CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-186

SUMMARY REVIEW

Summary Review of NDA 22-186 for Regulatory Action

Date	August 7, 2008
From	Wiley A. Chambers, MD Acting Division Director, DAIOP
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-186
Applicant Name	Akorn, Inc.
Date of Submission	April 5, 2007 amended March 28, 2008
Proprietary Name / Established (USAN) Name	AK-Fluor (fluorescein injection) 10% and 25%
Dosage Forms / Strength	Injection / 10 and 25%
Proposed Indication(s)	Diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Rhea Lloyd
Clinical Team Leader Review	William Boyd
Statistical Review	Christopher Khedouri
Pharmacology Toxicology Review	Maria Rivera
CMC Review/OBP Review	Ko-Yu Lo/George Lunn
Sterility Assurance Review	Stephen Langille
Clinical Pharmacology Review	Sarah Robertson
DDMAC	Sheila Ryan
CDTL Review	William Boyd
OSE/DMETS	Laura Pincock

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

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. Fluorescein sodium has been in clinical use since before1938

although the formulation, manufacturing, and labeling have changed many times in the past 70 years. The initial launch date of AK-Fluor was in December 1975 in France. It has also been marketed in the United States for many years without an approved new drug application.

2. Background

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). Sodium fluorescein is used 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.

3. CMC

I concur with the chemistry and sterility assurance reviewers recommending approval regarding the manufacturing of the drug product and drug substance. These include issues related to a lack of sterility assurance of this product have been resolved. The manufacturing site inspections are now acceptable.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical/Statistical-Efficacy

I concur with the medical officer's review. The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis' Fundescein-25. NDA 17-869 supports the use of 500mg of fluorescein injection, USP. In addition, there are hundreds of articles describing the clinical use of sodium fluorescein.

7. Safety

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis' Fundescein-25. In addition, there are hundreds of articles describing the clinical use of sodium fluorescein.

8. Pediatrics

Sodium fluorescein has a long history of use in pediatric patients. The pediatric dosing schedule was established in NDA 17-869.

9. Other Relevant Regulatory Issues

There are no additional significant regulatory issues with this application.

10. Labeling

The labeling while based on NDA 17-869 has been reformatted to be consistent the new Physician Labeling rule. The proposed draft package insert has been reviewed, found acceptable and is included in the Medical Officer Review #3 dated July 23, 2008.

11. Decision/Action

NDA 22-186, AK-Fluor (fluorescein injection, USP) 10% and 25% should be approved with the labeling submitted on July 16, 2008. All outstanding review issues have been resolved. The application contains information and/or reference to Agency findings from previous fluorescein injection applications for the use of fluorescein injection 500mg either as 10% or 25% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. There are no recommendations for additional postmarketing studies.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
8/8/2008 10:00:52 AM
MEDICAL OFFICER

Wiley Chambers
8/8/2008 10:01:37 AM
MEDICAL OFFICER

Division Director Memorandum
Wiley A. Chambers, MD
NDA 22-186 AK-Fluor (fluorescein injection, USP)

Summary Review of NDA 22-186 for Regulatory Action

Date	February 5, 2008
From	Wiley A. Chambers, MD Acting Division Director, DAIOP
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-186
Applicant Name	Akorn, Inc.
Date of Submission	April 5, 2007
Proprietary Name / Established (USAN) Name	AK-Fluor (fluorescein injection) 10% and 25%
Dosage Forms / Strength	Injection / 10 and 25%
Proposed Indication(s)	Diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature
Action:	*Not Approvable*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Rhea Lloyd
Clinical Team Leader Review	William Boyd
Statistical Review	Christopher Khedouri
Pharmacology Toxicology Review	Maria Rivera
CMC Review/OBP Review	Ko-Yu Lo
Sterility Assurance Review	Stephen Langille
Clinical Pharmacology Review	Sarah Robertson
DDMAC	Sheila Ryan
CDTL Review	William Boyd
OSE/DMETS	Laura Pincock

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DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

1. Introduction

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. Fluorescein sodium has been in clinical use since before1938 although the formulation, manufacturing, and labeling have changed many times in the past 70 years. The initial launch date of AK-Fluor was in December 1975 in France. It has also been marketed in the United States for many years without an approved new drug application.

2. Background

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). Sodium fluorescein is used 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.

3. CMC

I concur with the issues raised by the chemistry and sterility assurance reviewers regarding the manufacturing of the drug product and drug substance. These include issues related to a lack of sterility assurance of this product. There are significant safety concerns related to the issue that the sterility of the product cannot be assured at the time of use. In addition, manufacturing site inspections were not acceptable and are a primary basis for the non-approval of this application at this time. See Decision/Action, below in this review.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical/Statistical-Efficacy

I concur with the medical officer's review. The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis' Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the

retina and iris vasculature. NDA 17-869 supports the use of 3 mL of 25% fluorescein injection. NDA 21-980 supports the use of 5 mL of 10% fluorescein injection. In addition, there are hundreds of articles describing the clinical use of sodium fluorescein.

7. Safety

The application relies upon the Agency's findings of safety and efficacy contained in the Approval for NDA 17-869, Novartis' Fundescein-25, and NDA 21-980, Alcon's Fluorescite, for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. In addition, there are hundreds of articles describing the clinical use of sodium fluorescein.

8. Pediatrics

Sodium fluorescein has a long history of use in pediatric patients. The pediatric dosing schedule was established in NDA 17-869.

9. Other Relevant Regulatory Issues

There are no additional significant regulatory issues with this application.

10. Labeling

The labeling while based on NDA 17-869 and NDA 21-980 has been reformatted to be consistent the new Physician Labeling rule. The proposed draft package insert is included at the end of this review.

11. Decision/Action

FDA inspection of the [redacted], and Akorn, Inc., Decatur, IL, manufacturing facilities revealed significant deviations from the Current Good Manufacturing Practice (cGMP) regulations. Before the application may be approved, it will be necessary for the manufactures to comply with cGMP. b(4)

In addition, as described in the Microbiology (sterility assurance) review and listed below, there are issues related to a potential lack of sterility assurance. Specifically,

1. [redacted] b(4)

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 1

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/s/

Wiley Chambers
2/6/2008 02:47:23 PM
MEDICAL OFFICER

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