CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-186

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW

NDA #:	22,186
Drug Name:	AK-Fluor (fluorescein sodium injection), 25% (2 mL Vial) and 10% (5 mL Vial)
Indication(s):	Diagnostic fluorescein angiography or angioscopy of the fundus and of the iris vasculature.
Applicant:	Akorn, Inc.
Date(s):	4-5-07
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
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Clinical Reviewer:	Rhea Lloyd, M.D.
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1. EXECUTIVE SUMMARY

1.1 Introduction

In NDA 22-186, Akorn is seeking the approval of AK-Fluor 25%, Fluorescein Sodium 25% (2 mL vial) and AK-Fluor 10%, Fluorescein Sodium 10% (5 mL vial), both with a total dose of 500 mg fluorescein. Akorn has submitted a 505(b)(2) application based on the approval of Fluorescite (NDA 21-980). As a 505(b)2, NDA 22-186 relies upon the Agency's findings of safety and efficacy contained in the summary bases of approval for Alcon's Fluorescite (NDA 21-980) and Novartis's Fundescein-25 (NDA 17-869). Fluorescite and Fundescein-25 contain the same active ingredient as AK-Fluor (fluorescein sodium). There is more than a 30 year history of use in the U.S. for both AK-Fluor and Fluorescite with adequate demonstration of effectiveness and safety. Akorn, Inc. has not conducted any pre-clinical or clinical studies using fluorescein sodium injection. Akorn, Inc. has requested to revise the package insert exactly to match the RLD, Fluorescite 10%.

1.2 Conclusions and Recommendations

Based on the evidence provided, a 505(b) (2) application supports the effectiveness of AK-Fluor (fluorescein injection, USP) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. Safety and effectiveness of fluorescein sodium injection, 10% and 25% has been adequately assessed per the above mentioned SBAs. In addition, no overall differences in safety or effectiveness have been observed with regards to age, gender or ethnicity. It should be noted, however, that assessments of the overall safety and efficacy may be limited due to lack of prospectively designed, adequate and well controlled studies in the current submission.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

AK-Fluor (fluorescein injection, USP) 10% and 25% is a sterile aqueous solution containing sodium fluorescein and is indicated in diagnostic fluorescein angiography or angioscopy of the fundus and iris vasculature, i.e., diagnosis and evaluation of ocular diseases. Fluorescein sodium is a pre-1938 drug product, although the formulation, manufacturing, and labeling have changed several times in the past 50 years. There is more than a 30 year history of use of this particular product, AK-Fluor, with adequate demonstration of effectiveness and safety. The initial launch date of AK-Fluor was in December 1975 in France. Distribution data submitted by Akorn, Inc. indicate that the total number of units sold between January 2003 and June 2007 as follows: b(4)

- AK-Fluor 10% - Domestic ( ) and Foreign ( )
- AK-Fluor 25% - Domestic ( ) and Foreign ( )

2.1.2 Rationale for Drug Product Development

Fluorescein angiography is most useful for studying the retinal circulation, and therefore is used to evaluate patients with diabetic retinopathy, vascular occlusive diseases such as retinal vein and

arterial occlusions, and wet macular degeneration. Alcon's Fluorescite, NDA 21-980, is the only approved New Drug Application for fluorescein injection 10%. Funduscein-25 (fluorescein sodium injectable) by Novartis (NDA 17-869), was discontinued for reasons other than safety and effectiveness .

2.2 Data Sources

- Files of \\Cdsesub1\nonectd\N22186\N_000

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

There are no clinical studies performed or submitted within Akorn's submission of NDA 22-186 for AK-Fluor. This 505 (b) (2) application relies upon the Agency's findings of safety and efficacy contained in the Summary Bases of Approval (SBAs) for NDA 21-980, Fluorescite and NDA 17-869, Fundescein-25. Evidence provided from the above SBAs, postmarketing experience and literature references provide some evidence regarding the safety and efficacy of fluorescein sodium injection, 10% and 25%. In addition, no overall differences in efficacy have been observed with regards to age, gender or ethnicity. However, it should be noted that assessments of the overall safety and efficacy may be limited due to lack of prospectively designed, adequate and well controlled studies.

3.2 Evaluation of Safety

Safety of fluorescein sodium injection, 10% and 25% has been adequately assessed per the above mentioned SBAs. No overall differences in safety have been observed between according age, gender or ethnicity. There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population. Safety evaluations were based on the following sources:

- Literature references not specifically citing Akorn's AK-Fluor product or citing another fluorescein sodium product.
- A Novartis-prepared Periodic Safety Update Report (PSUR 4) prepared for the European Union covering 01 April 2003 to 31 March 2006.
- An Akorn-prepared AK-Fluor Investigation Report dated July 20, 2004.
- Akorn's AK-Fluor 15-day Alert Reports submitted 2004 through 2006.

For more information, refer also to the medical review of AK-Fluor by Dr. Rhea Lloyd.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Safety and effectiveness in special populations have been adequately assessed per the Summary Bases of Approval (SBAs) for Fluorescite (NDA 21-980) and Fundescein-25 (NDA 17-869). Based on the medical review of NDA 21-980, there were no overall differences in safety or effectiveness observed between elderly and other adult patients as well as no overall differences in safety or effectiveness with regards to gender or ethnicity. Safety and effectiveness in pediatric patients have also been established. There is also no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

5. CONCLUSIONS

Based on the evidence provided, a 505(b) (2) application supports the effectiveness of AK-Fluor (fluorescein injection, USP) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. Safety and effectiveness of fluorescein sodium injection, 10% and 25% has been adequately assessed per the above mentioned SBAs. In addition, no overall differences in safety or effectiveness have been observed with regards to age, gender or ethnicity. It should be noted, however, that assessments of the overall safety and efficacy may be limited due to lack of prospectively designed adequate and well controlled studies in the current submission.

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