CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-186

MEDICAL REVIEW(S)

Medical Officer's Review #3
Draft Labeling

NDA 22-186	**Submission Date:**	July 16, 2008
	Receipt Date:	July 16, 2008
	Review Date:	July 23, 2008

Applicant:

Akorn, Inc.
2500 Millbrook Drive
Buffalo Grove, IL 60089-4694

Applicant's Representative:

Sam Boddapati, PhD
Vice President, Regulatory Affairs
847-353-4909

Drug:

AK-Fluor (fluorescein injection, USP) 10% and 25%

Pharmacologic Category:

diagnostic dye

Submitted:

On March 28, 2008, the applicant submitted a Complete Response to the Not Approvable letter dated February 6, 2008. This submission addresses all of the CMC deficiencies listed in the February 6, 2008 letter. A revised package insert was also submitted and was the subject of the June 27, 2008, review.

The applicant has submitted a revised package insert in response to the FDA emails dated July 2, 2008 which requested various changes in the previously submitted package insert.

In response to the FDA email dated July 16, 2008, the applicant has submitted the following package insert which incorporates all previous requested revisions and the revision to the second sentence of Section 12.3.

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 3

Reviewer's Comments:

The carton and container labeling for AK-Fluor 10% submitted in the original NDA dated April 5, 2007 was reviewed in the Medical Officer's Review dated February 4, 2008. The carton and container labeling for AK-Fluor 25% is consistent with the 10%. The AK-Fluor carton and container labeling were acceptable.

Recommended Regulatory Action:

The remaining Product Quality Microbiology deficiencies listed in the Approvable letter dated, February 6, 2008, have been resolved. It is recommended that NDA 22-186 be approved with the following minor spelling change to the label:

1. In the second sentence of Section 5.2, a spelling error has been corrected. The word "curve" should be revised to "nerve."

The application supports the safety and effectiveness of AK-Fluor (fluorescein injection) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There are no recommendations for additional postmarketing studies.

Rhea A. Lloyd, MD
Medical Officer

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/s/

Rhea Lloyd
7/25/2008 01:41:55 PM
MEDICAL OFFICER

William Boyd
7/25/2008 01:44:20 PM
MEDICAL OFFICER

Medical Officer's Review #2
Draft Labeling

NDA 22-186	**Submission Date:**	March 28, 2008
	Receipt Date:	April 8, 2008
	Review Date:	June 27, 2008

Applicant:

Akorn, Inc.
2500 Millbrook Drive
Buffalo Grove, IL 60089-4694

Applicant's Representative:

Sam Boddapati, PhD
Vice President, Regulatory Affairs
847-353-4909

Drug:

AK-Fluor (fluorescein injection, USP) 10% and 25%

Pharmacologic Category:

diagnostic dye

Submitted:

The applicant has submitted a Complete Response to the Not Approvable letter dated February 6, 2008. This submission addresses all of the CMC deficiencies listed in the February 6, 2008 letter.

A revised package insert was also submitted and is the subject of this review. Following is the draft labeling for the product included in the February 6, 2008, letter with additional changes from other disciplines.

The sponsor's deletions are noted by and additions by underline within the review.
The reviewer's deletions are noted by and additions by underline within the review.

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 4

Recommended Regulatory Action:

It is recommended that the draft labeling be approved with the revisions noted in this review.

Rhea A. Lloyd, MD
Medical Officer

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/s/

Rhea Lloyd
6/27/2008 02:58:59 PM
MEDICAL OFFICER

Wiley Chambers
6/30/2008 10:45:58 AM
MEDICAL OFFICER

Medical Officer's Review of NDA 22-186
Draft Labeling

NDA 22-186	**Submission Date:** March 28, 2008 **Receipt Date:** April 8, 2008 **Review Date:** May 15, 2008
Applicant:	Akorn, Inc. 2500 Millbrook Drive Buffalo Grove, IL 60089-4694
Applicant's Representative:	Sam Boddapati, PhD Vice President, Regulatory Affairs 847-353-4909
Drug:	AK-Fluor (fluorescein injection, USP) 10% and 25%
Pharmacologic Category:	diagnostic dye
Submitted:	The applicant has submitted a Complete Response to the Not Approvable letter dated February 6, 2008. This submission addresses all of the CMC deficiencies listed in the February 6, 2008 letter. A revised package insert was also submitted and is the subject of this review. Following is the draft labeling for the product included in the February 6, 2008, letter. The sponsor's deletions are noted by and additions by underline within the review. The reviewer's deletions are noted by and additions by underline within the review.

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 5

Recommended Regulatory Action:

It is recommended that the draft labeling be approved with the revisions noted in this review.

Rhea A. Lloyd, MD
Medical Officer

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/s/

Rhea Lloyd
5/15/2008 11:43:37 AM
MEDICAL OFFICER

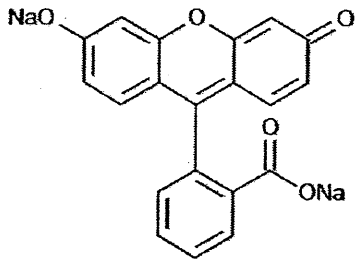
William Boyd
5/15/2008 11:48:18 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-186
Submission Code	Original
Letter Date	April 5, 2007
Stamp Date	April 6, 2007
PDUFA Goal Date	February 6, 2008
Reviewer Name	Rhea A. Lloyd, M.D.
Review Completion Date	January 31, 2008
Established Name	fluorescein injection
(Proposed) Trade Name	AK-Fluor
Therapeutic Class	4042210 diagnostic dye
Applicant	Akorn, Inc. 2500 Millbrook Drive Buffalo Grove, IL 60089 847-279-6100
Priority Designation	S

Formulation

Active ingredient: fluorescein sodium



Dosing Regimen

500 mg (100 mg/mL) or (250 mg/mL) via intravenous administration

Indication

Diagnostic fluorescein angiography or angioscopy of the fundus and of the iris vasculature

Intended Population

Adult and pediatric patients undergoing diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature

Table of Contents

1 Executive Summary

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-186 be approved with the labeling revisions included in this review once the CMC deficiencies are resolved.

The application supports the safety and effectiveness of AK-Fluor (fluorescein injection) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There are no recommendations for additional postmarketing studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

1.2.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

1.2.3 Other Phase 4 Requests

There are no recommended Phase 4 requests.

1.3 Summary of Clinical Finding

1.3.1 Brief Overview of Clinical Program

Sodium fluorescein is a water-soluble hydroxyxanthine dye. Fluorescence is the important property of fluorescein dye that makes it possible to selectively visualize fluorescein-colored solutions. Fluorescence occurs when a substance absorbs light of one wavelength and re-emits a portion of that light at a longer wavelength. In ophthalmic usage, a blue light (wavelength approximately 465-490 nm) is used to illuminate the dye and it is reflected back as a yellow-green light (wavelength approximately 520-530nm).

Fluorescein angiography has become an indispensable tool in ophthalmic practice for the diagnosis of neovascular ocular diseases, especially those that have a retinal component. Fluorescein angiography can be used to diagnose and document such diseases as choroidal neovascularization in age-related macular degeneration, neovascular diabetic retinopathy, and cystoid macular edema resulting from a variety of posterior ocular disease conditions, as well as diseases of the anterior segment of the eye.

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, though 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 (units) and Foreign (units)
- AK-Fluor 25% - Domestic (units) and Foreign (units).

Alcon filed NDA 21-980 for Fluorescite (fluorescein injection, USP) 10% which was approved on March 28, 2006. The total drug content approved in NDA 21-980 was 500 mg / 5 mL. Novartis' NDA 17-869 was approved on November 10, 1976, as Funduscein-25 25% and 10% were approved for a total dose of 750 mg/3mL ampules and 500 mg/ 5 mL ampules, respectively. Fundescein-25 has been discontinued but not for reasons of safety or efficacy.

In NDA 22-186, Akorn is seeking the approval of Fluorescein Sodium 25% (2 mL vial) with a total dose of 500 mg fluorescein and Fluorescein Sodium 10% (5 mL vial) with a total dose of 500 mg fluorescein based on the approval of NDA 21-980. As a 505(b)(2) application, NDA 22-186 is relying upon the Agency's findings of safety and efficacy contained in the Approval for NDA 21-980 Fluorescite and NDA 17-869 Fundescein-25.

Akorn, Inc. has not conducted any clinical studies using fluorescein sodium injection.

Reviewer's Comment:
The sponsor's assertion that AK-Fluor has been manufactured and distributed under "grandfather" status is incorrect. AK-Fluor has been illegally marketed in the United States without a New Drug Application.

1.3.2 Efficacy

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

1.3.3 Safety

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There is more than a 30 year history of use of this particular product, AK-Fluor, with adequate demonstration of effectiveness and safety. Distribution data submitted by Akorn, Inc. indicate that the total number of units sold between January 2003 and June 2007 as follows:

- AK-Fluor 10% - Domestic ([redacted] units) and Foreign ([redacted] units) b(4)
- AK-Fluor 25% - Domestic ([redacted] units) and Foreign ([redacted] units).

This review reveals no new safety findings for AK-Fluor based on the submitted postmarketing data. There is no evidence of abuse potential for this product.

1.3.4 Dosing Regimen and Administration

The proposed normal adult dose of AK-Fluor (fluorescein injection) 10% and 25% is 500 mg (100 mg/mL) or (250 mg/mL) via intravenous administration.

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).

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

1.3.5 Drug-Drug Interactions

Specific drug interaction studies have not been submitted.

1.3.6 Special Populations

Safety and effectiveness of fluorescein sodium injection, 10% and 25% has been adequately assessed in special populations in NDAs 17-869 and 21-980.

No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

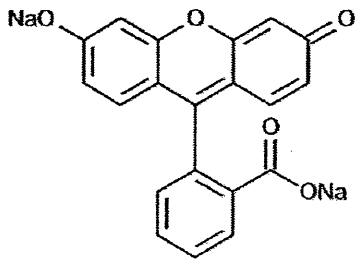
Safety and effectiveness in pediatric patients have been established.

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

2 Introduction and Background

2.1 Product Information

AK-Fluor (fluorescein injection, USP) 10% and 25% contains fluorescein sodium (equivalent to fluorescein 10% w/v and 25% w/v). It is a sterile solution for use intravenously as a diagnostic aid. Its chemical name is spiro[isobenzofuran-1(3*H*),9'-[9*H*]xanthene]-3-one, 3'6'-dihydroxy,disodium salt. The active ingredient is represented by the chemical structure:



Reviewer's Comment:
AK-Fluor has been illegally marketed previously without a New Drug Application in the United States.

2.2 Currently Available Treatment for Indications

Sodium fluorescein and indocyanine green (ICG) are two diagnostic dyes which are most commonly used to perform diagnostic ocular angiography. These dyes are used to obtain different diagnostic information on the retinal and choroidal circulations.

Fluorescein angiography is 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 subject of an approved New Drug Application for fluorescein injection 10%. One drug product, fluorescein injection 25%, is approved although discontinued for reasons other than safety and effectiveness, NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) 3 mL – Novartis.

2.3 Availability of Proposed Active Ingredient in the United States

Alcon's Fluorescite, NDA 21-980, is the subject of an approved New Drug Application for fluorescein injection 10%. It is currently marketed in the United States.

Fluorescein injection 25%, was discontinued for reasons other than safety and effectiveness, NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) – Novartis.

2.4 Important Issues with Pharmacologically Related Products

No safety or effectiveness concerns have arisen in other members of this pharmaceutical class, whether marketed or investigational.

2.5 Presubmission Regulatory Activity

AK-Fluor has been illegally marketed previously without a New Drug Application in the United States.

On March 28, 2006, Alcon's NDA 21-980, Fluorescite (fluorescein injection, USP) 10% was approved. Additionally, one drug product, fluorescein injection 25%, was discontinued for reasons other than safety and effectiveness, NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) – Novartis.

There was no previous IND held by Akorn for this product. There was no Pre-NDA meeting requested or held for this drug product.

2.6 Other Relevant Background Information

The use of fluorescein sodium in retinal angiography was first described in 1961 by Novotny and Alvis.[1] Since this time, it has become the gold standard for evaluation of the choroidal and retinal vasculature.

From July 16, 2003, Novartis Pharma obtained Fluorescein Injection 10% from Akorn, Inc. USA, for distribution in Europe under the name Fluorescein 10% Faure, Solution for Injection. Akorn, Inc. discontinued marketing this drug through Novartis Pharma in 2006.

1 Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. Circulation 1961;24:82-6.

Table 2.6 - Cumulative World-Wide Market Authorization Status for AK-Fluor

Country	First Authorization Date	Tradename if not Fluorescein
Algeria	May 30, 1996	Fluoresceine 10% Faure
Belgium	May 4, 1991	Fluoresceine 10% Faure
Bulgaria	March 6, 2001	Fluoresceine 10% Faure
France	September 19, 1975	Fluoresceine sodique 10% Faure; Renewal May 30, 2000
Hungary	September 3, 1991	Fluorescein 10%; Renewal September 16, 2004
Israel	April 30, 1988	Fluoresceine 10%
Lebanon	December 30, 1978	Fluoresceine 10% Faure
Malta	October 24, 2001	Fluoresceine 10% Faure
Morocco	January 5, 1993	Fluoresceine 10% Faure; Renewal September 1, 1999
Poland	August 10, 1979	Fluoresceine 10%; Renewal August 9, 2004
Portugal	June 5, 2002	Fluoresceine 10%
Senegal	December 30, 1995	Fluoresceine 10% Faure; Renewal February 6, 2002
Spain	June 26, 2003	Fluoresceina oculos 10%
Sri Lanka	September 2, 2002	Fluoresceine 10% Faure; Voluntarily withdrawn June 6, 2003
Switzerland	October 23, 1987	Fluoresceine 10% Faure; Renewal August 10, 1999
Tunisia	May 2, 1977	Fluoresceine 10% Faure

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

Akorn has manufactured AK-Fluor, fluorescein sodium injection illegally without an NDA. Akorn marketed this drug under this status in both ampules and vials. The manufacturing of drug product in ampules was discontinued as of December 31, 2006. The current NDA is filed seeking the approval of 5 mL vial for fluorescein sodium 10% (500 mg fluorescein) and 2 mL vial of fluorescein sodium 25% (500 mg fluorescein). The drug product was manufactured at Akorn's Decatur, Illinois facility in ——— until it was decommissioned December 31, 2006. Subsequently, manufacture of the drug product was shifted to ——— at the same facility. The drug product is ——— sterilized for product sterility assurance.

b(4)

Potential visible particles were suspected to be present in two lots of AK-Fluor ampules (Lot numbers 21264 and 21274, 5 mL ampules) which were marketed in France and were reported to the Agency in two adverse drug events. These adverse drug events occurred in France where AK-Fluor was marketed by Novartis.. Upon further investigation by Novartis and Akorn, the fine transient precipitate was identified as fluorescein sodium. Further, Akorn has investigated the particles in AK-Fluor samples at [redacted], for the identification of particulates and to [redacted] for the chemical identification. b(4)

AK-Fluor (fluorescein injection) 10% and 25% is is proposed as a sterile clear red-orange aqueous solution containing fluorescein sodium. It contains USP grade drug substance and NF grade pharmaceutical excipients without a preservative. It is formulated at pH [redacted] to achieve optimal stability for the active product, using sodium hydroxide and hydrochloric acid for maintaining a basic pH. Sodium hydroxide is used to [redacted] b(4)

The proposed packaging is as follows:
AK-Fluor (fluorescein injection, USP) 10% is filled in single dose 5 mL vials in packs of 12.
AK-Fluor (fluorescein injection, USP) 25% is filled in single dose 2 mL vials in packs of 12.

The Product Microbiology consult is pending. No preliminary issues were identified.

Reviewer's Comment:
There are multiple outstanding Chemistry, Manufacturing and Controls problems and deficiencies which have not yet been resolved. The application is not approvable from a CMC perspective.

3.2 Animal Pharmacology/Toxicology

The application relies upon the Agencies findings for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for demonstration of safety and efficacy for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

AK-Fluor (fluorescein injection, USP) 10% and 25% has been marketed in the US for over 30 years. Fluorescein sodium has been extensively studied for PK and PD properties, diagnostic utility for many ocular diseases, and safety of the formulation. Since the proposed indication is 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. No toxicity studies were submitted in this NDA submission.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

No new clinical studies were performed or have been submitted with the New Drug Application. This application relies upon the Agency's findings of safety and efficacy contained in NDA 21-980, Fluorescite and NDA 17-869, Fundescein-25.

The major sources of clinical data utilized in this review include:

- 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.

4.2 Tables of Clinical Studies

No new clinical studies were conducted for this NDA submission. The application relies upon the Agency's findings of safety and efficacy in NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for demonstration of safety and efficacy for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

4.3 Review Strategy

No new clinical data was submitted in this NDA submission. The application relies upon the Agency's findings of safety and efficacy in NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

4.4 Data Quality and Integrity

No new clinical data was submitted in this NDA submission.

There were no Division of Scientific Investigations (DSI) audits performed.

4.5 Compliance with Good Clinical Practices

No new clinical data was submitted in this NDA submission.

4.6 Financial Disclosures

No new clinical studies were performed or were included in this NDA submission. Consequently, no completed certification and disclosure forms were provided.

5 Clinical Pharmacology

No new preclinical or clinical studies were performed or were included in this NDA submission. The application relies upon the Agency's findings in NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

5.1 Pharmacokinetics

Fluorescein sodium administered by the intravenous route into the antecubital vein is visible in the central retinal artery of the eye within 7 to 14 seconds. A yellowish discoloration of the skin is apparent within a few minutes of IV administration. The discoloration begins to fade 6 to 12 hours after IV administration. Various estimates of volume of distribution indicate that fluorescein distributes well into interstitial space (0.5 L/kg). Between 50 and 84% of fluorescein is bound to plasma proteins (expecially albumin) and 15 to 17% is bound to erythrocytes.

Fluorescein undergoes rapid metabolism to fluorescein monoglucuronide. After IV administration of fluorescein sodium (14 mg/kg) to 7 healthy subjects, approximately 80% of the fluorescein present in plasma was converted to its glucuronide conjugate after a period of 1 hour post dose, indicating relatively rapid conjugation. Fluorescein monoglucuronide is about 1/3 to 1/4 as fluorescent as fluorescein, depending on the wavelength of excitation of the blue light.

Fluorescein and its metabolites are primarily eliminated via renal excretion. After IV administration, the urine remains slightly fluorescent for 24 to 36 hours. A renal clearance of 1.75 mL/min/kg and a hepatic clearance (due to conjugation) of 1.50 mL/min/kg have been estimated. The systemic clearance of fluorescein was essentially complete by 48 to 72 hours after administration of 500 mg fluorescein.

5.2 Pharmacodynamics

There is no preclinical data or clinical data presented or referenced that indicate fluorescein sodium affects cardiac conduction unless as a result of an anaphylactic reaction. There is no preclinical data or clinical data presented or referenced that indicate fluorescein sodium adversely affects pulse, blood pressure, or respiration unless associated with an anaphylactic reaction.

5.3 Exposure-Response Relationships

AK-Fluor is intended for single intravenous administration by a physician as part of a diagnostic test (fluorescein angiogram).

There is adequate clinical experience with the proposed drug product, AK-Fluor. There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

6 Integrated Review of Efficacy

6.1 Indication

The proposed indication, diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature, is acceptable.

6.1.1 Methods

No new clinical data was submitted in this NDA submission.

6.1.2 General Discussion of Endpoints

No new clinical data was submitted in this NDA submission.

Fluorescein angiography is an indispensable tool in ophthalmic practice for the diagnosis of neovascular ocular diseases, especially those that have a retinal component. Fluorescein angiography can be used to diagnose and document such diseases as choroidal neovascularization in age-related macular degeneration, neovascular diabetic retinopathy, and cystoid macular edema resulting from a variety of posterior ocular disease conditions, as well as diseases of the anterior segment of the eye.

Regarding the choice of endpoints for the proposed indication, the majority of the literature references and study reports cite diagnostic utility (i.e. the quality of the fluorescein angiogram obtained or visualization) as their efficacy endpoint.

6.1.3 Study Design

No new clinical data was submitted in this NDA submission. The application relies upon the Agency's findings of safety and efficacy contained in the Summary Bases of Approval (SBA) for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

6.1.4 Efficacy Findings

No clinical data was submitted in this NDA submission.

6.1.5 Clinical Microbiology

There is no Clinical Microbiology review for this product. It is not an anti-infective.

6.1.6 Efficacy Conclusions

The 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.

The application relies upon the Agency's findings in NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

7 Integrated Review of Safety

7.1 Methods and Findings

No new clinical data was submitted in this NDA submission. The application relies upon the Agency's findings of safety and efficacy for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

These additional sources of clinical data were also reviewed to assess the safety of AK-Fluor:

- 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.

7.1.1 Deaths

Reports of ten (10) deaths are included in the 15 day alert reports prepared by Akorn and submitted to the Agency between 01 January 2004 and December 31 2006. These deaths and one additional report (CVBU2003TN00827) are reported in the Periodic Safety Update Report (PSUR) 4 which covers 01 April 2003 through 31 March 2006. The individual case histories are presented here.

Individual Case Histories:

CASE #401025410 (CARDIORESPIRATORY ARREST; DEATH)
A 76 year-old male with aortic valve replacement received neosynephrine (eye drop) prior to angiography to achieve mydriasis to facilitate imaging of the retina. The patient went into cardiopulmonary arrest within a minute after IV AK-Fluor, resuscitation (full efforts) was unsuccessful. Patient's medical history was significant for an aortic valve prosthesis and treated by Previscan (fluinoine), essential hypertension (transolapril) and hypercholesterolemia (simvastatin). Investigation revealed that this patient was also on long term treatment with sotalol for extrasystoles. The patient had no history of allergy. This was the patient's first time receiving fluorescein.

CASE #402725410 (MALAISE, RESPIRATORY DIFFICULTIES, CYANOSIS, DEATH) b(6)
On [redacted], a 75 year-old male patient undergoing a retinal angiogram received an unknown dose of AK-Fluor 10% and about 50 seconds later he experienced a malaise and then respiratory difficulties, cyanosis, froth around the mouth and loss of consciousness. He was intubated, ventilated, and transferred in a resuscitation unit. On admission there, patient was in a coma with severe cyanosis, pulse 90, elevated BP, and oxygen saturation 70%. Resuscitation was not successful. An intra-cardiac clot was revealed. The patient had been concomitantly treated with propranolol for an unspecified indication. Additional history revealed that the patient had asthmatiform bronchitis, diabetes mellitus, migraine, and cataract.

CASE #402825410 (DEATH)
A 42 year-old male patient who suffered probable anaphylactic shock, cardio-respiratory arrest, ventricular fibrillation, coma, life support was given, intubation, cardiac massage, cardioversion, myocardial ischemia, intestinal ischemia, lactic acidosis, dialysis, shock dysgeusia, loss of consciousness, convulsion, and death after receiving 5 mL of AK-Fluor 10% followed by an unknown dose of ICG for an retinal angiogram procedure. He had already undergone 2 right eye angiograms retina with fluorescein because of functional disorder of the right eye with suspicious of sympathetic ophthalmia and vision decrease in the last year. He had an unspecified family history of cardiac disorder but no personal history and non known concomitant medication. On [redacted] after a pre-medication with tropicamide and phenylephrine the patient b(6)
received a vial of AK-Fluor without any problem. Three minutes later, he was administered ICG associated with 5% glucose. He immediately had a bad taste and the injection was discontinued; he might have received about 6 cc.

CASE #A403225410 (ANAPHYLACTIC SHOCK, LOSS OF CONSCIOUSNESS, DEATH)
An 82 year-old woman suffered a possible anaphylactic reaction, loss of consciousness, and death after receiving a single IV dose of AK-Fluor 10 % for an angiogram retina procedure. Patient was dilated with phenylephrine and tropicamide prior to receiving fluorescein. Patient's past medical history included Penicillin allergy, chronic bronchopathy, possible cardiac insufficiency and Wolff-Parkinson-White syndrome. This was the first time fluorescein was given.

CASE #403425410 (CARDIORESPIRATORY ARREST, MYOCARDIAL INFARCTION, DEATH)

72 year-old woman experienced shock, loss of consciousness and respiratory arrest 1.5 min after receiving 5 mL of AK-Fluor 10%. This patient had undergone 6 previous retinal angiograms. No previous history of allergy or cardiac disorder. Despite immediate resuscitative care, patient died of myocardial infarction in ventricular fibrillation. Past medical history includes heavy tobacco use, overweight, anxiety, hypercholesterolemia, POAG, AMD. Concomitant medications include beta blockers. Vials were found to be within specifications. Glass particles were found to be related to method of opening vials. Additional particles in vials were found to be fluorescein.

CASE #403525410 (CARDIAC ARREST, MYOCARDIAL INFARCTION; DEATH)
81 year-old woman who suffered cardiac arrest, myocardial infarction, and died after undergoing a retinal angiogram using AK-Fluor 10% injection. Past medical history is significant for angina pectoris and cardiac failure. The patient underwent retinal angiography due to central retinal vein thrombosis. Attempts at resuscitation were not successful. Diagnosis of myocardial infarction was made.

CASE #A403625410 (UNEXPLAINED DEATH)
An 87 year-old woman unexplainably expired hours after undergoing a retinal angiogram with AK-Fluor. This elderly patient had a history of old myocardial infarction. The procedure took place at 1000. After lunch, the patient fell asleep in an armchair. Her death was noticed at 1700.

CASE #400225020 (DEATH)
A 79 year-old female patient suffered a possible anaphylactic reaction and death after receiving 2 mL AK-Fluor for a retinal angiogram. The patient became nauseous, disoriented, diaphoretic, pale and unresponsive. With resuscitative efforts she gained orientation. She was transferred to a hospital by EMTs. At hospital, she became hypotensive, was intubated and given supportive medications. She expired after the injection of AK-Fluor.

CASE #A500525410 (RETROSTERNAL PAIN, THREADY PULSE, DEATH)
An 84 year-old woman with a history of hereditary retinal degeneration and age-related macular degeneration treated with dynamic phototherapy. Three months after this treatment, she underwent an angiogram retina with AK-Fluor. After the examination the patient presented a moderate retrosternal pain without loss of consciousness but with thready pulse. She was hospitalized and kept under supervision during one night without any obvious seriousness according to the nurse. At 6:00 am the patient was found dead. It was specified that the patient was feeling unwell for 3 days.

CASE #600125410 (HYPERHIDROSIS, SUDDEN DEATH)
A 74 year-old man with a history of diabetes, mild aortic stenosis, hypertension and low creatinine clearance. He was hospitalized following several episodes of malaise with falls for diabetes work-up. On [redacted], he underwent a retinal angiogram and received AK-Fluor at 16:20 which he appeared to tolerate well. On [redacted] at 0300, he was found to have excess sweating with normal BP and heart rate. At 05:30, the patient was found dead in his bed. b(6)

Reviewer's Comments:

These deaths and reactions are reported voluntarily from a population of uncertain size (versus a controlled clinical trial;, it may not always be possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7.1.2 Other Serious Adverse Events

Table 7.1.2-1 - Frequency of severe adverse reactions (based on 221,781 angiograms performed in 1984 by 2434 respondents of a US survey of practicing ophthalmologists) (table modified after Yannuzzi et al. 1986)2

	N = 221,781 Angiograms		
	Frequency	Percent	per 1 million
Respiratory reactions (laryngeal oedema, bronchospasm, anaphylaxis)	1:3,800	0.03	263
Cardiac reactions (circulatory shock, myocardial infarction, arrest)	1:5,300	0.02	189
Tonic-clonic seizure (adverse neurological reaction)	1:13,900	0.007	72
Any severe adverse reaction	1:1,900	0.053	526

Reviewer's Comments:

Table 7.1.2 A presents the frequency rates of severe adverse reactions associated with intravenous fluorescein as reported in the Fluorescein Angiography Complication Survey (USA and Puerto Rico). No significant correlation was found between the concentration of the fluorescein solutions (5%, 10%, or 25%) and the frequency of mild adverse reactions.3

In Yanuzzi's Fluorescein Angiography Complication survey, he proposes a classification of adverse reactions:

Mild adverse reaction. *A mild reaction was characterized as a transient effect which did not require treatment. It is also a reaction that has a rapid and complete resolution with no sequelae. Nausea, vomiting, extravasation, sneezing, pruritis, and inadvertent arterial injection were classified as mild.*

Moderate adverse reaction. *A moderate adverse reaction was also defined as a transient effect. With this type of complication, some form of medical treatment may be required. This reaction has complete but gradual resolution with no sequelae or threat to the patient's safety. Urticaria, syncope, other skin eruptions, thromboplebitis, pyrexia, local tissue necrosis, and nerve palsy were categorized as moderate adverse reactions.*

2 Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W, Zang E. Fluorescein angiography complication survey. Ophthalmology 1986;93(5):611 7
3 Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W, Zang E. Fluorescein angiography complication survey. Ophthalmology 1986;93(5):611 7

Severe adverse reaction. *A severe reaction was defined as one exhibiting prolonged effects which required intense treatment. It also posed a threat to the patient's safety, and it resulted in a variable recovery. A severe adverse reaction involved the respiratory, cardiac, or neurological systems. Respiratory adverse reactions included laryngeal edema, bronchospasm, and anaphylaxis. Cardiac adverse reactions included circulatory shock, MI, and cardiac arrest. A tonic-clinic seizure was classified as an adverse neurological reaction.*

7.1.3 Dropouts and Other Significant Adverse Events

Not applicable.

No new clinical data was submitted in this NDA submission.

7.1.4 Other Search Strategies

There were no unique or special safety studies were necessary or conducted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The majority of adverse event data was obtained from postmarketing spontaneous adverse event reports found in the Periodic Safety Update Report and from citations in literature.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor's categorization of adverse events in the Periodic Safety Update Report appears appropriate.

7.1.5.3 Incidence of common adverse events

Table 7.1.4.3 - Frequency of mild and moderate adverse reactions (based on 221,781 angiograms performed in 1984 by 2434 respondents of a US survey of practicing ophthalmologists) (table modified after Yannuzzi et al. 1986)4

	N = 221,781 Angiograms	
	Frequency	Percent
Mild adverse reactions (including nausea, vomiting, extravasation, sneezing, pruritus, inadvertent arterial injection)		2.6[a]
Moderate adverse reactions		
Urticaria	1:82	1.22
Syncope	1:337	0.30
Other (including thrombophlebitis, pyrexia, local tissue necrosis, nerve palsy)	1:769	0.13
Any moderate adverse reaction	1:63	1.59

[a] mean frequency rate, estimated by the reviewer on basis of the original frequency table, in which the frequencies ranged from <1% (in 44% of the respondents) to >10% (in 2% of the respondents)

Reviewer's Comments:

Table 7.1.4.3 presents the frequency rates of mild and moderate adverse reactions associated with intravenous fluorescein as reported in the Fluorescein Angiography Complication Survey (USA and Puerto Rico). No significant correlation was found between the concentration of the fluorescein solutions (5%, 10%, or 25%) and the frequency of mild adverse reactions (Yannuzzi et al. 1986).

7.1.5.4 Common adverse event tables

Not applicable. No new clinical studies were performed. Refer to Section 7.1.17 for review of the submitted postmarketing data.

7.1.5.5 Identifying common and drug-related adverse event

Not applicable. No new clinical studies were performed. Refer to Section 7.1.17 for review of the submitted postmarketing data.

7.1.5.6 Additional analyses and explorations

Not applicable. No new clinical studies were performed. Refer to Section 7.1.17 for review of the submitted postmarketing data.

4 Yannuzzi LA, Rohrer KT, Tindel LJ, Sobel RS, Costanza MA, Shields W, Zang E. Fluorescein angiography complication survey. Ophthalmology 1986;93(5):611 7

7.1.6 Less Common Adverse Events

Not applicable. No new clinical studies were performed. Refer to Section 7.1.17 for review of the submitted postmarketing data.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

There is no preclinical data or clinical data presented or referenced that indicate fluorescein sodium adversely affects blood chemistry, hematology, or urinalysis. There is a 30 year marketing history for this product without a New Drug Application. There is no post marketing data from Novartis's worldwide Periodic Safety Update Report for Fluorescein sodium 10% and 25% (01 April 2003 – 31 March 2006) that indicate this product adversely affects blood chemistry, hematology, or urinalysis.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Refer to Section 7.1.7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

Refer to Section 7.1.7.1.

7.1.7.4 Additional analyses and explorations

Refer to Section 7.1.7.1.

7.1.7.5 Special assessments

There are no special laboratory assessments indicated for this drug product.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

There is no post marketing data from Novartis's worldwide Periodic Safety Update Report for Fluorescein sodium 10% and 25% (01 April 2003 – 31 March 2006) that indicate this product adversely affects pulse, blood pressure or respiration unless associated with an anaphylactic reaction.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Refer to Section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

Refer to Section 7.1.8.1.

7.1.8.4 Additional analyses and explorations

Refer to Section 7.1.8.1.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

There is no post marketing data from Novartis's worldwide Periodic Safety Update Report for Fluorescein sodium 10% and 25% (01 April 2003 – 31 March 2006) that indicate this product affects cardiac conduction unless as a result of an anaphylactic reaction.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to Section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

Refer to Section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

Refer to Section 7.1.9.1.

7.1.10 Immunogenicity

AK-Fluor has been marketing this drug product in the United States for over 30 years. There is the known potential for generalized hives and itching, bronchospasm, and anaphylaxis as indicated in the labeling. Per the labeling of the reference listed drug, Fluorescite Injection 10%:

> "Caution is to be exercised in patients with a history of allergy or bronchial asthma. An emergency tray should be available in the event of possible reaction to FLUORESCITE® Injection 10%. Use only if the container is undamaged."

7.1.11 Human Carcinogenicity

Since AK-Fluor 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.

7.1.12 Special Safety Studies

There were no special safety studies performed or recommended for this drug product.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No evidence of drug abuse or withdrawal phenomena has been reported for AK-Fluor.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women.

There have been no reports of fetal complications from fluorescein sodium injection during pregnancy.

7.1.15 Assessment of Effect on Growth

Safety and effectiveness have been established in pediatric patients. There is no known effect on growth. The pediatric dosing is well supported in the literature.

Pursuant to 21 CFR§314.55(a), Akorn, Inc. requested a full waiver for the conduct of any additional studies in pediatric patients due to the summarized evidence demonstrating safe and effective use in the pediatric patient population.

Since children possess a small blood volume, the fluorescein dose is adjusted by body weight. To ensure a similar concentration of the dye in blood vessels as in adults, the recommended dose is 35 mg for each ten pounds of body weight (7.7 mg/kg body weight).

7.1.16 Overdose Experience

No information is available on overdosage in humans. There were no spontaneous reports, literature reports, or health professional reports of overdosage. The proposed dose in this application is 500 mg, 750 mg has been marketed and used with no observed increase in adverse events.

7.1.17 Postmarketing Experience

7.1.17.1 PERIODIC SAFETY UPDATE REPORT 4 (PSUR 4)

This is the fourth PSUR for Fluorescein (fluorescein sodium) solution for injection, covering the time period from 01 April 2003 until 31 March 2006 which was prepared by Novartis, Akorn, Inc.'s licensed partner in Europe. This report summarizes the safety data received and processed by Clinical Safety and Epidemiology of Novartis Pharma from worldwide sources for the period covering from 01 April 2003 until 31 March 2006. This PSUR includes case reports and other safety data obtained from Akorn Inc. who is marketing the product in the USA. The report was submitted on behalf of both companies.

In June 2002, Novartis was requested by the French Health Authority to withdraw the Fluorescein 20% formulation from the market due to a higher reporting rate of serious adverse events compared to the 10% formulation in France. As a precautionary measure and because improved imaging techniques provide adequate images using lower concentrations, the company decided to discontinue marketing of Fluorescein 20% in all countries where Fluorescein 10% is available. Simultaneously approval for the 10% formulation was sought in countries where only the 20% formulation was available. To date, the manufacture of Fluorescein 20% has been discontinued.

Patient Exposure
During the review period there were no investigational clinical trials sponsored by Novartis or Akorn. An estimate of patient exposure is calculated based on worldwide sales volume number of ampules sold. During the period of the PSUR in total approximately [redacted] million units of Fluorescein 10% and [redacted] units of Fluorescein 20% (Spain) were sold by Novartis. In addition, approximately [redacted] ampules of AK-Fluor 10% were sold by Akorn. b(4)

Update of regulatory authority or marketing authorization holder actions taken for safety reasons
On 20 February 2004, the French Health Products Safety Agency (AFSSAPS) issued a letter to prescribers restating the risk of serious, mostly anaphylactic, and sometimes fatal unwanted effects associated with injectable fluorescein.

In July 2004, the Portuguese Health Authorities issued a safety alert warning of possible serious hypersensitivity reactions associated with the use of Fluorescein solution for injection. In January 2005, the Portuguese Health Authorities issued another safety alert warning containing the following information:

- Hypersensitivity reactions are unpredictable and more frequent in patients who showed previous lower tolerance to the product (nausea and vomiting) and who have a history of allergy.
- Patients on treatment with beta-blockers, including ophthalmic solutions, are considered as subjects at risk, since in the event of reactive shock or hypotension, adrenaline injection and plasma expansion is less effective in these patients.

- Due to the risk of hypersensitivity, detailed pre-investigation questioning is mandatory (allergy history, bronchial asthma, concomitant treatments, namely with beta blockers) and following the examination patients should be monitored for, at least, 30 minutes.
- The risk makes it mandatory for emergency resuscitation equipment to be available in the examination room, as described in the National Patient Leaflet.
- In patients identified as being at risk, the utility of the examination for the diagnosis should be balanced against the risk. In these patients pre-medication that might prevent hypersensitivity reactions might be advantageous, but it may be unable to prevent serious adverse reactions.

Following French national pharmacovigilance investigations, a Dear Doctor Letter (DDL) was issued in January 2005 by the French health authorities warning about serious hypersensitivity reactions. The frequency of serious hypersensitivity reactions was found to increase.

As requested by the Swiss Health Authorities, a letter to prescribers was sent in February 2005 which contained a warning about the use of beta-blockers during fluorescein angiography and about the importance to ensure a fixed venous access.

Hypersensitivity reactions with fatal outcome are explicitly listed in the Core Data Sheet for Fluorescein 10% solution for injection. The document also contains a clear guidance on the necessity to have suitable resuscitation equipment readily available during the angiographic procedure as well as a clear guidance on the necessity to perform a careful risk-benefit analysis prior to performing retinal angiography with fluorescein.

Reviewer's Comment:
The safety alert warnings issued do not represent new information regarding fluorescein sodium.

The Core Data Sheet currently includes adequate information regarding warnings and precautions, the risk of hypersensitivity reactions and the need for adequate available resuscitative equipment during the procedure.

Changes to Reference Safety Information
The Core Data Sheet (CDS) was amended three times during the reporting period. The following amendments were made:

- Section 4.3 Contraindications was amended to remove beta-blocker use as an absolute contraindication and change to a relative contraindication.
- Section 4.4, Special warnings and precautions for use was amended as follows:
  - "Before administration a complete medical history must be obtained, including history of allergy, history of cardio-pulmonary disease, concomitant medication (in particular beta blockers, including eye drops)."
  - A warning that any use of beta-blockers may rarely cause lethal anaphylactic reactions which require "... more intensive resuscitation measures due to the reduced efficacy of epinephrine and volume expansion."

- "The patient must be kept under close observation for at least 30 minutes after angiography."

- Section 4.5, Interaction with other medicinal product and other forms of interaction now includes and warning regarding the interference of beta-blockers in anaphylactic/anaphylactoid reactions.
- Section 4.8 the Undesirable effects were reorganized to present adverse drug reactions according to the MedDRA terminology and were assigned the most relevant System Organ Class (SOC).
- Additionally, a review of the non-clinical information available for fluorescein in published literature was performed and amendments were made to Sections 4.3 Preclinical Safety Data and 4.6 Pregnancy and lactation.

Individual Case Histories

A total of 118 cases have been reported during the review period. Details on the distribution of the cases are presented below.

Table 7.1.17.1-1 – Overview of Reported Cases by Report Type

Type of Report	Serious		Non-Serious		Total
	Unlisted	Listed	Unlisted	Listed	
Spontaneous	6	55	20	37	118

Table 7.1.17.1-2
Distribution of Serious Reports by Med DRA System Organ Class of the Primary Event

MedDRA System Organ Class	Serious spontaneous reports		Non-serious spontaneous reports	
	Unlisted	Listed	Unlisted	Listed
Cardiac disorders	0	3	1	0
Ear and labyrinth disorders	0	0	1	0
Eye disorders	0	0	1 *	0
Gastrointestinal disorders	0	3	2	10
General disorders and administration site conditions	4	6	4 *	10*
Immune system disorders	0	25	0	0
Injury, poisoning and procedural complications	0	0	1	2
Investigations	0	1	1	0
Musculoskeletal and connective tissue disorders	0	0	1	0
Nervous system disorders	2	6	3	4
Psychiatric disorders	0	0	4	0
Renal urinary disorders	0	0	1*	0
Respiratory, thoracic and mediastinal disorders	0	1	0	0

Skin and subcutaneous tissue disorders	0	4	0	11*
Vascular disorders	0	6	0	0
TOTAL	**6**	**55**	**20**	**37**

* Included one non-health care professional report

Of the above listed serious reports ten cases had a fatal outcome. The case history narratives for all of the cases except Case CVBU2003TN00827 are reported in Section 7.1.1 Deaths. Case CVBU2003TN00827 is presented below.

Case # CVBU2003TN00827: A 59 year old female patient with diabetic retinopathy received an infusion with fluorescein 10% and became extremely agitated. The infusion was stopped and immediately the patient experienced a cardiac arrest. Cardiorespiratory resuscitation was unsuccessful. The blood pressure had been normal just before the cardiac arrest. The autopsy report concluded that the death was probably due to an anaphylactic shock with fatal complications. In addition, pulmonary edema was found.

Additional Serious Unlisted cases:

PHRM2004FR03133: An 80 year old man with a history of diabetes mellitus and a "heavy cardiac history", first received an injection of AK-Fluor. After the injection he experienced retrosternal pain. The examination was stopped. An ECG was performed: sinus rhythm, no conduction disturbance, non-significant anteroseptal segment elevation, and a QT interval of 0.40 (normal at 0.38) were noticed. The patient left the hospital after 1 to 2 hours without warning anyone. The physicians in hospital advised him to consult his cardiologist. The patient's outcome was not reported.

PHBS2004AT08274: A 51 year old female patient with a history of pituitary gland surgery in 2001 and since surgery persisting rhinorrhea and headache received fluorescein (manufacturer unknown) intrathecally, 3 mL of a 5 % solution, for liquor fistula localization. A few hours later, the patient with no history of epilepsy developed a series of grand mal convulsions. The patient was hospitalized. A CT of the skull showed no evidence of hemorrhage. The patient completely recovered.

PHRM2004FR03749: A 75 year old female patient with a history of essential hypertension and diabetes mellitus received an injection of AK-Fluor on 24 Nov 2004. Five to ten minutes after the examination, she experienced a fall, obnubilation, complete left upper limb motor deficit during 5 to 10 minutes, then left upper limb hypertonia. She recovered within 15 to 20 minutes. During the episode, blood pressure was at 190/110 mmHg and 170/100 mmHg 20 minutes later; glucose was 200 mg/dL. The patient was administered sodium chloride and oxygen therapy. An MRI showed the presence of 2 small lacunar ischemic accidents. A cervical echo-doppler revealed a very tight stenosis leading to a hemodynamic occlusion of the right internal carotid artery. A cardiac echography showed left ventricular hypertrophy. The final diagnosis was a right internal carotid artery subocclusive stenosis responsible for a transient hemodynamic ischemic accident. The

outcome was reported as complete recovery. The reporting Health Authority assessed the causal relationship as unlikely.

Relevant New Safety Findings
In the previous PSUR no relevant safety findings were identified requiring close monitoring. The analysis of adverse events reports received during the current review period did into reveal any relevant safety findings. There were no studies completed during the review period yielding safety information with potential impact on the product information.

Increased frequency of reports of listed events
In the 3-year period covered by this PSUR 118 spontaneous adverse event reports (61 serious) were received with a total of approximately [redacted] ampules sold. In comparison in the combined period covered by PSURs 2 and 3 from 01 Jun 2000 until 31 March 2003 a total of 52 reports were received (31 serious). In the combined periods of PSUR 2 and 3 approximately [redacted] ampules were sold. Taking the patient exposure into account, the total number of reports increased from [redacted] per million patients treated in the period covered by PSUR 2 and 3 to [redacted] per million patients treated in the period covered by PSUR 4. This increase is at least partly explained by more stringent reporting procedures in more recent periods and increased awareness following the warning letters distributed in some European countries. The increase in reporting rate show some variation as is shown in the following table. b(4)

Table 7.1.17.1-3 Distribution of reports by country

Country	Number of reports in PSUR 2 and 3	Number or reports in PSUR 4
France	38	73
Spain	1	14
Belgium	0	8
USA	1	8
Portugal	0	6
Switzerland	5	0
Germany	4	3
Other countries with each 1 report	3	6
TOTAL	**52**	**118**

In order to investigate possible increases in reporting incidence of individual events, the events from spontaneous reports in PSUR 2 and 3 ([redacted] ampules sold) were compared with those from spontaneous reports in PSUR 4 (with [redacted] ampules sold) for each MedDRA System Organ Class (SOC), which contained more than 2 events in either period (>1% of the total of reported events), irrespective of listedness or seriousness assessment or whether the event was reported as leading diagnosis or as a related event. b(4)

Reviewer's Comment:
No new relevant safety findings were identified. The sponsor's updates to the Core Data Sheet were appropriate.

Table 7.1.17.1-4
Number of Events Reported in Spontaneous Cases by System Organ Class in PSUR 2, 3 and 4 (SOCs with more than 2 events are shown)

MedDRA System Organ Class	Absolute number of events		Number of Reports per million ampules sold	
	PSUR 2 and 3	PSUR 4	PSUR 2 and 3	PSUR 4
Cardiac disorders	6	24		
Eye disorders	8	5		
Gastrointestinal disorders	17	47		
General disorders and administration site conditions	17	58		
Immune system disorders	19	27		
Injury, poisoning and procedural complications	-	6		
Investigations	3	26		
Metabolism and nutrition disorders	1	5		
Musculoskeletal and connective tissue disorders	4	7		
Nervous system disorders	16	55		
Psychiatric disorders	-	7		
Respiratory disorders	15	18		
Skin and subcutaneous tissue disorders	26	59		
Surgical and medical procedures	-	13		
Vascular disorders	14	26		
Total number of events*	**149**	**389**		
Total number of spontaneous patient reports	**52**	**118**		

b(4)

* Total number of events includes events with < 5 reports per MedDRA System Organ Class

Applicant explanations for the increased reporting in each SOC:

- Cardiac disorders - mainly caused by 4 reports of tachycardia and 3 reports in both bradycardia and ventricular fibrillation. Symptoms were associated with other events (i.e., pain, anaphylactic reactions, vasovagal syncope).
- Gastrointestinal disorders - due to an increase in reporting incidences of nausea and vomiting which are correctly listed as the most common events.
- General disorders – reports of malaise increased and represent a non-specific event often associated with other events such as, nausea, vomiting, syncope, hypersensitivity, etc.
- Investigations – Blood pressure decrease was reported 4 times, immeasurable 5 times usually associated with anaphylaxis
- Nervous system disorders – An increase in convulsions (1 to 5), headache (0 to 5) and loss of consciousness (1 to 18) were noted. Psychiatric disorders included 4 reports of anxiety from a single reporter.
- Skin disorders – Increase in reports of erythema, hyperhidosis, various types of rash and urticaria.

- Surgical and medical procedures – Increase from 0 to 13 events were explained by more stringent procedures during the period covered by PSUR 3.

Reviewer's Comment:
There is no evidence of a significant increase in the frequency of individual listed events reviewed during this period which would reflect a meaningful change in occurrence of listed events requiring a modification of the information presented in the CDS.

No new relevant safety findings were identified. The safety data remain in accord with the previous cumulative experience and the safety information presented in the Core Data Sheet.

Table 7.1.17.1-5 Non-Serious, Unlisted Spontaneous Reports
April 1, 2003 – March 31, 2006

Body System	MedDRA Preferred Term	Literature Case	Spontaneous Reports	Total
Cardiac Disorders	Tachycardia	0	1	1
	Subtotal	**0**	**1**	**1**
Ear and labyrinth disorders	Vertigo	0	1	1
	Subtotal	**0**	**1**	**1**
Eye Disorders	Erythropsia	0	1	1
	Photopsia	0	1	1
	Subtotal	**0**	**2**	**2**
Gastrointestinal disorders	Diarrhea	0	1	1
	Feces discolored	0	1	1
	Nausea	0	1	1
	Subtotal	**0**	**3**	**3**
General disorders and administration site conditions	Drug intolerance	0	1	1
	Extravasation	0	1	1
	Fatigue	0	1	1
	Malaise	0	1	1
	Peripheral edema	0	1	1
	Pyrexia	0	1	1
	Subtotal	**0**	**6**	**6**
Immune system disorders	Hypersensitivity	0	1	1
	Subtotal	**0**	**1**	**1**
Injury, poisoning and procedural complications	Excoriation	1	0	1
	Injury	0	1	1
	Subtotal	**1**	**1**	**2**
Investigations	Blood pressure increased	0	1	1
	Subtotal	**0**	**1**	**1**
Metabolism and nutrition disorders	Anorexia	0	2	2
	Subtotal	**0**	**2**	**3**
Musculoskeletal and connective tissue disorders	Joint stiffness	1	0	1
	Joint swelling	1	0	1
	Subtotal	**2**	**0**	**2**

Body System	MedDRA Preferred Term	Literature Case	Spontaneous Reports	Total
Nervous system disorders	Diabetic neuropathy	0	1	1
	Head discomfort	0	1	1
	Headache	0	1	1
	Paresthesia	0	1	1
	Sciatica	0	1	1
	Syncope	0	1	1
	Subtotal	**0**	**6**	**6**
Psychiatric Disorders	Anxiety	0	4	4
	Nervousness	0	1	1
	Subtotal	**0**	**5**	**5**
Renal and urinary disorders	**Chromaturia**	0	1	1
	Subtotal	**0**	**1**	**1**
Skin and subcutaneous tissue disorders	Rash erythematous	1	0	1
	Rash macular	1	0	1
	Rash papular	0	1	1
	Rash pruritic	1	1	2
	Subtotal	**3**	**2**	**5**
Vascular disorders	Flushing	0	1	1
	Hot flush	0	1	1
	Hypertension	0	1	1
	Subtotal	**0**	**3**	**3**
TOTAL		**6**	**36**	**42**

Reviewer's Comment:

The reports were generally consistent with reactions accompanying the procedure and hypersensitivity to fluorescein sodium. No new relevant safety findings were identified.

Table 7.1.17.1-6 Non-Serious, Listed Spontaneous Reports
April 1, 2003 – March 31, 2006

Body System	MedDRA Preferred Term	Spontaneous Reports
Gastrointestinal disorders	Nausea	11
	Vomiting	3
	Subtotal	**14**
General disorders and administration site conditions	Application site dermatitis	1
	Application site pruritus	1
	Chest pain	1
	Drug ineffective	3
	Feeling hot	2
	Injection site extravasation	3
	Injection site edema	1
	Injection site vesicles	1
	Malaise	4
	Subtotal	**17**

Body System	MedDRA Preferred Term	Spontaneous Reports
Immune system disorders	Hypersensitivity	1
	Subtotal	**1**
Injury, poisoning and procedural complications	Drug exposure during pregnancy	2
	Subtotal	**2**
Musculoskeletal and connective tissue disorders	Arthralgia	1
	Back pain	1
	Subtotal	**2**
Nervous system disorders	Dizziness	1
	Syncope	1
	Syncope vasovagal	2
	Subtotal	**4**
Skin and subcutaneous tissue disorders	Blister	1
	Dermatitis contact	1
	Erythema	3
	Pruritus	7
	Rash	1
	Rash generalized	1
	Urticaria	5
	Subtotal	**19**
Vascular disorders	Flushing	1
	Hot flush	1
	Hypotension	1
	Subtotal	**3**
TOTAL		**62**

Reviewer's Comment:

No new relevant safety findings were identified. The safety data remain in accord with the previous cumulative experience and the safety information presented in the Core Data Sheet.

Table 7.1.17.1-7 Serious, Listed Spontaneous Reports
April 1, 2003 – March 31, 2006

Body System	MedDRA Preferred Term	Spontaneous Reports
Cardiac disorders	Bradycardia	3
	Cardiac arrest	2
	Cardio-respiratory arrest	4
	Cyanosis	2
	Intracardiac thrombus	1
	Myocardial infarction	2
	Myocardial ischemia	1
	Palpitations	1
	Tachycardia	3
	Ventricular extrasystoles	1

Body System	MedDRA Preferred Term	Spontaneous Reports
	Malaise	4
	Subtotal	**23**
Ear and labyrinth disorders	Vertigo	1
	Subtotal	**1**
Eye disorders	Conjunctival edema	1
	Eyelid edema	1
	Ocular icterus	1
	Subtotal	**3**
Gastrointestinal disorders	Abdominal discomfort	1
	Diarrhea	2
	Gastrointestinal disorder	1
	Intestinal ischemia	1
	Nausea	14
	Salivary hypersecretion	1
	Vomiting	10
	Subtotal	**30**
General disorders and administration site conditions	Chest pain	1
	Extravasation	1
	Face edema	2
	Feeling hot	2
	Injection site pain	1
	Injection site vesicles	1
	Malaise	19
	Multi-organ failure	1
	Pain	1
	Swelling	1
	Subtotal	**30**
Hepatobiliary disorders	Hepatic failure	1
	Subtotal	**1**
Immune system disorders	Anaphylactic reaction	3
	Anaphylactic shock	**13**
	Anaphylactoid reaction	**1**
	Drug hypersensitivity	**1**
	Hypersensitivity	**7**
	Subtotal	**25**
Infections and infestations	Rash pustular	1
	Subtotal	**1**
Injury, poisoning and procedural complications	Fall	1
	Subtotal	**1**
Investigations	Blood pressure decreased	4
	Blood pressure immeasurable	5
	Blood pressure increased	1
	Blood pressure systolic decreased	1
	C-reactive protein increased	1
	Coagulation factor V level	1

Body System	MedDRA Preferred Term	Spontaneous Reports
	decreased	
	Electrocardiogram abnormal	1
	Electrocardiogram repolarisation abnormality	1
	Heart rate decreased	2
	Oxygen saturation decreased	2
	Platelet count decreased	1
	Prothrombin level decreased	1
	Pulse abnormal	1
	Pulse absent	1
	Subtotal	**23**
Metabolism and nutrition disorders	Anorexia	1
	Decreased appetite	1
	Lactic acidosis	1
	Subtotal	**3**
Musculoskeletal and connective tissue disorders	Back pain	1
	Joint stiffness	1
	Myalgia	1
	Subtotal	**3**
Nervous system disorders	Clonus	1
	Coma	2
	Convulsion	5
	Depressed level of consciousness	1
	Dizziness	1
	Dysgeusia	1
	Dyskinesia	1
	Headache	4
	Hypotonia	1
	Loss of consciousness	18
	Paresthesia	1
	Syncope vasovagal	3
	Subtotal	**39**
Psychiatric Disorders	Agitation	2
	Subtotal	**2**
Renal and urinary disorders	Urinary incontinence	1
	Subtotal	**1**
Respiratory, thoracic and mediastinal disorders	Aspiration	1
	Asthma	1
	Cough	1
	Dysphonia	1
	Dyspnea	5
	Pharyngolaryngeal pain	1
	Pulmonary edema	1
	Sneezing	1
	Snoring	1

Body System	MedDRA Preferred Term	Spontaneous Reports
	Throat irritation	1
	Throat tightness	3
	Subtotal	**17**
Skin and subcutaneous tissue disorders	Angioneurotic edema	3
	Blister	1
	Cold sweat	1
	Erythema	4
	Hyperhidrosis	8
	Periorbital edema	1
	Pruritus	2
	Pruritus generalized	3
	Rash	3
	Rash macular	1
	Rash maculo-papular	1
	Rash papular	2
	Skin warm	1
	Swelling face	1
	Urticaria	1
	Vascular purpura	1
	Subtotal	**34**
Surgical and medical procedures	Cardiac massage	3
	Cardioversion	3
	Dialysis	1
	Intubation	4
	Life support	2
	Subtotal	**13**
Vascular disorders	Circulatory collapse	3
	Flushing	1
	Hemodynamic instability	1
	Hemorrhage	1
	Hypertension	1
	Hypotension	5
	Pallor	**3**
	Shock	**3**
	Vasculitis necrotizing	1
	Vasodilation	**1**
	Subtotal	**20**
TOTAL		**270**

Reviewer's Comment:

No new relevant safety findings were identified. The safety data remain in accord with the previous cumulative experience and the safety information presented in the Core Data Sheet.

7.1.17.2 AK-FLUOR INVESTIGATION REPORT, GLOBAL INVESTIGATION 04RA011

Akorn, Inc. opened global investigation No. 04RA011 on July 20, 2004 for the AK-Fluor, (Fluorescein Sodium Injection) complaints and adverse events received for the last twelve (12) months specifically, the twelve (12) "15 Day Alert" reports that were considered unexpected foreign/domestic events in accordance with 21 CFR 314.80.

Akorn, Inc. received 29 complaint reports from domestic users (USA) of which sixteen (16) reports were adverse drug experiences, which includes three (3) events that are considered serious unexpected events which required "15 Day Alert" reports to be filed, and thirteen (13) quality complaints. In addition, Akorn has received thirty-one (31) foreign reports from Novartis Pharma, France of which twenty-eight (28) are adverse drug, which include nine events that were considered serious unexpected events that required "15 Day Alert" reports to be filed, and three quality complaints. The adverse drug experiences reported by Novartis, France include one report received from Novartis, Spain. Akorn, Inc. is the commercial supplier of Fluorescein Injection, USP, 10% (ampules) to Novartis Pharma. Novartis Pharma is responsible for handling and reporting to Akorn all complaints and adverse events obtained in the European Union.

Because of the foreign (primarily France) adverse drug experiences, the French Health Products Safety Agency (AFSSAPS) issued a letter to prescribers, information for ophthalmologists and hospital pharmacists, on February 20, 2004, Restatement of the risks and special precautions for use associated with injectable fluorescein. The letter outlines a drug safety survey of 10% fluorescein and confirmed that:

- Such reactions are always unpredictable but are more frequent in patients who, except for nausea and vomiting, have poorly tolerated a previous injection of this product or who have a history of allergy.
- Subjects on beta-blockers, including in ophthalmic solution, are considered as subjects at risk since, in the event of reactive shock or hypotension, adrenaline injection and plasma expanders are ineffective in such patients.
- Due to the risk of a hypersensitivity reaction, detailed pre-investigation questioning (allergy history, concomitant treatments, notably beta-blockers, etc.) is mandatory, as is the routine monitoring of all patients during the investigation and for the 30 minutes following.
- The risk makes it mandatory for emergency resuscitation equipment to be available in the investigation room.
- In the patients identified as being at risk, the utility of the diagnosis must be balanced against the risk of serious unwanted effects. Although premedication is recognized as desirable in these patients, it may be unable to prevent serious accidents.

The French Health Products Safety Agency initiated a working group on Fluorescence Angiography. The group convened on June 24, 2004 to discuss their concerns with AK-Fluor. In summary, the physical, chemical, and product release controls are performed according to the highest quality standards. Based on the Pharmacovigilance information, the working group did considering updating the "special warnings and special precautions of use" paragraph of the

SmPC to include concomitant treatments (beta-blockers, ACE inhibitors, etc.) and other risk factors, rules of good practice and precautions of use of fluorescein. In addition, France, under the aegis of the French Society of Ophthalmology, will update the angiography indications. Also, it is essential that practitioners have at their disposal the necessary means to provide cardio-respiratory resuscitation and that they are knowledgeable and current in their use.

Akorn's, AK-Fluor, Fluorescein Sodium Injection is distributed worldwide. AK-Fluor is manufactured in four different product strengths and configurations. The primary market for AK-Fluor product code 5009 is Europe. European manufacturers observed the increase in market share last year due to the short supply situation in Europe. As a result of the crisis situation in Europe Novartis Pharma sourced and approved Akorn as their commercial supplier to Europe. Novarti Pharma distributes the product to — European countries. Akorn, Inc. data revealed over a ——fold increase in Akorn's distribution of AK-Fluor 10% product code 5009 since 2002. A review of the trend data by product doe by year indicates that the complaints experienced are proportional and within distribution patterns. b(4)

Akorn, Inc. has reviewed all complaint and adverse event reports related to the use of AK-Fluor, however, the emphasis of this investigation is focused on the twelve "15 Day Alert" reports that were considered serious unexpected foreign/domestic events and the AK-Fluor lots associated with each reported event.

Akorn, Inc. reviewed all quality data related to the manufacture of the AK-Fluor products surrounding this global investigation and Akorn has concluded that the AK-Fluor Injection products were manufactured to the highest quality standards and were in compliance with Akorn's policies, procedures, specifications, and any applicable laws and regulation.

Reviewer's Comment
The adverse drug experience data presented in the AK-Fluor Global Investigation report was also presented and is reviewed in the Periodic Safety Update Report (PSUR) 4.

A quality assurance review of the batch records for which adverse experience reports were received found no discrepancies with the production or testing of the lots that would account for the adverse drug events.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

During the review period there were no investigational clinical trials sponsored by Novartis or Akorn. An estimate of patient exposure is calculated based on worldwide sales volume number of ampules sold. During the period of the PSUR in total approximately ——— units of Fluorescein 10% and — units of Fluorescein 20% (Spain) were sold by ——. In addition, b(4)

approximately [redacted] ampules of AK-Fluor 10% were sold by Akorn. Assuming one unit per patient and per treatment approximately [redacted] patients were treated with Fluorescein 10% and approximately [redacted] with Fluorescein 20%. b(4)

7.2.1.1 Study type and design/patient enumeration

The application relies upon the Agency's findings of safety and efficacy for Novartis's Fundescein-25, NDA 17-869, and Alcon's Fluorescite, NDA 21-980 for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

These additional sources of clinical data were also reviewed to assess the safety of AK-Fluor:

- 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.

7.2.1.2 Demographics

No new preclinical or clinical data was submitted in this NDA submission.

Worldwide safety information is available for AK-Fluor (See Appendix 10.4 Reports of Postmarketing Experience). There is adequate safety information by gender, ethnicity, age, and underlying disease process.

7.2.1.3 Extent of exposure (dose/duration)

An estimate of patient exposure is calculated based on worldwide sales volume number of ampules sold. During the period of the PSUR in total approximately [redacted] units of Fluorescein 10% and [redacted] of Fluroescein 20% (Spain) were sold by Novartis. In addition, approximately [redacted] ampules of AK-Fluor 10% were sold by Akorn. b(4)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.1 Other studies

All clinical data sources provided in the New Drug Application were utilized in the review of safety for this product.

7.2.2.2 Postmarketing experience

AK-Fluor has been illegally marketed in the United States for approximately 30 years without a New Drug Application.

For detailed adverse event tables for dates between 01 April 2003 and 31 March 2006 for AK-Fluor 10% and AK-Fluor 25%, see Section 7.1.17.1 Postmarketing Experience.

7.2.2.3 Literature

Reviewer's Comment:

The sponsor did not submit a complete literature search for articles regarding the various aspects of ocular fluorescein fundus angiography. This reviewer performed a PubMed literature search on this subject which revealed a total of 2175 publications of which 107 were classified as Clinical Trials.

7.2.3 Adequacy of Overall Clinical Experience

The application relies upon the Agency's findings of safety and efficacy contained in the Summary Bases of Approval (SBA) for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

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. AK-Fluor has been illegally marketed in the United States for approximately 30 years without a New Drug Application. An estimate of patient exposure is calculated based on worldwide sales volume number of ampules sold.

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 (———).

Reviewer's Comment:

The dose and duration of the drug used in the cited literature and safety surveys were adequate to determine safety for the intended use. There is adequate safety information by gender, ethnicity, age, and underlying disease process.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

There is adequate routine clinical testing reported in the literature, safety surveys, and a Periodic Safety Update prepared for the European Union.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Fluorescein undergoes rapid metabolism to fluorescein monoglucuronide. After IV administration of fluorescein sodium (14 mg/kg) to 7 healthy subjects, approximately 80% of fluorescein in plasma was converted to glucuronide conjugate after a period of 1 hour post dose, indicating relatively rapid conjugation. Fluorescein monoglucuronide is about 1/3 to 1/4 as fluorescent as fluorescein, depending on the wavelength of excitation of the blue light.

Fluorescein and its metabolites are mainly eliminated via renal excretion. After IV administration, the urine remains slightly fluorescent for 24 to 36 hours. A renal clearance of 1.75 mL/min/kg and a hepatic clearance (due to conjugation) of 1.50 mL/min/kg have been estimated. The systemic clearance of fluorescein was essentially complete by 48 to 72 hours after administration of 500 mg fluorescein.

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There has adequate evaluation for potential adverse events for this drug and for drugs in this class, and there are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted for the assessment of safety for AK-Fluor is adequate and of good quality. There is a tremendous amount of information provided in the Alcon-prepared Periodic Safety Update Report 4 prepared for the European Union covering 01 April 2003 to 31 March 2006.

7.2.9 Additional Submissions, Including Safety Update

The Safety Update has not yet been submitted by the applicant.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Care must be taken to avoid extravasation during injection as the high pH of fluorescein solution can result in local tissue damage. The following complications resulting from extravasation of fluorescein have been noted to occur: Sloughing of the skin, superficial phlebitis, subcutaneous granuloma, and toxic neuritis along the median curve in the antecubital area. Complications resulting from extravasation can cause severe pain in the arm for up to several hours. When significant extravasation occurs, the injection should be discontinued and conservative measures to treat damaged tissue and to relieve pain should be implemented.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Refer to Section 7.1.

7.4.1.1 Combining data

Refer to Section 7.1.

7.4.2 Explorations for Predictive Factors

Refer to Section 7.1.

7.4.3 Causality Determination

Since administration of the drug product requires an intravenous injection, some adverse events may be related to the injection procedure itself (i.e. syncope) versus the drug (i.e. nausea, vomiting, and anaphylaxis). Since the drug is utilized by a physician for a single diagnostic procedure (fluorescein angiogram), the distinction between drug-related and procedure related may not be critical.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

The normal adult dose is 500 mg via IV administration, either AK-Fluor Injection 10% (100 mg/mL) or AK-Fluor 25% (250 mg/mL).

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).

No information is available on overdosage in humans.

8.2 Drug-Drug Interactions

Specific drug interaction studies are not reported.

No additional adverse drug-drug interactions were noted in the literature review.

8.3 Special Populations

No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

Safety and effectiveness in pediatric patients have been established.

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

8.4 Pediatrics

Safety and effectiveness have been established in pediatric patients in NDA 17-869 and NDA 21-980.

Pursuant to 21 CFR§314.55(a), Akorn requested a full waiver for the conduct of any additional studies in pediatric patients due to the summarized evidence demonstrating safe and effective use in the pediatric patient population.

Since children possess a small blood volume, the fluorescein dose is adjusted by body weight. To ensure a similar concentration of the dye in blood vessels as in adults, the recommended dose is 35 mg for each ten pounds of body weight (7.7 mg/kg body weight).

8.5 Advisory Committee Meeting

An Advisory Committee was neither necessary nor convened for this drug product.

8.6 Literature Review

Reviewer's Comment:

The sponsor did not submit a complete literature search for articles regarding the various aspects of ocular fluorescein fundus angiography. This reviewer performed a PubMed literature search on this subject which revealed a total of 2175 publications of which 107 were classified as Clinical Trials.

8.7 Postmarketing Risk Management Plan

There are no recommended Phase 4 clinical study commitments.

8.8 Other Relevant Materials

There are no other relevant materials to be included.

9 Overall Assessment

9.1 Conclusions

There is a 30 year history of use of this product in the United States with adequate demonstration of effectiveness and safety as determined in this clinical review.

9.2 Recommendation on Regulatory Action

It is recommended that NDA 22-186 be approved from a clinical perspective with the labeling revisions in this review once the outstanding CMC deficiencies are resolved.

The application supports the safety and effectiveness of AK-Fluor (fluorescein sodium injection) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no recommended Phase 4 clinical study commitments.

9.3.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

9.3.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

9.4 Labeling Review

Refer to Section 10.1.

9.5 Comments to Applicant

Not applicable.

10 Appendices

10.1 Line-by-Line Labeling Review

Following is Akorn's proposed labeling submitted in an amendment to the original New Drug Application on August 8, 2007.

Reviewer proposed deletions are noted by and additions by underline within the following labeling.

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

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Rhea Lloyd
2/4/2008 12:57:10 PM
MEDICAL OFFICER

William Boyd
2/4/2008 01:52:03 PM
MEDICAL OFFICER

CLINICAL TEAM LEADER REVIEW #2

Application Type	NDA
Submission Number	22-186
Submission Code	AZ
Letter Date	March 28, 2008
Stamp Date	March 31, 2008
PDUFA Goal Date	September 30, 2008
Reviewer Name	William M. Boyd, M.D.
Review Completion Date	July 23, 2008
Established Name	fluorescein injection
(Proposed) Trade Name	AK-Fluor
Therapeutic Class	4042210 diagnostic dye
Applicant	Akorn, Inc. 2500 Millbrook Drive Buffalo Grove, IL 60089 847-279-6100
Priority Designation	S
Formulation	Active ingredient: fluorescein sodium
Dosing Regimen	500 mg (100 mg/mL) or (250 mg/mL) via intravenous administration
Indication	diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature
Intended Population	patients undergoing diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature

Clinical Team Leader Memorandum with Labeling
William M. Boyd, M.D.
NDA 22-186
AK-FLUOR® 10% (fluorescein injection, USP)
AK-FLUOR® 25% (fluorescein injection, USP)

SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-186 be approved with the labeling revisions included in this review now that the remaining Product Quality Microbiology deficiencies have been resolved.

The application supports the safety and effectiveness of AK-Fluor (fluorescein injection) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There are no recommendations for additional postmarketing studies.

1.1.1 Not Approvable Issues Resolved

b(4)

FDA inspection of the [redacted] and Akorn, Inc., Decator, IL, manufacturing facilities revealed significant deviations from the Current Good Manufacturing Practice (cGMP) regulations. A satisfactory resolution of these violations was required before this application could be approved. Per the February 6, 2008, not approvable letter:

> Before the application may be approved, it will be necessary for the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of the drug substance and the drug product to comply with cGMP.
>
> In addition, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product are inadequate to preserve its quality, purity, and stability. Specifically,
>
> 1. b(4)

b(4)

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 2

Reviewer's Comments:

The applicant's submissions dated March 28, 2008, and July 8, 2008, were reviewed by the Chemists. These nine (9) issues were satisfactorily answered by the applicant per the Chemistry reviews dated July 9, 2008, and July 11, 2008.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

1.2.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

1.2.3 Other Phase 4 Requests

There are no recommended Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Sodium fluorescein is a water-soluble hydroxyxanthine dye. Fluorescence is the important property of fluorescein dye that makes it possible to selectively visualize fluorescein-colored solutions. Fluorescence occurs when a substance absorbs light of one wavelength and re-emits a portion of that light at a longer wavelength. In ophthalmic usage, a blue light (wavelength approximately 465-490 nm) is used to illuminate the dye and it is reflected back as a yellow-green light (wavelength approximately 520-530nm).

Fluorescein angiography has become an indispensable tool in ophthalmic practice for the diagnosis of neovascular ocular diseases, especially those that have a retinal component. Fluorescein angiography can be used to diagnose and document such diseases as choroidal neovascularization in age-related macular degeneration, neovascular diabetic retinopathy, and cystoid macular edema resulting from a variety of posterior ocular disease conditions, as well as diseases of the anterior segment of the eye.

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 has been used since before 1938, though the formulation, manufacturing, and labeling have changed several times in the past 70 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 (———)

Alcon filed NDA 21-980 for Fluorescite (fluorescein injection, USP) 10% which was approved on March 28, 2006. The total drug content approved in NDA 21-980 was 500 mg / 5 mL. Novartis' NDA 17-869 was approved on November 10, 1976, as Funduscein-25 25% was approved for a total dose of 750 mg/3mL ampules. Fundescein-25 has been discontinued but not for reasons of safety or efficacy.

In NDA 22-186, Akorn is seeking the approval of Fluorescein Sodium 25% (2 mL vial) with a total dose of 500 mg fluorescein and Fluorescein Sodium 10% (5 mL vial) with a total dose of 500 mg fluorescein based on the approval of NDA 21-980. As a 505(b)(2) application, NDA 22-186 is relying upon the Agency's findings of safety and efficacy contained in the Approval for NDA 21-980 Fluorescite and NDA 17-869 Fundescein-25.

Akorn, Inc. has not conducted any clinical studies using fluorescein sodium injection.

1.3.2 Efficacy

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

Fluorescein angiography has become an indispensable tool in ophthalmic practice for the diagnosis of neovascular ocular diseases, especially those that have a retinal component. Fluorescein angiography can be used to diagnosis and document such diseases as choroidal neovascularization in age-related macular degeneration, neovascular diabetic retinopathy, and cystoid macular edema resulting from a variety of posterior ocular disease conditions, as well as diseases of the anterior segment of the eye.

1.3.3 Safety

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There is more than a 30 year history of use of this particular product, AK-Fluor, with adequate demonstration of effectiveness and safety. Distribution data submitted by Akorn, Inc. indicate that the total number of units sold between January 2003 and June 2007 as follows:

- AK-Fluor 10% - Domestic [redacted], and Foreign [redacted) b(4)
- AK-Fluor 25% - Domestic [redacted] and Foreign [redacted] s).

This review reveals no new safety findings for AK-Fluor based on the submitted postmarketing data. There is no evidence of abuse potential for this product.

1.3.4 Dosing Regimen and Administration

The proposed normal adult dose of AK-Fluor (fluorescein injection) 10% is 500 mg (100 mg/mL) via intravenous administration. The proposed normal adult dose of AK-Fluor (fluorescein injection) 25% is 500 mg (250 mg/mL) via intravenous administration.

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).

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

1.3.5 Drug-Drug Interactions

Specific drug interaction studies are not reported.

1.3.6 Special Populations

Safety and effectiveness of fluorescein sodium injection, 10% and 25% has been adequately assessed in special populations in NDAs 17-869 and 21-980.

No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

Safety and effectiveness in pediatric patients have been established.

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

LINE-BY-LINE LABELING REVIEW

Akorn's proposed labeling was submitted in an amendment to the original New Drug Application on July 16, 2008; the labeling has been reviewed and is considered acceptable provided there is correction of a misspelled word in Section 5.2.

4 Page(s) Withheld

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 3

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/s/

William Boyd
8/4/2008 08:07:57 AM
MEDICAL OFFICER

Wiley Chambers
8/8/2008 09:29:32 AM
MEDICAL OFFICER

CLINICAL TEAM LEADER REVIEW

Application Type	NDA
Submission Number	22-186
Submission Code	Original
Letter Date	April 5, 2007
Stamp Date	April 6, 2007
PDUFA Goal Date	February 6, 2007
Reviewer Name	William M. Boyd, M.D.
Review Completion Date	February 4, 2007
Established Name	fluorescein injection
(Proposed) Trade Name	AK-Fluor
Therapeutic Class	4042210 diagnostic dye
Applicant	Akorn, Inc. 2500 Millbrook Drive Buffalo Grove, IL 60089 847-279-6100
Priority Designation	S
Formulation	Active ingredient: fluorescein sodium
Dosing Regimen	500 mg (100 mg/mL) or (250 mg/mL) via intravenous administration
Indication	diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature
Intended Population	patients undergoing diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature

SUMMARY TABLE OF CONTENTS 3

SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-186 be approved with the labeling revisions included in this review once the CMC deficiencies are resolved.

FDA inspection of the ——————————— and Akorn, Inc., Decator, IL, manufacturing facilities revealed significant deviations from the Current Good Manufacturing Practice (cGMP) regulations. A satisfactory resolution of these violations is required before this application can be approved. b(4)

The application supports the safety and effectiveness of AK-Fluor (fluorescein injection) 10% and 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There are no recommendations for additional postmarketing studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

1.2.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

1.2.3 Other Phase 4 Requests

There are no recommended Phase 4 requests.

1.3 Summary of Clinical Finding

1.3.1 Brief Overview of Clinical Program

Sodium fluorescein is a water-soluble hydroxyxanthine dye. Fluorescence is the important property of fluorescein dye that makes it possible to selectively visualize fluorescein-colored solutions. Fluorescence occurs when a substance absorbs light of one wavelength and re-emits a portion of that light at a longer wavelength. In ophthalmic usage, a blue light (wavelength approximately 465-490 nm) is used to illuminate the dye and it is reflected back as a yellow-green light (wavelength approximately 520-530nm).

Fluorescein angiography has become an indispensable tool in ophthalmic practice for the diagnosis of neovascular ocular diseases, especially those that have a retinal component. Fluorescein angiography can be used to diagnose and document such diseases as choroidal neovascularization in age-related macular degeneration, neovascular diabetic retinopathy, and cystoid macular edema resulting from a variety of posterior ocular disease conditions, as well as diseases of the anterior segment of the eye.

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 has been used since before1938 drug, though the formulation, manufacturing, and labeling have changed several times in the past 70 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:

- AK-Fluor 10% - Domestic ( ) and Foreign ( )
- AK-Fluor 25% - Domestic ( ) and Foreign ( ). b(4)

Alcon filed NDA 21-980 for Fluorescite (fluorescein injection, USP) 10% which was approved on March 28, 2006. The total drug content approved in NDA 21-980 was 500 mg / 5 mL. Novartis' NDA 17-869 was approved on November 10, 1976, as Funduscein-25 25% and 10% were approved for a total dose of 750 mg/3mL ampules and 500 mg/ 5 mL ampules, respectively. Fundescein-25 has been discontinued but not for reasons of safety or efficacy.

In NDA 22-186, Akorn is seeking the approval of Fluorescein Sodium 25% (2 mL vial) with a total dose of 500 mg fluorescein and Fluorescein Sodium 10% (5 mL vial) with a total dose of 500 mg fluorescein based on the approval of NDA 21-980. As a 505(b)(2) application, NDA 22-186 is relying upon the Agency's findings of safety and efficacy contained in the Approval for NDA 21-980 Fluorescite and NDA 17-869 Fundescein-25.

Akorn, Inc. has not conducted any clinical studies using fluorescein sodium injection.

1.3.2 Efficacy

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

Fluorescein angiography has become an indispensable tool in ophthalmic practice for the diagnosis of neovascular ocular diseases, especially those that have a retinal component. Fluorescein angiography can be used to diagnosis and document such diseases as choroidal neovascularization in age-related macular degeneration, neovascular diabetic retinopathy, and cystoid macular edema resulting from a variety of posterior ocular disease conditions, as well as diseases of the anterior segment of the eye.

1.3.3 Safety

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis's Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

There is more than a 30 year history of use of this particular product, AK-Fluor, with adequate demonstration of effectiveness and safety. Distribution data submitted by Akorn, Inc. indicate that the total number of units sold between Januarv 2003 and June 2007 as follows: b(4)

- AK-Fluor 10% - Domestic [redacted] and Foreign [redacted]
- AK-Fluor 25% - Domestic [redacted] and Foreign [redacted]

This review reveals no new safety findings for AK-Fluor based on the submitted postmarketing data. There is no evidence of abuse potential for this product.

1.3.4 Dosing Regimen and Administration

The proposed normal adult dose of AK-Fluor (fluorescein injection) 10% and 25% is 500 mg (100 mg/mL) or (250 mg/mL) via intravenous administration.

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).

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

1.3.5 Drug-Drug Interactions

Specific drug interaction studies are not reported.

1.3.6 Special Populations

Safety and effectiveness of fluorescein sodium injection, 10% and 25% has been adequately assessed in special populations in NDAs 17-869 and 21-980.

No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

Safety and effectiveness in pediatric patients have been established.

There is no information to suggest that dosage adjustment is necessary in the renally or hepatically impaired patient population.

LINE-BY-LINE LABELING REVIEW

Reviewer's Comments: *Akorn's proposed labeling was submitted in an amendment to the original New Drug Application on August 8, 2007; the labeling has been reviewed and is considered acceptable provided the following changes are made:*

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 5

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/s/

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