CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-980

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-980
Submission Code	Original
Letter Date	March 16, 2006
PDUFA Goal Date	March 29, 2006
Reviewer Name	Wiley A. Chambers, M.D.
Review Completion Date	March 17, 2006
Established Name	fluorescein injection
(Proposed) Trade Name	Fluorescite
Therapeutic Class	4042210 diagnostic dye
Applicant	Alcon, Inc.
Priority Designation	P
Formulation	Active ingredient: fluorescein sodium
Dosing Regimen	500 mg (100 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

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SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 21-980 be approved with the labeling listed in this review.

The application supports the safety and effectiveness of Fluorescite (fluorescein injection, USP) 10% 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

Fluorescite (fluorescein injection, USP) 10% is a sterile aqueous solution containing sodium fluorescein and is indicated in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature, i.e., diagnosis and evaluation of ocular diseases. Fluorescein sodium is a pre-1938 drug product, although the formulation, manufacturing, and labeling have changed several times in the past 50 years. Fluorescite has been marketed previously without a New Drug Application in the United States.

There is a 30 year history of use of this particular product, Fluorescite, with adequate demonstration of effectiveness and safety. Based on the number of units sold between January 1996 and June 2005 for Fluorescite 10% [redacted] units) and Fluorescite 25% [redacted] units), Alcon estimates that over [redacted] angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period.

There are currently no approved New Drug Applications for fluorescein injection 10%. There is one discontinued drug product for fluorescein injection 25% [NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) – Novartis]. This drug product was not discontinued for reasons of safety or efficacy.

Sodium fluorescein is a water-soluble hydroxyxanthine dye. Fluorescence is an important property of fluorescein dye that makes it possible to selectively visualize fluorescein-colored solutions. 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 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.

Alcon, Inc. conducted separate clinical studies of several fluorescein formulations in the early 1970's when the dye was first introduced to the market for ocular diagnosis.

1.3.2 Efficacy

The application supports the effectiveness of Fluorescite (fluorescein injection, USP) 10% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

The major sources of clinical data in support of efficacy for Fluorescite utilized in this application include:

1) Four (4) Alcon clinical studies performed in the 1970's
2) Literature references citing Alcon's Fluorescite product
3) Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
4) An Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

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

There is a 30 year history of use of this product in the United States (marketed by Alcon without a New Drug Application) with adequate demonstration of safety. Alcon reports that [redacted] units of Fluorescite 10% have been sold worldwide during the period from 1 January1996 to 30 June 2005.

There is no evidence of abuse potential for this product. The revised labeling found in this review adequately describes the drug's adverse event profile and the precautions necessary to administer the drug for its intended use.

1.3.4 Dosing Regimen and Administration

The normal adult dose of Fluorescite (fluorescein injection, USP) 10% is 500 mg (100 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 Fluorescite (fluorescein injection, USP) 10% in special populations has been adequately assessed.

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.

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/s/

Wiley Chambers
3/17/2006 10:04:28 AM
MEDICAL OFFICER

Janice Soreth
3/28/2006 03:47:53 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-980
Submission Code	Original
Letter Date	September 28, 2005
Stamp Date	September 29, 2005
PDUFA Goal Date	March 29, 2006
Reviewer Name	William M. Boyd, M.D.
Review Completion Date	March 6, 2006
Established Name	fluorescein injection
(Proposed) Trade Name	Fluorescite
Therapeutic Class	4042210 diagnostic dye
Applicant	Alcon, Inc.
Priority Designation	P
Formulation	Active ingredient: fluorescein sodium
Dosing Regimen	500 mg (100 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

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 21-980 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Fluorescite (fluorescein injection, USP) 10% 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 optional or recommended Phase 4 requests.

1.3 Summary of Clinical Finding

1.3.1 Brief Overview of Clinical Program

Fluorescite (fluorescein injection, USP) 10% is a sterile aqueous solution containing sodium fluorescein and is indicated in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature, i.e., diagnosis and evaluation of ocular diseases. Fluorescein sodium is a pre-1938 drug product, although the formulation, manufacturing, and labeling have changed several times in the past 50 years. Fluorescite has been illegally marketed previously without a New Drug Application in the United States.

There is a 30 year history of use of this particular product, Fluorescite, with adequate demonstration of effectiveness and safety. Based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% [redacted] and Fluorescite 25% [redacted], Alcon estimates that over [redacted] angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period.

There are currently no approved New Drug Applications for fluorescein injection 10%. There is one discontinued drug product for fluorescein injection 25% [NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) – Novartis]. This drug product was not discontinued for reasons of safety or efficacy.

Sodium fluorescein is a water-soluble hydroxyxanthine dye. Fluorescence is an 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 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.

Alcon, Inc. conducted separate clinical studies of several fluorescein formulations in the early 1970's when the dye was first introduced to the market for ocular diagnosis. These study reports would not meet the current criteria for study reports as set forth in ICH 3 Structure and Content of Clinical Study Reports.

1.3.2 Efficacy

The application supports the effectiveness of Fluorescite (fluorescein injection, USP) 10% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

The major sources of clinical data in support of efficacy for Fluorescite utilized in this review include:

1) Four (4) Alcon clinical studies performed in the 1970's
2) Literature references citing Alcon's Fluorescite product
3) Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.

4) an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

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

There is a 30 year history of use of this product in the United States (marketed by Alcon without a New Drug Application) with adequate demonstration of safety. Alcon reports that [redacted] units of Fluorescite 10% have been sold worldwide during the period from 1 January1996 to 30 June 2005.

There is no evidence of abuse potential for this product. The revised labeling found in this review adequately describes the drug's adverse event profile and the precautions necessary to administer the drug for its intended use.

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.

1.3.4 Dosing Regimen and Administration

The normal adult dose of Fluorescite (fluorescein injection, USP) 10% is 500 mg (100 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. Refer to Section 10.2 of the Clinical Review (Labeling).

1.3.6 Special Populations

Safety and effectiveness of Fluorescite (fluorescein injection, USP) 10% in special populations has been adequately assessed.

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.

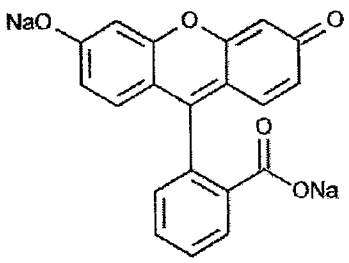
Safety and effectiveness in pediatric patients have been established.

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

Fluorescite (fluorescein injection, USP) 10% contains fluorescein sodium (equivalent to fluorescein 10% 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:



Fluorescein sodium is a pre-1938 drug product. Fluorescite 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 the two primary dyes used to perform diagnostic ocular angiography, and since the information gained from each procedure is different, they are used to complement and enhance the diagnostic information gained separately from each.

Fluorescein angiography is most useful for studying the retinal circulation, whereas ICG is better suited for studying the deeper choroidal circulation. Fluorescein angiography is most frequently used for evaluation of patients with diabetic retinopathy, occlusive diseases such as retinal vein and arterial occlusions, and evaluation for wet macular degeneration. ICG angiography is most frequently used when blood is present in the macula of patients with the wet form of age related macular degeneration (AMD), as this may make interpretation of fluorescein angiography more difficult.

2.3 Availability of Proposed Active Ingredient in the United States

There are currently no approved New Drug Applications for fluorescein injection 10%. There is one discontinued drug product for fluorescein injection 25% [NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) – Novartis]. This drug product was not discontinued for reasons of safety or efficacy.

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

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.

Fluorescite has been illegally marketed previously without a New Drug Application in the United States. Fluorescein sodium is a pre-1938 drug product, although the formulation, manufacturing, and labeling have changed several times in the past 50 years.

There are currently no approved New Drug Applications for fluorescein injection 10%. There is one discontinued drug product for fluorescein injection 25% [NDA 17-869 for Funduscein-25 (fluorescein sodium injectable) – Novartis]. This drug product was not discontinued for reasons of safety or efficacy.

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

In March 2001, the Division received a communication from Alcon regarding a potential shortage of fluorescein sodium product. [redacted] A medical necessity evaluation form was completed by the Division in April 2001. Alcon was urged to submit a New Drug Application for its product.

In this 505(b) (2) application, Alcon requested a 6 month priority review as it was notified by the CDER Drug Shortages program, Drug Shortage Team, that the Agency is concerned about the availability of fluorescein sodium in the United States.

2.6 Other Relevant Background Information

The use of fluorescein sodium in retinal angiography was first described in 1961 by Novotny and Alvis.[1]

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

To date, Fluorescite has been marketed or approved in 41 countries (Table 2.6). The first known registration date (November 1971) was for Fluorescite 10% in the Czech Republic, and the most recent registration was for Fluorescite 10% and 25% in Singapore (April 2001).

Table 2.6 - Cumulative World-Wide Market Authorization Status for Fluorescite 10%

Country	FLUORESCITE®		
	5%	10%	25%
ARGENTINA	+	+	+
AUSTRALIA		+	+
CANADA		+	+
CHINA		+	
COLOMBIA		+	
COSTA RICA		+	+
CROATIA		+	
CURACAO		+	
CZECH REPUBLIC		+	+
ECUADOR		+	
EGYPT		+	
FINLAND	+		
FINLAND (sold w/o registration)		+	+
GERMANY		+	
HONG KONG		+	+
HUNGARY		+	+
IRAQ		+	
JAPAN		+	
KAZAKHSTAN		+	
KOREA		+	
KUWEIT (cancelled)			
KYRGYZSTAN		+	
LITHUANIA		+	
MYANMAR		+	
NEW ZEALAND		+	+
PARAGUAY		+	
PERU		+	
PHILIPPINES		+	
POLAND		+	
ROMANIA		+	+
RUSSIA		+	
SINGAPORE		+	+
SLOVAK REPUBLIC		+	+
TAIWAN		+	+
THAILAND		+	
TURKEY		+	
U S S R		+	+
UNITED STATES		+	
URUGUAY		+	
UZBEKISTAN		+	+
YUGOSLAVIA (not required)		+	
SOUTH AFRICA			+
MALAYSIA			+
Number of Countries for Each Product	**2**	**39**	**17**

Reviewer's Comments:

No units of Fluorescite 5% were sold during the period 01 January 1996 – 30 June 2005.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Although Alcon has marked Fluorescite Injection, 10% in the USA for over 30 years, new drug substance and drug product manufacturers were introduced in the current application. A new container closure system, glass vial (instead of glass ampoule), was used in the current application. Fluorescite (fluorescein injection, USP) 10% is a sterile clear red-orange aqueous solution containing fluorescein sodium (equivalent to fluorescein 10%). It contains USP grade drug substance and NF grade pharmaceutical excipients without a preservative. It is formulated at pH 9.4 to achieve optimal stability for the active, using sodium hydroxide and hydrochloric acid for maintaining a basic pH. Sodium hydroxide is used tc [redacted] Fluorescite (fluorescein injection, USP) 10% is filled in 5 mL [redacted] clear molded glass vials with [redacted] grey chlorobutyl stoppers and [redacted] flip-off aluminum seals. [redacted]
The proposed shelf-life of the drug product is [redacted]

Although the drug substance is manufactured by [redacted]., the applicant provided additional information on the drug substance quality control, including characterization, impurity profile, reference standards, and stability studies. The drug product is manufactured by International Medication Systems, Ltd. (IMS). The applicant provided adequate information on the drug product quality control, including raw material control, manufacturing, packaging, specification, analytical procedures. Upon request, the updated stability testing protocol and stability data were provided.

The Product Microbiology consult is pending, but here were no preliminary issues identified.

3.2 Animal Pharmacology/Toxicology

Fluorescite has been marketed in the US and throughout the world for over 30 years. The drug has been extensively studied for PK and PD properties, diagnostic utility for many ocular diseases, and safety of the formulation. Since Fluorescite is indicated for use as a diagnostic agent intended for single use, no repeated-dose toxicity, genotoxicity, reproductive toxicity, and carcinogenicity studies were conducted by the sponsor. In this NDA submission, only single dose toxicity study reports were included. The results obtained from these studies indicated that the intravenous LD_{50} values for fluorescein in mice were not affected by volume changes and by rubber plunger exposure. At 10 mg/kg, no acute toxicity was seen in mice and dogs. Fluorescein sodium from different sources showed similar LD_{50} and clinical signs. There are no specific concerns from the pharmacology/toxicology viewpoint regarding clinical use of Fluorescite.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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

- Four (4) Alcon clinical studies performed in the 1970's
- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

Alcon, Inc. conducted separate clinical studies of several fluorescein formulations in the early 1970's when the dye was first introduced to the market for ocular diagnosis. These study reports would not meet the current criteria for study reports as set forth in ICH 3 Structure and Content of Clinical Study Reports.

4.2 Tables of Clinical Studies

Table 4.2 A – Summary of Alcon Clinical Studies Performed in the 1970's

Protocol No.	Study Design	Subj/Pat Population	Treatment Groups	Dosing Regimen	Total No. Exposed to Active Drug
72-2-01 David Paton, M.D., Johnny Justice, M.D. Baylor College of Medicine, Houston, Texas	Prospective Mono-center Parallel Open label To provide data on clinical safety as well as diagnostic utility	Patients with Macular degeneration. Diabetic retinopathy. Macular Edema. Intraocular tumors, and vascular occlusions as well as normal volunteers	2 ml of 25% solution 5 ml of 10% solution FLUORESCITE®	Single administration of 5 ml or 2 ml of either test medication	Alcon FLUORESCITE 10% n=99 —Sodium Fluorescein 10% n= 105
72-2-01 — David Paton, M.D., Johnny Justice, M.D. Baylor College of Medicine, Houston, Texas Lawrence Yannuzzi, M.D. New York	Prospective Two centers Parallel Double-masked (10% solutions) Open (5% solution) To determine the effects of formulation differences on side effects	Patients requiring fluorescein angiography	1) 5 ml of 10% (A 4%) 2) 5 ml of 10% (B 0) (=comparative brand) 3)5 ml of 10% (C 4%) 4) 5 ml of 10% (C 0) (=Fluorescite 10%) 5) 10 ml of 5% (A 2%) (fluorescein raw material: — and concentration of sodium bicarbonate)	Single administration of 5 ml or 10 ml of each formulation	490 patients total 1) n= 99 2) n= 105 3) n=94 4) n=99 5) n=93
72-2-02 John Lynn, M.D. Southwestern Medical School, Dallas, Texas	Phase I Safety	Patients requiring fluorescein angiography	Alcon FLUORESCITE 25% Alcon FLUORESCITE 10%	Single administration of ml of either formulation	Alcon FLUORESCITE 25% n=39 Alcon FLUORESCITE 10% n=9
72-2-03 I.S. Begg, M.D University of British Columbia, Canada.	To determine the effects of different formulations on diagnostic utility and side effects	Patients requiring fluorescein angiography	Alcon FLUORESCITE 25% — Sodium Fluorescein 25%	Single administration of 2 ml of either formulation	Alcon FLUORESCITE 25% n=98 — Fluorescein 25% n=98
Total Subj/Pat Exposure					**Alcon FLUORESCITE = 735** **— Fluorescein = 203**

Reviewer's Comments:

The Summary of Alcon Clinical Studies seen above (NDA Table 2.5.4.2.1-1, Table 2.7.4.6.1-1, and Table 5.2-1) prepared by Alcon contains errors:

- *Both treatment groups in trial 72-2-01 received 5 mL of 10% sodium fluorescein solution, either Alcon's formulation or ——— s formulation. A 25% solution was not utilized in this trial.*

- *The volunteers in trial 72-2-02 received either 2 ml of the 25% formulation or 5 ml of the 10% formulation; the enrolled subjects were normal volunteers, not patients requiring fluorescein angiography.*

Table 4.2 B – Literature references citing Alcon's Fluorescite product for efficacy

Trial Info	# Pts/ FAs	Aim of Study	Fluorescein Dose (IV)	Study Duration/Observation Period
Willerson et al 1976[2]	49 normal volunteers 25% 9 normal volunteers 10%	To evaluate diagnostic utility and safety of different concentrations	5 mL of 10% 2 mL of 25% (Fluorescite 10%, Fluorescite 25%)	Not provided

Reviewer's Comments:

Alcon cites numerous other literature references for their Fluorescite product in NDA Table 2.5.4.3.4-1 "Studies on Alcon Fluorescite in the Published Literature," but these references did not evaluate the efficacy of the product; they only evaluated safety, despite their conclusion that fluorescein angiography is a safe and effective procedure. These references are not included here.

Table 4.2 B – Literature references citing other fluorescein preparations for efficacy

Trial Info	# Pts/ FAs	Aim of Study	Fluorescein Dose (IV)	Study Duration/ Observation Period
Justice et al. 1977[3]	41 normal volunteers 42 patients	To compare effects of different concentrations	5 mL of 10% 3 mL of 25% (Fundescein 10, Funduscein 25)	Not provided

Reviewer's Comments:

Alcon cites numerous other literature references for their Fluorescite product in NDA Table 2.5.4.3.4-3 "Studies of Other Fluorescein Preparations," but these references did not evaluate the efficacy of the product; they only evaluated safety, despite their conclusion that fluorescein angiography is a safe and effective procedure. These references are not included here.

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2 Willerson D, Tate GW Jr, Baldwin HA, Hearnsberger PL. Clinical evaluation of fluorescein 25%. Ann Ophthalmol 1976;18(7):833-4, 837-41.

3 Justice J Jr, Paton D, Beyrer CR, Seddon GG. Clinical comparison of 10 percent and 25 percent intravenous sodium fluorescein solutions. Arch Ophthalmol 1977;95(11):2015-6.

Photostat copies of references should not be illegible (i.e. Justice, 1977).

Table 4.2 C – Literature References in Large Complication Surveys with Source of Fluorescein Unknown

Trial Info	Concentrations of Fluorescein Surveyed	Observation Period	Number of Angiograms Surveyed	Countries Surveyed
Yanuzzi et al 1986[4]	10% 25%	1984	221,781	USA, Puerto Rico
Zografos et al 1983[5]	5% 10% 20% 25%	1977-1979	594,687	30 Countries

Reviewer's Comments:

Cited references in support of a New Drug Application should be translated into English. Copies of references should not be submitted to the application in a foreign language (i.e. Zografos et al 1983).

Appears This Way
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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.

5 Zografos L. Enquête internationale sur l'incidence des accidents graves ou fatals pouvant survenir lors d'une angiographie fluorescéinique. Klin Mbl Augenheilk 1983 (182):460-462.

Table 4.4 D – Literature References for Safety in Studies with > 1000 Subjects

Trial Info	Concentrations of Fluorescein Included	Observation Period	Number of Patients and/or Angiograms	Countries Surveyed
Lepri et al 1997[6]	5% 10% 20% 25%	Not provided	6524 patients 10,003 FA	Italy
Jennings et al 1994[7]	10% 25%	1988-1991	1173 patients	USA
Kwiterovich et al 1991[8]	10%	1988-1989	2025 patients 2789 FA	USA
Karhunen et al 1986[9]	10%	9 years	9909 patients 9909 FA	Finland
Marcus et al 1984[10]	10% 25%	10 years	5460 patients	USA
Butner et al 1983[11]	10% 25%	Not provided	5000 FA	USA
Pacurariu et al 1982[12]	10%	Not provided	1800 patients 2631 FA	USA

6 Lepri A, Salvini R, Rizzo L, Cetica P, Grechi S, Di Filippo A, Conti M, Benvenuti S, Novelli GP. [Accident during retinal fluorescein angiography]. [Article in Italian] Minerva Anestesiol 1997;63(4):133-40.

7 Jennings BJ, Mathews DE. Adverse reactions during retinal fluorescein angiography. J Am Optom Assoc 1994;65(7):465-71.

8 Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB, Fine SL. Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. Ophthalmology 1991;98(7):1139-42.

9 Karhunen U, Raitta C, Kala R. Adverse reactions to fluorescein angiography. Acta Ophthalmol (Copenh) 1986;64(3):282-6.

10 Marcus DF, Bovino JA, Williams D. Adverse reactions during intravenous fluorescein angiography. Arch Ophthalmol 1984;102(6):825.

11 Butner RW, McPherson AR. Adverse reactions in intravenous fluorescein angiography. Ann Ophthalmol 1983;15(11):1084-6.

12 Pacurariu RI. Low incidence of side effects following intravenous fluorescein angiography. Ann Ophthalmol 1982;14(1):32-6.

Reviewer's Comments:

Cited references in support of a New Drug Application should be translated into English. Copies of references should not be submitted to the application in a foreign language (i.e. Lepri et al 1997).

4.3 Review Strategy

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

- Four (4) Alcon clinical studies performed in the 1970's
- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

4.4 Data Quality and Integrity

The four Alcon-sponsored historical studies were conducted in the 1970's. There is no evidence that these studies were not conducted in accordance with acceptable clinical ethical standards.

There were no Division of Scientific Investigations (DSI) audits. The case report forms for the four Alcon-sponsored historical studies were provided by Alcon, and these were reviewed for completeness and quality.

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

4.5 Compliance with Good Clinical Practices

The four Alcon-sponsored historical studies were conducted in the 1970's. There is no evidence that these studies were not conducted in accordance with acceptable clinical ethical standards.

4.6 Financial Disclosures

Although four clinical studies are contained in this application, these historical studies were conducted in the 1970's, prior to the issuance of the Financial Disclosure Rule (21 CFR Parts 54, 312 and 314) and are part of the substantiation of well established use for this product that has been marketed in the United States for over 30 years. Consequently, no completed certification and disclosure forms are provided.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Within 7 to 14 seconds after IV administration into antecubital vein, fluorescein appears in the central artery of the eye. Within a few minutes of IV administration of fluorescein sodium, a yellowish discoloration of the skin occurs, which begins to fade after 6 to 12 hours of dosing. Various estimates of volume of distribution indicate that fluorescein distributes well into interstitial space (0.5 L/kg).

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.

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

Fluorescite 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, Fluorescite. 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:

> Fluorescite Injection 10% is indicated in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature

is acceptable. Refer to Section 10.2 of the Clinical Review (Labeling) for additional information.

6.1.1 Methods

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

- Four (4) Alcon clinical studies performed in the 1970's
- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

6.1.2 General Discussion of Endpoints

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.

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

Comments on Study Design per se are limited in this Section to the four Alcon clinical trials conducted in the 1970's. Comments on Study design as they pertain to literature references for efficacy are found in Section 6.1.4.

Alcon, Inc. conducted separate clinical studies of several fluorescein formulations in the early 1970's when the dye was first introduced to the market for ocular diagnosis. These study reports would not meet the current criteria for study reports as set forth in ICH 3 Structure and Content of Clinical Study Reports.

Reviewer's Comments:

Although case report forms are submitted for the four clinical studies performed by Alcon in the 1970's, the study report submitted lack sufficient detail to determine if the trials were adequate and well controlled. The reports themselves are 2-3 pages of photocopied, typewritten pages. There are no actual protocols, case report forms, data sets, or consent forms for review.

ALCON CLINICAL PROTOCOLS

Following is a brief synopsis of each Alcon trial:

ALCON PROTOCOL 72-2-01

BRIEF SUMMARY

This study was conducted to compare a new fluorescein formulation, Alcon Fluorescein 10%, to Sodium Fluorescein 10% ( ), another commercially available product at the time. The study was conducted with patients who required fluorescein angiography for diagnosis of various ocular diseases at the Baylor College of Medicine in Houston, Texas, with David Paton, M.D., and Johnny Justice, M.D. as investigators. Each patient was interviewed by the investigator prior to administration of the test medication to determine brief patient history (age, sex, weight, race, previous fluorescein angiograms).

Medications were assigned in random order to the patients according to a pre-assigned, randomized patient numbering system. Although the investigators did not have a code for the numbering system, the test was not considered blinded due to a difference in color between the two products.

A total of 204 patients were enrolled in the study, with 99 patients receiving a single intravenous administration of Alcon Fluorescein 10% and 105 patients receiving , Sodium Fluorescein 10%. Each patient received 5 ml of test medication except one, aged 6 years, who received 3 ml. Ten patients experienced extravasation of the test medication and therefore received a quantity less than 5 ml (exact quantity received unknown).

MEDICATIONS

- Sodium Fluorescein 10% (Alcon laboratories, Inc.), a sterile aqueous solution containing 10% sodium fluorescein solubilized with 4.06% sodium bicarbonate
- Sodium Fluorescein 10% , a sterile aqueous solution containing 10% sodium fluorescein in water for injection.

Table 6.1.3 A - Protocol 72-2-01 Patient Demographics

History	Sodium Fluorescein 10% (Alcon laboratories, Inc.) N=99	Sodium Fluorescein 10% N=105
Age – mean	54.6 years (1 not recorded)	51.2 years (2 not recorded)
Age – range	10-89 years	6-81 years
Weight – mean	156.4 lbs (3 not recorded)	154.3 lbs (3 not recorded)
Weight – range	70-253 lbs	55-235 lbs
Sex	47 male 52 female	59 male 46 female
Race	80 white 19 black	87 white 15 black 2 other 1 not recorded
Previous Angiograms	24 yes 75 no	25 yes 78 no 2 not recorded

Reviewer's Comments:

A photocopy of the original clinical study report, dated October 4, 1972, was reviewed.

The Summary of Alcon Clinical Studies (NDA Table 2.5.4.2.1-1, Table 2.7.4.6.1-1, and Table 5.2-1) prepared by Alcon contains an error – both treatment groups in this trial received 5 mL of 10% sodium fluorescein solution, either Alcon's formulation or [redacted] formulation. A 25% solution was not utilized in this trial.

ALCON PROTOCOL 72-2-01 (A,B,C)

BRIEF SUMMARY
New formulations of Alcon Fluorescein 10% and 5% were evaluated in this study and compared to Fluorescein Sodium 10% [redacted] Approximately 100 subjects were enrolled into each of the five treatment groups.

The study was conducted at two centers, Baylor University School of Medicine in Houston with David Paton, M.D., and Johnny Justice, M.D. as investigators and at Manhattan Eye and Ear Hospital in New York with Lawrence Yannuzzi, M.D.

Where possible, patients were assigned in random order and under double blind conditions.

MEDICATIONS

1. Sodium Fluorescein 10% (Alcon laboratories, Inc.). [redacted], with 4% sodium bicarbonate [99 patients]
2. Sodium Fluorescein 10% [redacted] with no bicarbonate [105 patients]
3. Sodium Fluorescein 10% (Alcon laboratories, Inc.). [redacted], with 4% sodium bicarbonate [94 patients]
4. Sodium Fluorescein 10% (Alcon laboratories, Inc.). [redacted], with no bicarbonate [99 patients]
5. Sodium Fluorescein 5% (Alcon laboratories, Inc.), [redacted] with 2% sodium bicarbonate [93 patients].

Reviewer's Comments:

A photocopy of the original clinical study report, dated April 9, 1973, was reviewed.

All of the 10% formulations were coded to allow double-masked conditions, but the color difference between groups 1 and 2 was apparently obvious. Since the quantity of drug administered in group 5 was different, there could be no masking.

No patient demographics were provided in the submitted clinical study report.

ALCON PROTOCOL 72-02-02

BRIEF SUMMARY

Protocol 72-2-02 was a Phase 1 open label clinical study in normal human volunteers conducted to determine the safety and utility of Alcon Fluorescein Sodium for Injection 25% [redacted] compared to commercially available Alcon Fluorescite 10%. John R. Lynn, M.D. conducted the study, at Southwestern Medical School in Dallas, Texas. A total of 39 volunteers received the 25% formulation while 9 volunteers received Fluorescite 10%. The volunteers received 2 ml of the 25% formulation or 5 ml of the 10% formulation, and were monitored for signs and symptoms of side effects following rapid intravenous administration. Fluorescein levels were determined for each blood and urine sample to estimate clearance rate of the fluorescein dye. In addition, each subject underwent rapid sequence fundus photography immediately post-injection to determine the diagnostic utility of both formulations.

MEDICATIONS

- Alcon Fluorescein Sodium for Injection 25% [redacted]
- commercially available Alcon Fluorescite 10%.

Table 6.1.3 B - Protocol 72-2-02 Patient Demographics

History	Alcon Fluorescein Sodium for Injection 25% ([redacted] N=39	commercially available Alcon Fluorescite 10% N=9
Age – mean	27.5	28.1
Age – range	17-40	20-51
Weight – mean	150.3	133.1
Weight – range	105-220	110-200
Sex	17 male 22 female	3 male 6 female
Race	38 white 1 black	9 white 0 black

Reviewer's Comments:

A photocopy of the original clinical study report, dated October 25, 1973, was reviewed.

The Summary of Alcon Clinical Studies (Table 2.5.4.2.1-1 and Table 5.2-1) prepared by Alcon contains errors: the volunteers in this trial received either 2 ml of the 25% formulation or 5 ml of the 10% formulation; the enrolled subjects were normal volunteers, not patients requiring fluorescein angiography.

There is not an adequate description of the formulations utilized in this protocol within the submitted study report. It is implied that the commercially available Alcon Fluorescite 10% is the same as the formulation used in Group 4 in Protocol 72-2-01 [redacted] and the same formulation as the product currently marketed by Alcon in the U.S. without a New Drug Application.

ALCON PROTOCOL 72-02-03

BRIEF SUMMARY
This study evaluated fluorescein for injection 25% (Fluorescite 25%, Alcon) compared to Fluorescein Sodium Injection 25% [redacted] for incidence of side effects and diagnostic utility. A total of 196 subjects were enrolled into the study, with 98 subjects in each treatment group. The study was prospective, randomized, and double masked.

Patients who presented for routine diagnostic intravenous fluorescein angiography for various ocular diseases were enrolled by the investigator, I.S. Begg, M.D., at the Department of Ophthalmology, University of British Columbia, Vancouver, Canada. Each patient received rapid intravenous administration of 2 ml of the test medication. Each patient was monitored for

signs and symptoms of side effects, and the investigator subjectively evaluated the results of each angiogram for comparison of the diagnostic utility of the test formulations.

MEDICATIONS

6. Fluorescite 25% (Alcon Laboratories)
7. Fluorescein Sodium Injection

Table 6.1.3 C Protocol 72-2-03 Patient Demographics

History	Fluorescite 25% (Alcon Laboratories) N=98	Fluorescein Sodium Injection N=98
Age – mean	53.4	54.8
Age – range	18-86 years	13-85 years
Weight – mean	140 lbs	152
Weight – range	85-258 lbs	94-226 lbs
Sex	48 male 50 female	51 male 46 female
Race	91 white 3 black 2 other 2 not recorded	95 white 0 black 2 other 1 not recorded
Previous Angiograms	24 yes 75 no	25 yes 78 no 2 not recorded

Reviewer's Comments:

A photocopy of the original clinical study report, dated October 17, 1973, was reviewed.

6.1.4 Efficacy Findings

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

- Four (4) Alcon clinical studies performed in the 1970's
- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

ALCON CLINICAL PROTOCOLS

ALCON PROTOCOL 72-2-01

Table 6.1.4 A - Protocol 72-2-01 Subjective Evaluation of the Quality of Angiography

Subjective Grade	Sodium Fluorescein 10% (Alcon laboratories, Inc.) N=99	Sodium Fluorescein 10% [redacted] N=105
Poor	0 (0.0%)	0 (0.0%)
Adequate	15 (15.2%)	15 (14.3%)
Good	46 (46.5%)	36 (34.3%)
Excellent	38 (38.3%)	54 (51.4%)

Reviewer's Comments:

There are no significant differences in the subjective grading of Alcon's fluorescein versus [redacted] fluorescein. Both produced "Adequate" or better quality angiograms for the subjects.

This is, however, a single-center, open label trial.

ALCON PROTOCOL 72-2-01 [redacted]

Table 6.1.4 B - Protocol 72-2-01 [redacted] Angiogram Grade

Subjective Angiogram Grade	Group 1 N=99 Sodium Fluorescein 10% (Alcon laboratories, Inc.), [redacted] with 4% sodium bicarbonate	Group 2 N=105 Sodium Fluorescein 10% [redacted] with no bicarbonate	Group 3 N=94 Sodium Fluorescein 10% (Alcon laboratories, Inc.), [redacted] with 4% sodium bicarbonate	Group 4 N=99 Sodium Fluorescein 10% (Alcon laboratories, Inc.), [redacted] with no bicarbonate	Group 5 N=93 Sodium Fluorescein 5% (Alcon laboratories, Inc.), [redacted] with 4% sodium bicarbonate
Poor (0)	0	0	3	1	9
Adequate (1)	15	15	7	12	16
Good (2)	46	36	32	29	45
Excellent (3)	38	54	52	57	21

1 Each investigator subjectively graded the overall results of the procedure, using such judgment criteria as media clarity, sharpness of contrast in capillaries, etc.

Reviewer's Comments:

There was no difference between the five formulations with respect to diagnostic utility of the angiograms produced; however, the 5% formulation was seen to be less desirable for use in

diagnosis than the 10% formulations due to the greater luminescence of the higher concentration.

ALCON PROTOCOL 72-02-02

Per Alcon, during the photography sequence, the observer made a subjective determination of the quality of the angiogram by grading poor, moderate, good or excellent film focus. No significant differences were established.

Reviewer's Comments:

There is no graphic or tabular report of the fluorescein grading results in this study report.

ALCON PROTOCOL 72-02-03

Table 6.1.4 C - Protocol 72-2-03 Diagnostic Utility

FILM FOCUS - SUBJECTIVE

	Excellent	Good	Moderate	Poor	Not recorded/ Not done
25%	42	31	11	13	1
10%	45	20	14	19	0

DELAYED PHOTO - SUBJECTIVE

	Excellent	Good	Moderate	Poor	Not recorded/ Not done
25%	42	31	11	13	1
10%	45	20	14	19	0

MAXIMUM DENSITY COMPARED TO STEP WEDGE - OBJECTIVE

	1	2	3	4	5	6	Not recorded/ Not done
25%	2	3	7	13	52	21	0
10%	4	6	3	17	51	14	2

Reviewer's Comments:

Angiograms were rated using subjective grading of poor to excellent for judgments of film focus and quality of delayed photographs. An objective assessment using the step-wedge method of angiogram comparison was used. Comparison of both subjective and objective analyses of the angiograms obtained during the study demonstrated no remarkable differences between the test formulations.

Literature Reference Citing Alcon's Fluorescite Product for Efficacy

Willerson et al 1976 is a report of an open label, efficacy and safety evaluation of two commercially available preparations of fluorescein injection: Alcon's Fluorescite 10% and Fluorescite 25%.

49 normal human volunteers were injected with Fluorescite 25%.; 9 normal human volunteers were injected with Fluorescite 10%. Each subject was monitored for signs and symptoms of adverse reactions during the test procedure (e.g. BP, serum and urine fluorescein concentrations). Each test subject was evaluated by rapid sequence fundus photography immediately after injection for a comparison of the diagnostic utility of the two preparations. The photographer made a subjective determination of the quality of the angiogram by grading the film focus as poor, moderate, good, or excellent. The developed angiograms were later graded by quality by the investigators.

Reviewer's Comments:

All 9 Fluorescite 10% subjects had their angiograms read as excellent in quality. 3 Fluorescite 25% subjects were reported as "poor "film focus; 33 were reported as "excellent. " 3 subjects had failed visualization due to infiltration of the fluorescein injection.

Presumably the remaining 10 Fluorescite 25% subjects had their angiograms read as "moderate" or "good."

Literature References Citing Other Fluorescein Preparations for Efficacy

Justice et al 1977 is a report of a double-blind, crossover trial in 41 normal volunteers and 42 patients with diverse ophthalmic disorders. The populations were not combined – each was treated as a "separate" identical trial.

The sequence of injections was according to a randomized assistant who did know the drug concentration but who did not participate in visualization of the dye or in angiogram grading.

Visualization of the dye as it entered the vascular filling phase, and the contrast of the quality of the serial and five-minute phase angiograms were scored according to 0 – 4 scale with 0 representing no FA and 4 representing an excellent FA.

The entire procedure was repeated after a minimum of 7 days using the alternate concentration from the one used initially.

Reviewer's Comments:

Both the 10 and 25% solutions of fluorescein sodium yielded good to excellent results in fundus photography and were equally well tolerated.

In the volunteer group, there was a significant difference in the paired comparison and visualization with the 25% concentration with $p < 0.001$. No distinction could be determined in the serial angiogram quality and five-minute phase angiogram. In the patient group, there was a significant difference in serial angiogram quality with $p < 0.01$, five-minute phase angiogram with $p < 0.05$, and paired comparison with the 25% concentration with $p < 0.005$. No distinction could be determined in the visualization rating.

Dose Finding in Fluorescein Angiography

Fluorescein dose finding for fundus photography has evolved primarily through experience and paralleled the improvement of angiographic procedures. Per Alcon, the empirically found optimum dose for good quality angiograms is 500 mg fluorescein, dissolved in a volume of either 5 mL or 2 mL resulting in 10% and 25% solutions, respectively.

Reviewer's Comments:

Flower 1973[13] evaluated injected dye bolus concentration, injected dye bolus volume, and use of a saline flush for both fluorescein and ICG (indocyanine green) angiograms in humans and monkeys. There was no improvement in the quality of angiograms produced with increasing concentration of fluorescein.

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 Fluorescite (fluorescein injection, USP) 10% for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

The major sources of clinical data in support of efficacy for Fluorescite utilized in this review include:

- Four (4) Alcon clinical studies performed in the 1970's
- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

13 Flower RW. Injection technique for indocyanine green and sodium fluorescein dye angiography of the eye. Invest Ophthalmol & Vis Sci 1973;12(12):881-95.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Reports of eleven (11) deaths are included in the Periodic Safety Update Report prepared by Alcon for the European Union for a 10-year reporting time period between 01 January 1996 and 30 June 2005.

Reviewer's Comments:

These 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.

Approximately ——— units of fluorescein sodium-containing products marketed by Alcon were distributed during the period covered by this safety report.

Individual Case Histories:

CASE #67537 (CARDIAC ARREST; DEATH)
A 59-year-old female patient was admitted to hospital ——— for evaluation and possible treatment of bilateral proliferative diabetic retinopathy. Three months prior to this admission, the patient had undergone fluorescein angiography at another hospital with no abnormal reactions. On ———, the patient received METOCLOPRAMIDE IV for nausea followed by 2 ml of product IV without incident. The patient walked to her room unaided but complained shortly after of general fatigue. 2.5 hours later, she complained of general fatigue and drowsiness. Her vital sings appeared stable at BP=122/64 mmHg, TEMP=36.9 C, HR=72 BPM. 5.75 hours after angiography her vitals were 150/84 mmHg, 36.9 C, 72 BPM. 7.5 hours after angiography, she walked to the bathroom, but was found 30 minutes later on her bed with no cardiac or pulmonary function. She was resuscitated and taken to another hospital for ICU admission. At this time, a myocardial infarct was ruled out by EKG and her brain CT was normal. 15 days following angiography, the patient had improved sufficiently (clinical course, treatment not described) to be discharged from ICU on ——— However, the patient's condition worsened and she died ———. No autopsy was performed,

CASE #23208 (ABDOMINAL PAIN; DYSPNEA; DEATH; ANAPHYLACTIC REACTION; PULMONARY EDEMA)
Physician reports that a 68 year-old female patient died within 10 minutes of using product. The physician was said to have injected 0.5 ml and waited and unspecified length of time before injecting the remainder of the product. After about 5-8 minutes; the patient suffered pain in the abdomen and dyspnea. Patient was placed on respirator and oxygen was supplied. Cardiac

massage was performed and the patient was also treated with epinephrine injection without success. In a preliminary expert opinion on this autopsy by court order, the above file memo is discussed as follows: "in view of the post-mortem findings cardiovascular failure in the presence of significant pathological changes of the heart is to be assumed the cause of death. Especially the facts that critical heart weight is exceeded and that there is massive fatty infiltration of the right ventricular wall, point to a failure-prone heart. No clear indications of an allergic process resulting in death can be reduced (sic)."

CASE #58998 (DEATH; ANAPHYLACTIC REACTION)
Pharmacist reports 73 year-old patient with multiple medical problems collapsed immediately following injection. Resuscitation was started immediately, however, the patient died during transport to hospital. The pharmacist reports that the ophthalmologist advised the patient of the risks associated with the use of the product and asked the patient if he had any pre-existing allergies. The patient consented to the procedure and advised that he had no known allergies. The doctor had an emergency tray ready for use as per the product information.

CASE #16668 (DEATH)
Ophthalmic nurse reports a patient received the product in the morning and died that afternoon without visible explanation. An autopsy was performed but did not reveal the cause of death. Follow-up: physician reports there were no indications the patient was in distress when she went home 30 minutes following injection. The physician reports the patient died 5 hours later after an acute dyspneic attack. The patient had a significant history of pulmonary fibrosis and possible collagenosis. Post mortem results were inconclusive as to cause of death.

CASE #25368 (DEATH)
Pharmacist reports that a patient died in her house 10 hours after a fluorescein angiography had been performed. Autopsy was to be performed.

CASE #6298 (ANAPHYLACTIC REACTION; DEATH)
Coroner's report indicating patient died due to anaphylactic shock on [redacted] was received 3 September 1996.

CASE #14124 (ANAPHYLACTIC REACTION; DEATH: PNEUMONIA ASPIRATION)
ER physician reports a 64 y/o diabetic patient was brought to the emergency room about one month ago with anaphylaxis following injection of product. The patient possibly suffered an AE with onset about 10 minutes after the IV administration of the product. The Pt. lost consciousness briefly (syncope), regained consciousness, and was then found to have hypoglycemia for which she was given some lemonade. About 10 minutes later she developed labored, 'rattly' breathing (dyspnea), and very rapid pulse, prompting urgent call to the ambulance service. Ambulance officers recorded an ECG, which suggested ventricular tachycardia. The Pt. was transferred to intensive care where she experienced ventricular fibrillation and a cardiac arrest. Resuscitation was initially successful. An ECG suggested an inferior myocardial infarction (not confirmed by autopsy). At 18.30 hours on the evening of [redacted], the hospital notes record "multisystems failure" including respiratory failure. Overnight in hospital, her condition continued to deteriorate and death was certified at 05.45 on [redacted]

CASE #14850 (ANAPHYLACTIC SHOCK: DEATH)
Authors report fatal anaphylactic shock in a 69- y/o female. Patient received 5 ml of 20 % solution and complained of paresthesia of the lips and fingers 30 seconds later. The patient experienced severe respiratory difficulty even following immediate administration of hydrocortisone IV. ECG done 45 minutes after onset of symptoms revealed sinusoidal rhythm at 105 BPM without acute myocardial changes; chest x-ray revealed impressive pulmonary edema. The patient was admitted to ICU approximately 130 minutes after onset of symptoms and was noted to be extremely agitated with cold, veined skin, frothy fluid tinged with dye from the mouth, tachycardia and hypotension. Chest auscultation revealed bilateral basal rales; laboratory tests revealed hypoxemia, hypercapnia and acidosis. The patient experienced cardiopulmonary arrest and died approximately 13 hours after administration of the dye. Patient had no history of allergies or anaphylactic reactions. This was the fifth FLUORESCEIN angiogram performed within 18 months. Citation: *Fineschi V, Monasterolo G, Rosi R, Turillazzi E. Fatal anaphylactic shock during fluorescein angiography. Forensic Sci Int. 100 (1999): 137-142.*

CASE #21957 (ANAPHYLACTIC SHOCK: CYANOSIS: DYSPNEA; BLOOD PRESSURE DECREASED; HEART RATE DECREASED; ATRIAL FIBRILLATION)
Ophthalmologist reports that patient with a history of right lower leg thrombosis presented to ophthalmology clinic with decreased visual acuity. Fluorescein angiography [5 ml 10% Fluorescite IV over 15 sec] confirmed a central retinal vein occlusion. Angiography completed without incident. 15 minutes later, an IV infusion of urokinase was begun. Within 1 minute, the patient experienced anaphylactic shock characterized by cyanosis and difficulty breathing with decreased blood pressure and pulse. The patient was intubated and external cardiac massage initiated. Epinephrine and dopamine were administered. Atrial fibrillation was noted; cardioversion was not successful. Percutaneous cardiac pacing and angiography were attempted, but the patient died.

CASE #25323 (ANAPHYLACTIC SHOCK; CARDIAC ARREST; DISCOMFORT; FALL; VOMITING; CONVULSION;
CYANOSIS)
Ophthalmologist reports that a 71 year-old female patient died after product was administered for fluorescein angiography procedure. She had undergone the procedure two times previously without incident. On [redacted], patient was administered product. She complained of discomfort and fell down. She was treated with cardiopulmonary resuscitation, went into cardiac arrest and died.

CASE #29647 (CEREBRAL INFARCTION; LOSS OF CONSCIOUSNESS)
Physician reports that a patient developed cerebral infarction following use of product during fluorescein angiography. The patient was ambulatory after completing the procedure and released home. More than 6 hours later, she was found unconscious. The physician provided additional details on 02-Nov-2004. Primperan injection (metoclopramide HCL) 2 ml IM was administered 30 minute prior to the procedure which was completed without difficulties. The procedure and reported event occurred on [redacted], and the patient died on [redacted].
The physician stated the patient had experienced multiple cerebral infarctions on 12-Oct-1993.

Per reporter, the event was not directly caused by product because it occurred 6 hours after injection of product and does not relate to pharmacology and pharmacokinetics of product.

7.1.2 Other Serious Adverse Events

Table 7.1.2 A - 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)

	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 (Yannuzzi et al. 1986).

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 wee 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.*

Severe adverse reaction. *A severe reaction was defined as on exhibiting prolonged effects which required intense treatment. It also posed as 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.

Table 7.2.1 B - Incidence of serious and fatal complications in association with intravenous fluorescein angiography (results of large survey of 260 clinics in 30 countries) (after Zografos 1983)

	N = 594,687 Angiographies				
	Fatal outcome		Serious adverse events		TOTAL
	N	per 1 million	N	per 1 million	per 1 million
Anaphylactic shock	2	3.4	8	13.5	16.8
Cardiac arrest	3	5.0	4	6.7	11.8
Myocardial infarction	2	3.4	4	6.7	10.1
Decompensation with cardiac failure	3	5.0			5.0
Cerebrovascular complication	2	3.4			3.4
Severe state of shock			11	18.5	18.5
Collapse after intra-arterial injection of fluorescein			1	1.7	1.7
Respiratory insufficiency			5	8.4	8.4
TOTAL	12	20.2	33	55.5	75.7
Total risk	1: 49,557		1:18,020		1:13,215

Reviewer's Comments:

All of the serious and fatal complications noted by Zografos 1983 are recognized complications of fluorescein injection, i.e. anaphylactic shock, cardiac arrest, MI, cardiac failure CVA, shock/circulatory collapse, respiratory failure.

7.1.3 Dropouts and Other Significant Adverse Events

There is no dropout profile information provided for the four Alcon 1970's trials, and no accurate dropout profile for the cited literature references describing other clinical trials.

7.1.4 Other Search Strategies

There were no unique or special safety studies found 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 elicitation is either from spontaneous reports found in the Periodic Safety Update and or from citations in literature. The four Alcon 1970's clinical trials lack specific documentation on the methodology of adverse event collection.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Alcon's categorization of adverse events in the Periodic Safety Update appears appropriate. The categorization of adverse events in the two large surveys and in the pooled summary table with prevalence of adverse events in literature reported trials of > 1000 subjects is more difficult to evaluate since source materials are not provided.

7.1.5.3 Incidence of common adverse events

Table 7.1.3.3 - 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)

	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 7.1.3.3 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

Table 7.1.5.4 A - Prevalence of adverse events/reactions in studies with more than 1000 patients

Severity classification according to Yannuzzi et al. 1986		Lepri et al. 1997	Jennings & Mathews 1994 (F/o)	Kwiterovich et al. 1991	Karhunen et al. 1986 (F)	Marcus et al. 1984 (10%)	Marcus et al. 1984 (25%)	Butner & McPherson 1983	Pacuariu 1982 (F)
	No of Patients	**6524** [a]	**1173**	2025	**9909**	**2360**	**3100**	--	**1800**
	No of Angiograms	10003	--	**2789** [b]	9909	--	--	**5000**	2631
		%							
	ALL	*7.5*	*2.2*	*4.8*	--	*9.20*	*9.55*	*4.82*	*5.4*
Mild	NAUSEA	3.8	0.8	2.9	4.6	5.97	6.39	2.24	3.6
Mild	VOMITING	0.4	0.2	1.2	1.3	1.06	1.42		0.5
Mild	RETCHING / VOMITING							1.78	
Mild	EXTRAVASATION		0.2					0.16	
Mild	LOCAL COMPLICATIONS								0.16 [h]
Mild	DIZZINESS				0.6	0.30	0.064		
Mild	SNEEZING / RHINORRHEA			0.04		0.21	0.16		
Moderate	THROAT SENSATION					0.34	0.13		
Moderate	URTICARIA / PRURITUS	1.84 [g]	0.6	0.5	0.5	0.89	0.84	0.34	0.5
Moderate	ALLERGIC REACTION								0.7 [i]
Moderate	SYNCOPE			0.07				0.06	0.5
Severe	DYSPNEA			0.07			0.064	0.08	
Severe	BREATHLESSNESS				0.05				
Severe	LARYNGEAL EDEMA / PHARYNGEAL EDEMA					0.042			
Severe	SEVERE HYPOTENSION	0.06				0.085			
Severe	CHEST PAIN	0.03			0.06 [c]	0.085			
Severe	INSULIN SHOCK		0.1						
Severe	COLLAPSE	0.03 [d]			0.2				
Severe	VASOVAGAL REACTION	1.18 [f]				0.13	0.42		
Severe	ANAPHYLACTOID REACTION (SHOCK)					0.042			
Severe	MYOCARDIAL INFARCTION				0.03	0.042			0.06 [k]
Severe	OTHER	0.1 [e]	0.3				0.064	0.16 [l]	

(F) = FLUORESCITE®
(F/o) = FLUORESCITE® and other preparations
[a] bold = reference for frequency rates
[b] when multiple procedures on the same patient were excluded, the frequency of reactions remained within 0.5%
[c] cases without myocardial infarction
[d] 2 cases with resuscitation due to respiratory arrest or laryngeal spasm
[e] 7 cases with miscellaneous reactions (vagal crisis, apnea; tachycardia, bradycardia and pain, syncope, myoclonia, renal colic)
[f] syncope, bradycardia, hypotension, etc.
[g] summarized as "anaphylactoid reactions: rash, erythema, pruritus
[h] 3 cases: Thrombophlebitis; pain in the arm; numbness of the thump following extravasation (injection into dorsal hand vein)
[i] 9 cases with hives and pruritus; 1 case with stuffy nose, coryza, sneezing, chemosis and lacrimation; 1 itching, burning; 1 redness, itchiness
[k] 1 hour after injection
[l] including dizziness, light-headedness, diarrhea, lip edema and headache.

Reviewer's Comments:

The most frequent adverse events in this pooled table across 8 studies with > 1000 subjects each are nausea and vomiting, urticaria/itching, and vasovagal reaction

A basic pattern in the prevalence of mild, moderate and severe reactions to intravenous fluorescein can be seen. In general, mild and transient reactions which do not require medical treatment are observed occasionally while moderate or serious events occur rarely or very rarely.

POSTMARKETING EXPERIENCE

The evaluation of the post-marketing experience is primarily based on the Periodic Safety Update Report prepared by Alcon for the European Union for a 10-year reporting time period between 01 January 1996 and 30 June 2005. This Periodic Safety Update Report summarizes the safety data received from worldwide sources (including the United States) by Alcon's Department of Product Safety.

In the time period between 01 January 1996 and 30 June 2005, Alcon received 368 spontaneous adverse event reports world-wide associated with the use of Fluorescite 10% and 8 spontaneous adverse event reports associated with the use of Fluorescite 25%. No evidence of previously unidentified toxicity or changes in characteristics of known reactions was found during the 10-year period.

Approximately ———units of fluorescein sodium-containing products marketed by Alcon were distributed during the period covered by this safety report. No company-sponsored studies were conducted during the time period reviewed.

Overall, two hundred and eighty-two (282) spontaneous case reports, meeting minimum reporting criteria, were received; ninety-four (94) cases, involving eighty-five (85) different reaction terms, were regarded as serious. Most of the reports associated with fluorescein sodium (dye solution) describe labeled hypersensitivity reactions that range from urticaria to severe hypersensitivity reactions.

Table 7.1.5.4 B - Fluorescite 10% Injection Adverse Event Summary from Periodic Safety Update Report

FLUORESCITE® 10% Injection	N
Cases meeting minimum reporting criteria	278
Cases from health professionals with no identifiable patient	75
Cases from non-health professionals	15
TOTAL	**368**

In the time period between 01 January 1996 and 30 June 2005, Alcon received three hundred and sixty-eight (368) spontaneous adverse event reports world-wide associated with the use of Fluorescite 10% Injection. In cases where product strength was not reported, they were ascribed to 10%, the most widely used.

Two hundred and seventy-eight (278) of these reports fulfilled minimum reporting criteria (per Pharmacovigilance rules governing medicinal products in the European Union, a reportable adverse drug reaction requires the following information: an identifiable health-care professional reporter, an identifiable patient, at least one suspected substance/medicinal product, and at least one suspected adverse reaction.)

Seventy-five (75) cases lacking patient details were spontaneously reported by health professionals. Fifteen (15) cases from non-health professionals were reported.

Table 7.1.5.4 C - Fluorescite 25% Injection Adverse Event Summary Periodic Safety Update Report

FLUORESCITE® 25% Injection	N
Cases meeting minimum reporting criteria	4
Cases from health professionals with no identifiable patient	4
Cases from non-health professionals	0
TOTAL	8

In the time period between 01 January 1996 and 30 June 2005, Alcon received eight (8) spontaneous adverse event reports world-wide associated with the use of Fluorescite 25% Injection. Four (4) of these reports fulfilled minimum reporting criteria as described above.

In the time period between 01 January 1996 and 30 June 2005, Alcon received no spontaneous adverse event reports associated with Fluorescite 5% Injection.

Appears This Way
On Original

Table 7.1.5.4 D - Fluorescite 10% Injection and Fluorescite 25% Injection Sales Numbers from Periodic Safety Update Report

FLUORESCITE® 10% Injection

Presentation	Units sold world-wide					
	1996	1997	1998	1999	2000	2001
5ml						

Presentation	Units sold world-wide				
	2002	2003	2004	2005(*)	TOTAL
5ml					

FLUORESCITE® 25% Injection

Presentation	Units sold world-wide					
	1996	1997	1998	1999	2000	2001
2ml						

Presentation	Units sold world-wide				
	2002	2003	2004	2005(*)	TOTAL
2ml					

(*) 01 January to 30 June 2005

Reviewer's Comments:

— *units of Fluorescite 5% were sold during the time period between 01 January 1996 and 30 June 2005.*

See Appendix 10.4 Reports of Postmarketing Experience for detailed tables of adverse reactions by organ system.

7.1.5.5 Identifying common and drug-related adverse event

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.

7.1.5.6 Additional analyses and explorations

Safety information is available from over 30 countries between 01 January 1996 and 30 June 2005 for Fluorescite 10% (See Appendix 10.4 Reports of Postmarketing Experience). There is adequate safety information by gender, ethnicity, age, and underlying disease process.

7.1.6 Less Common Adverse Events

Less common adverse events are noted in Appendix 10.4 Reports of Postmarketing Experience. These adverse events are organized by organ system affected.

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 Dug Application. There is no post marketing data from Alcon's worldwide Periodic Safety Update Report for Fluorescite 5, 10, and 25% (01 January 1996 – 30 June 2005) 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

See above.

7.1.7.3 Standard analyses and explorations of laboratory data

See above.

7.1.7.4 Additional analyses and explorations

See above.

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 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. There is a 30 year marketing history for this product without a New Dug Application. There is no post marketing data from Alcon's worldwide Periodic Safety Update Report for Fluorescite 5, 10, and 25% (01 January 1996 – 30 June 2005) 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

See above.

7.1.8.3 Standard analyses and explorations of vital signs data

See above.

7.1.8.4 Additional analyses and explorations

See above.

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 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 a 30 year marketing history for this product without a New Dug Application. There is no post marketing data from Alcon's worldwide Periodic Safety Update Report for Fluorescite 5, 10, and 25% (01 January 1996 – 30 June 2005) 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

See above.

7.1.9.3 Standard analyses and explorations of ECG data

See above.

7.1.9.4 Additional analyses and explorations

See above.

7.1.10 Immunogenicity

Alcon 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:

> Caution is to be exercised in patients with a history of allergy or bronchial asthma. An emergency tray including such items as 0.1% epinephrine for intravenous or intramuscular use; an antihistamine, soluble steroid, and aminophylline for IV use; and oxygen should always be available in the event of possible reaction to FLUORESCITE® Injection 10%

and

> If a potential allergy is suspected, an intradermal skin test may be performed prior to intravenous administration, i.e., 0.05 mL injected intradermally to be evaluated 30 to 60 minutes following injection. Given the sensitivity and specificity of skin testing, a negative skin test is not proof that a patient is not allergic to fluorescein.

Per Alcon's worldwide Periodic Safety Update Report for Fluorescite 5, 10, and 25% (01 January 1996 – 30 June 2005), there were 12 spontaneous anaphylactic reactions reported and two additional anaphylactic reactions noted in the literature.

7.1.11 Human Carcinogenicity

Since Fluorescite is indicated for use as a diagnostic agent intended for single use, no repeated-dose toxicity, genotoxicity, reproductive toxicity, and carcinogenicity studies were conducted by the sponsor. In this NDA submission, only single dose toxicity study reports were included.

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 Fluorescite.

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 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 summarized in this submission.

Pursuant to 21 CFR§314.55(a), Alcon 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.

7.1.17 Postmarketing Experience

Alcon estimates that over —illion angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% —— units) and Fluorescite 25% (—— units).

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

Alcon estimates that over —— ngiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% (—— units) and Fluorescite 25% (—— units).

Safety information is available from over 30 countries between 01 January 1996 and 30 June 2005 for Fluorescite 10% (See Appendix 10.4 Reports of Postmarketing Experience). There is adequate safety information by gender, ethnicity, age, and underlying disease process.

7.2.1.1 Study type and design/patient enumeration

Because a variety of sources were used in the evaluation of safety and effectives, there is not a single table which summarizes study type and enumeration.

The major sources of clinical data in support of efficacy and safety for Fluorescite utilized in this review include:

- Four (4) Alcon clinical studies performed in the 1970's

- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

See tables in Section 4.2, Section 7.1, and Appendix 10.4.

7.2.1.2 Demographics

Fluorescite has been marketed for 30 years. Alcon estimates that over ——— angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% (——— units) and Fluorescite 25% (—— units).

Safety information is available from over 30 countries between 01 January 1996 and 30 June 2005 for Fluorescite 10% (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)

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

Table 7.2.1.3 - Fluorescite 10% Injection and Fluorescite 25% Injection Sales Numbers from Periodic Safety Update Report

FLUORESCITE® 10% Injection

Presentation	Units sold world-wide					
	1996	1997	1998	1999	2000	2001
5ml						

Presentation	Units sold world-wide				
	2002	2003	2004	2005(*)	TOTAL
5ml					

FLUORESCITE® 25% Injection

Presentation	Units sold world-wide					
	1996	1997	1998	1999	2000	2001
2ml						

Presentation	Units sold world-wide				
	2002	2003	2004	2005(*)	TOTAL
2ml					

(*) 01 January to 30 June 2005

Reviewer's Comments:

No units of Fluorescite 5% were sold during the time period between 01 January 1996 and 30 June 2005

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

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

- Four (4) Alcon clinical studies performed in the 1970's
- Literature references citing Alcon's Fluorescite product
- Literature references not specifically citing Alcon's Fluorescite product or citing another fluorescein sodium product.
- an Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

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

Alcon estimates that over [redacted] angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% ([redacted] units) and Fluorescite 25% ([redacted] units).

Fluorescite has been illegally marketed in the United States for 30 years without a New Drug Application. For detailed adverse event tables for dates between 01 January 1996 and 30 June 2005 for Fluorescite 10% and Fluorescite 25%, see Appendix 10.4 Reports of Postmarketing Experience.

7.2.2.3 Literature

Per Alcon, for the period between 1965 and March 2004, literature search in PubMed revealed a total of 8,917 publications dealing with various aspects of ocular fluorescein fundus angiography, of which 326 were classified as Clinical Trials. In contrast, clinical studies investigating specifically the safety and efficacy of fluorescein (Fluorescite, Alcon, Inc.) in the context of ocular fundus angiography are relatively rare, and only 19 relevant publications including two surveys have been identified.

Reviewer's Comments:

A literature search conducted by this reviewer failed to identify any significant literature references not cited by Alcon in Section 5.4 of the New Drug Application. All 100 cited references are provided in Section 5.4.

7.2.3 Adequacy of Overall Clinical Experience

There is adequate clinical experience with the proposed drug product, Fluorescite. Fluorescite has been illegally marketed in the United States for 30 years without a New Drug Application. Alcon estimates that over [redacted] angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% ([redacted] units) and Fluorescite 25% ([redacted] units).

The dose and duration of the drug used in the cited literature and safety surveys were adequate to determine safety for the intended use.

Safety information is available from over 30 countries between 01 January 1996 and 30 June 2005 for Fluorescite 10% (See Appendix 10.4 Reports of Postmarketing Experience). 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

Fluorescite has been marketed in the US and throughout the world for over 30 years. The drug has been extensively studied for PK and PD properties, diagnostic utility for many ocular diseases, and safety of the formulation. Since Fluorescite is indicated for use as a diagnostic agent intended for single use, no repeated-dose toxicity, genotoxicity, reproductive toxicity, and carcinogenicity studies were conducted by the sponsor. In this NDA submission, only single dose toxicity study reports were included. At 10 mg/kg, no acute toxicity was seen in ice and dogs. Fluorescein sodium from different sources showed similar LD_{50} and clinical signs. There are no specific concerns from the pharmacology/toxicology viewpoint regarding clinical use of Fluorescite.

7.2.5 Adequacy of Routine Clinical Testing

There is adequate clinical experience with the proposed drug product, Fluorescite. Fluorescite has been illegally marketed in the United States for 30 years without a New Drug Application. Alcon estimates that over [redacted] angiographic procedures with Fluorescite 10% and 25% have been performed world-wide within the 10-year reporting time period based on the number of units sold between 01 January 1996 and 30 June 2005 for Fluorescite 10% ([redacted] units) and Fluorescite 25% [redacted] units).

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

There is adequate clinical experience with the proposed drug product, Fluorescite.

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 Fluorescite is adequate and of good quality. There is a tremendous amount of information provided in the Alcon-prepared Periodic Safety Update Report prepared for the European Union covering 01 January 1996 to 30 June 2005.

In the time period between 01 January 1996 and 30 June 2005, Alcon received 368 spontaneous adverse event reports world-wide associated with the use of Fluorescite 10% and 8 spontaneous adverse event reports associated with the use of Fluorescite 25%. No evidence of previously unidentified toxicity or changes in characteristics of known reactions was found during the 10-year period.

Approximately, [redacted] units of fluorescein sodium-containing products marketed by Alcon were distributed during the period covered by this safety report. No company-sponsored studies were conducted during the time period reviewed.

Overall, two hundred and eighty-two (282) spontaneous case reports, meeting minimum reporting criteria, were received; ninety-four (94) cases, involving eighty-five (85) different

reaction terms, were regarded as serious. Most of the reports associated with fluorescein sodium (dye solution) describe labeled hypersensitivity reactions that range from urticaria to severe hypersensitivity reactions. See Appendix 10.4 Reports of Postmarketing Experience.

7.2.9 Additional Submissions, Including Safety Update

The Safety Update was submitted on March 10, 2006. Per Alcon:

> A further evaluation of all spontaneous postmarketing adverse events with fluorescein sodium 10% and 25% for injection since the NDA submission through March 1, 2006, does not present any safety concerns. The reported events are consistent in type and frequency with the previous cumulative experience observed with these products.

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

7.4.1.1 Pooled data vs. individual study data

Individual study data are not as useful in this application because the study reports submitted for the four Alcon 1970's studies lack sufficient detail to determine if the trials were adequate and well controlled. Most useful are the two surveys cited (Yanuzzi et al 1986 and Zografos et al 1983) and Table 7.1.3.4 A which lists the prevalence of adverse events/reactions in studies with more than 1000 patients.

7.4.1.2 Combining data

The prevalence of adverse events/reactions in studies with more than 1000 patients provides the basis for Table 7.1.3.4 A.

7.4.2 Explorations for Predictive Factors

Safety and effectiveness of Fluorescite (fluorescein injection, USP) 10% in special populations has been adequately assessed.

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.

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

Fluorescein dose finding for fundus photography has evolved primarily through experience and paralleled the improvement of angiographic procedures. The level of confidence in this dosing regimen is very high -

The normal adult dose of Fluorescite Injection 10% is 500 mg (100 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).

No information is available on overdosage in humans.

Approximately, [redacted] units of fluorescein sodium-containing products marketed by Alcon were distributed during the period between 01 January 1996 and 30 June 2005. This number includes distribution in the United States.

8.2 Drug-Drug Interactions

Specific drug interaction studies are not reported. Refer to Section 10.2 of the Clinical Review (Labeling).

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

8.3 Special Populations

Safety and effectiveness of Fluorescite (fluorescein injection, USP) 10% in special populations has been adequately assessed.

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.

Alcon has been marketing this drug product in the United States for over 30 years. The pediatric dosing is well supported in the literature summarized in this submission.

Pursuant to 21 CFR§314.55(a), Alcon 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

No Advisory Committee was necessary nor convened for this drug product.

8.6 Literature Review

Per Alcon, for the period between 1965 and March 2004, literature search in PubMed revealed a total of 8,917 publications dealing with various aspects of ocular fluorescein fundus angiography, of which 326 were classified as Clinical Trials. In contrast, clinical studies investigating specifically the safety and efficacy of fluorescein (Fluorescite, Alcon, Inc.) in the context of ocular fundus angiography are relatively rare, and only 19 relevant publications including two surveys have been identified.

Reviewer's Comments:

A literature search conducted by this reviewer failed to identify any significant literature references not cited by Alcon in Section 5.4 of the New Drug Application. All 100 cited references are provided in Section 5.4.

8.7 Postmarketing Risk Management Plan

There are no recommended Phase 4 clinical study commitments.

8.8 Other Relevant Materials

The Division of Medication Errors and Technical Support (DMETS) was consulted on September 28, 2005, regarding the proposed use of the tradename, Fluorescite. A response was received on March 9, 2006. DDMAC finds the proprietary name, Fluorescite, acceptable from a promotional perspective. Labeling recommendations, where appropriate, were incorporated into the labeling review

The Division of Drug Marketing, Advertising, and Communications (DDMAC) was consulted on September 28, 2005, regarding the proposed labeling. A response was received on March 1, 2006, and recommendations, where appropriate, were incorporated into the labeling review.

9 OVERALL ASSESSMENT

9.1 Conclusions

There is a 30 year history of use of this product in the United States (illegally marketed by Alcon without a New Drug Application) with adequate demonstration of effectiveness and safety as determined in this clinical review.

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.

9.2 Recommendation on Regulatory Action

It is recommended that NDA 21-980 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Fluorescite (fluorescein injection, USP) 10% 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

See the Line-by-Line Labeling review, Section 10.2.

9.5 Comments to Applicant

Cited references in support of a New Drug Application should be translated into English. Copies of references should not be submitted to the application in a foreign language (i.e. Zografos et al 1983, Lepri et al 1997).

Photostat copies of references should be legible (i.e. Justice et al 1977).

10 APPENDICES

10.1 Review of Individual Study Reports

See Section 6.1 of this review and its associated subsections for individual study reports.

10.2 Line-by-Line Labeling Review

Following is Alcon's proposed labeling submitted with the original New Drug Application on September 28, 2005.

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

4 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Reviewer's Comments:

Storage statement should be revised do read: [redacted]

[redacted]

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Proposed Container Label

Reviewer's Comments:

10.3 References

Butner RW, McPherson AR. Adverse reactions in intravenous fluorescein angiography. Ann Ophthalmol 1983;15(11):1084-6.

Flower RW. Injection technique for indocyanine green and sodium fluorescein dye angiography of the eye. Invest Ophthalmol & Vis Sci 1973;12(12):881-95.

Jennings BJ, Mathews DE. Adverse reactions during retinal fluorescein angiography. J Am Optom Assoc 1994;65(7):465-71.

Justice J Jr, Paton D, Beyrer CR, Seddon GG. Clinical comparison of 10 percent and 25 percent intravenous sodium fluorescein solutions. Arch Ophthalmol 1977;95(11):2015-6.

Karhunen U, Raitta C, Kala R. Adverse reactions to fluorescein angiography. Acta Ophthalmol (Copenh) 1986;64(3):282-6.

Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB, Fine SL. Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. Ophthalmology 1991;98(7):1139-42.

Lepri A, Salvini R, Rizzo L, Cetica P, Grechi S, Di Filippo A, Conti M, Benvenuti S, Novelli GP. [Accident during retinal fluorescein angiography]. [Article in Italian] Minerva Anestesiol 1997;63(4):133-40.

Marcus DF, Bovino JA, Williams D. Adverse reactions during intravenous fluorescein angiography. Arch Ophthalmol 1984;102(6):825.

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

Pacurariu RI. Low incidence of side effects following intravenous fluorescein angiography. Ann Ophthalmol 1982;14(1):32-6.

Willerson D, Tate GW Jr, Baldwin HA, Hearnsberger PL. Clinical evaluation of fluorescein 25%. Ann Ophthalmol 1976;18(7):833-4, 837-41.

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

Zografos L. Enquête internationale sur l'incidence des accidents graves ou fatals pouvant survenir lors d'une angiographie fluorescéinique. Klin Mbl Augenheilk 1983 (182):460-462.

10.4 Reports of Postmarketing Experience

Reviewer's Comments:

These 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.

Line listings with individual cases from all Spontaneous Reports, Clinical Studies, and Literature Reports meeting minimum reporting criteria are provided in the Periodic Safety Update. This is a significant collection of data comprising 173 pages of text.

Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Thrombocytopenia	1	-	-
Sub-total	1		
CARDIAC DISORDERS			
Bradycardia	4	-	-
Cardiac arrest	3	-	2
Tachycardia	3	-	-
Angina pectoris	2	-	-
Atrial fibrillation	2	-	-
Cyanosis	1	-	1
Palpitations	2	-	-
Arrhythmia	1	-	-
Sinus bradycardia	1	-	-
Supraventricular tachycardia	1	-	-
Sub-total	23		
EAR AND LABYRINTH DISORDERS			
Ear disorder	1	-	-
Vertigo	1	-	-
Sub-total	2		
EYE DISORDERS			
Eyelid oedema	3	-	1
Eye pruritus	2	-	-
Ocular hyperaemia	1	-	-
Visual acuity reduced	1	-	-
Visual disturbance	1	-	-
Sub-total	9		

Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
GASTROINTESTINAL DISORDERS			
Nausea	36	-	1
Vomiting	30	-	1
Abdominal pain	8	-	-
Faecal incontinence	3	-	-
Rectal tenesmus	3	-	-
Pancreatitis acute	1	-	-
Dry mouth	1	-	-
Faeces discoloured	1	-	-
Hypoaesthesia oral	1	-	-
Oedema mouth	1	-	-
Salivary hypersecretion	1	-	-
Stomatitis	1	-	-
Swollen tongue	1	-	-
Tongue oedema	1	-	-
Sub-total	91		

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Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Death	6	-	2
Chest pain	6	-	-
Injection site hypersensitivity	5	-	-
Asthenia	4	-	-
Malaise	4	-	-
Pain	4	-	-
Application site pain	3	-	-
Discomfort	1	-	2
Face oedema	3	-	-
Oedema peripheral	3	-	-
Chills	2	-	-
Condition aggravated	2	-	-
Pyrexia	2	-	-
Unevaluable event	2	-	-
Chest discomfort	1	-	-
Extravasation	1	-	-
Feeling abnormal	1	-	-
Feeling hot	1	-	-
Injection site discolouration	1	-	-
Injection site extravasation	1	-	-
Injection site oedema	1	-	-
Injection site pain	1	-	-
Mucous membrane disorder	1	-	-
Sensation of foreign body	1	-	-
Sub-total	**61**		
HEPATOBILIARY DISORDERS			
Hepatocellular damage	1	-	-
Sub-total	**1**		

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Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
IMMUNE SYSTEM DISORDERS			
Anaphylactic reaction	12	-	2
Anaphylactic shock	9	-	2
Anaphylactoid reaction	4	-	-
Hypersensitivity	4	-	
Anaphylactoid shock	-	-	1
Sub-total		**34**	
INFECTIONS AND INFESTATIONS			
Pharyngitis	4	-	-
Rhinitis	1	-	-
Sub-total		**5**	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Injury	2	-	-
Fall	-	-	1
Sub-total		**3**	
INVESTIGATIONS			
Blood pressure decreased	4	-	-
Blood pressure increased	2	-	-
Pulse absent	1	-	1
Blood bilirubin	1	-	-
Electrocardiogram abnormal	1	-	-
Electroencephalogram abnormal	1	-	-
Heart rate decreased	1	-	-
Hepatic enzyme abnormal	1	-	-
Transaminases increased	1	-	-
Sub-total		**14**	
METABOLISM AND NUTRITION DISORDERS			
Hyperglycaemia	1	-	-
Sub-total		**1**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Pain in extremity	2	-	-
Arthralgia	1	-	-
Back pain	1	-	-
Sub-total		**4**	

Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
NERVOUS SYSTEM DISORDERS			
Syncope	16	-	-
Dizziness	9	-	-
Convulsion	8	-	1
Loss of consciousness	7	-	2
Headache	7	-	-
Hypoaesthesia	3	-	-
Grand mal convulsion	1	-	1
Somnolence	2	-	-
Amnesia	1	-	-
Complex partial seizures	-	-	1
Cerebral infarction	1	-	-
Cerebrovascular accident	1	-	-
Coma	1	-	-
Dysgeusia	1	-	-
Hemiplegia	1	-	-
Lethargy	1	-	-
Neuropathic pain	1	-	-
Paraesthesia oral	1	-	-
Paraparesis	1	-	-
Paraplegia	1	-	-
Simple partial seizures	1	-	-
Speech disorder	1	-	-
Syncope vasovagal	1	-	-
Sub-total		72	
PSYCHIATRIC DISORDERS			
Confusional state	4	-	-
Anxiety	1	-	-
Conversion disorder	1	-	-
Dysphoria	1	-	-
Thinking abnormal	1	-	-
Sub-total		8	
RENAL AND URINARY DISORDERS			
Urinary incontinence	5	-	-
Incontinence	3	-	-
Chromaturia	1	-	-
Neurogenic bladder	1	-	-
Renal pain	1	-	-
Sub-total		11	

Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	N	N	N
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Dyspnoea	23	-	-
Sneezing	6	-	-
Cough	4	-	-
Pulmonary oedema	4	-	-
Asthma	3	-	-
Respiratory arrest	3	-	-
Hypoventilation	1	-	-
Laryngeal oedema	1	-	-
Nasal congestion	1	-	-
Nasal oedema	1	-	-
Pharyngeal oedema	1	-	-
Pharyngolaryngeal pain	1	-	-
Pneumonia aspiration	1	-	-
Rhinorrhoea	1	-	-
Stridor	1	-	-
Yawning	1	-	-
Sub-total	53		

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Table 10.4 - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 10% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Urticaria	42	-	-
Pruritus	41	-	-
Dermatitis	14	-	-
Erythema	13	-	1
Blister	11	-	-
Exanthem	11	-	-
Hyperhidrosis	8	-	-
Rash	4	-	-
Rash maculo-papular	4	-	-
Generalised erythema	3	-	-
Photosensitivity reaction	3	-	1
Drug eruption	2	-	-
Skin discomfort	2	-	-
Cold sweat	1	-	-
Dermatitis exfoliative	1	-	-
Eczema	1	-	-
Pruritus generalised	1	-	-
Rash generalised	1	-	-
Rash vesicular	1	-	-
Psoriasis	-	-	1
Skin discolouration	1	-	-
Swelling face	1	-	-
Sub-total	**169**		
VASCULAR DISORDERS			
Shock	30	-	-
Hypotension	9	-	-
Vasodilatation	5	-	-
Hypertension	4	-	-
Pallor	4	-	-
Thrombophlebitis	3	-	-
Hot flush	2	-	-
Peripheral vascular disorder	2	-	-
Intermittent claudication	1	-	-
Vasospasm	1	-	-
Sub-total	**61**		
TOTAL	**623**		

Table 10.4 A - Coded (MEDDRA) Terms from Spontaneous Reports, Clinical Studies, and Literature Reports for Fluorescite 25% Injection

01 January 1996 to 30 June 2005

System Organ Class/	Spontaneous/ Regulatory bodies	Clinical Studies	Literature
Preferred Term (MedDRA, version 8.0)	**N**	**N**	**N**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Lymphadenopathy	1	-	-
Sub-total	**1**		
IMMUNE SYSTEM DISORDERS			
Anaphylactoid reaction	1	-	-
Sub-total	**1**		
NERVOUS SYSTEM DISORDERS			
Convulsion	1	-	-
Loss of consciousness	1	-	-
Sub-total	**2**		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Blister	1	-	-
Pruritus	1	-	-
Sub-total	**2**		
VASCULAR DISORDERS			
Thrombophlebitis superficial	-	-	1
Sub-total	**1**		
TOTAL	**7**		

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