seconds. A yellow discoloration of the skin occurs within a few minutes of injection and fades in 6 to 12 hours. The volume of distribution of fluorescein is approximately 0.5 L/kg. Fluorescein is metabolized to fluorescein monoglucuronide. At 60 minutes after administration approximately 80% of the fluorescein in plasma is converted to the glucuronide conjugate. The conjugate is around 1/3 to 1/34 as fluorescent at fluorescein, depending on the wavelength of excitation. As angiography is typically performed within minutes of IV administration, the effect of glucuronidation on ocular fluorescence as a diagnostic tool is minimal. Fluorescein and its metabolites are excreted in the urine, which becomes bright yellow during the first few hours following injection. The urine remains slightly fluorescent for 24 to 36 hours. The systemic

clearance of fluorescein is complete by 48 to 72 hours after administration of a 500 mg dose. The terminal elimination half-life of intravenous fluorescein is reported to be 3 hours. In a study conducted in 10 healthy male subjects by Barry et al., fluorescein excretion in the urine was measurable up to 24 hours post-dose, but the vast majority of elimination was complete within 12 hours of administration.

2.3. Intrinsic factors

2.3.1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphisms, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

There are no data available on the influence of intrinsic factors on fluorescein pharmacokinetics. See response to Question 2.3.2 below.

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteer vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.2.1. Elderly

Studies have not been conducted comparing the pharmacokinetics, safety or efficacy of fluorescein injection in elderly subjects vs. non-elderly subjects. The proposed product label for AK-Fluor, consistent with the approved label for Fluorescite®, contains the following statement: *No overall differences in safety or effectiveness have been observed between elderly and younger patients.* This statement is based on observational clinical experience.

2.3.2.2. Pediatric Patients

The proposed product label for AK-Fluor contains the following statement under "Pediatric Use": [redacted]. This statement is consistent with that of the approved product label for Fluorescite®. However, it is not clear what this statement is based on, as no pediatric studies appear to have been conducted. The following proposed dose appears to be based on clinical experience: *For children, the dose should be calculated on the basis of 35 mg for each ten pounds of body weight (7.7 mg/kg body weight).* This dose (7.7 mg/kg) is equivalent to the adult dose of 500 mg, based on a 65 kg adult. The proposed pediatric dose is consistent with the approved label for Fluorescite®.

b(4)

2.3.2.5. Renal Impairment

Studies have not been conducted in subjects with renal impairment. The following statement appears under "Use in Special Populations" in the proposed AK-Fluor package insert: [redacted] This is a new statement that does not appear in the product label for Fluorescite®. There is one case reported in which slightly higher plasma concentrations of free fluorescein and markedly elevated plasma concentrations of fluorescein glucuronide were reported in a diabetic patient with renal insufficiency compared to a healthy subject administered the same dose of fluorescein. This finding is consistent with fluorescein's predominantly renal route of elimination. However, fluorescein has been

b(4)

administered as a single dose for diagnostic use for over 30 years with no apparent safety issues for renally impaired patients.

2.3.2.6. Hepatic Impairment

The Sponsor did not submit any information regarding the pharmacokinetics of fluorescein in patients with hepatic impairment. The following statement appears under "Use in Special Populations" in the proposed AK-Fluor package insert: b(4) This is a new statement that does not appear in the product label for Fluorescite®.

2.3.2.7. Lactation

Fluorescein excretion in human breast milk has been demonstrated. One publication reported fluorescein in breast milk samples up to 76 hours after drug administration (the last sample obtained) following a standard injection of 5 mL of 10% fluorescein sodium to a female nursing patient. Because no further data on the excretion of fluorescein into breast milk is available, recommendations to minimize the exposure of fluorescein to a nursing infant cannot be made.

The following statement under Section 8.3 of the proposed label is consistent with that of the approved label for Fluorescite 10%: *Fluorescein has been demonstrated to be excreted in human milk. Caution should be exercised when AK-FLUOR® (fluorescein injection, USP) is administered to a nursing woman.*

2.4. Extrinsic factors

2.4.2. Drug-Drug Interactions

There have not been any studies conducted assessing the potential for drug interactions with fluorescein. However, the proposed label for AK-Fluor contains a warning regarding a higher risk of adverse reactions in patients b(4) This warning is based on a drug safety survey conducted in 2001 and reported in the French Healthy Products Safety Agency (FHPSA) Letter to Physicians (February 2004), and the findings of 15-day alert reports submitted by Akorn for the period of 1/2004 to the time of this NDA submission. The reports contain cases of death due to anaphylaxis and cardiac arrest in patients being chronically treated with beta blockers (including ophthalmic drops) and/or ACE inhibitors. Patients on these medications are considered to be at greater risk of death in the event of reactive shock or hypotension due to reduced efficacy of epinephrine and volume expanders.

2.4.2.5. Are there any metabolic/transport pathways that may be important?

Fluorescein is a known substrate for organic anion transport (OAT) proteins. However, the effect of OAT inhibitors (e.g. probenecid) on fluorescein pharmacokinetics has not been assessed.

2.5. General Biopharmaceutics

The proposed formulation of AK-Fluor for Injection consists of the active ingredient, fluorescein 500 mg, and the following inactive ingredients: sodium hydroxide and/or hydrochloric acid (to adjust pH to – 9.8) and purified water. This formulation is identical to that of Fluorescite®. b(4)

3. DETAILED LABELING RECOMMENDATIONS

See Appendix for annotated changes to the proposed label.

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

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