CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-980

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-980
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	9/29/2005
DRUG NAME:	FLUORESCITE®
INDICATION:	Diagnostic fluorescein angiography or angioscopy of retina and iris vasculture
SPONSOR:	Alcon, Inc., Mail Code R7-18, 6201 South Freeway, Fort Worth, TX 76134-2099 Tel: 817-551-4325; Fax: 817-551-4630
DOCUMENTS REVIEWED:	Module 4
REVIEW DIVISION:	Division of Anti-Infective and Ophthalmology Products (HFD-520)
PHARM/TOX REVIEWER:	Zhou Chen, MD, PhD
PHARM/TOX SUPERVISOR:	Terry Peters, DVM
DIVISION DIRECTOR:	Janice Soreth, MD
PROJECT MANAGER:	Alison Rodgers

Date of review submission to Division File System (DFS): February 16, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

An "approval" is recommended.

B. Recommendation for nonclinical studies

No additional studies are necessary.

C. Recommendations on labeling

The following changes are recommended for the "Pregnancy" section of the labeling.

Pregnancy

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

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®.

B. Pharmacologic activity

Sodium fluorescein is a water-soluble hydroxyxanthene dye with fluorescence properties. The drug responds to electromagnetic radiation or light between the wavelengths of 465-490 nm and emits yellowish-green light at wavelengths of 520-530 nm. The fluorescent color is detectable at the concentrations as low as — ppm. Fluorescent dye is useful in evaluating the clinical signs/lesions and

treatment of ocular diseases in the anterior and posterior eye segments. Fluorescein angiography is a routine procedure in research and clinical practice.

C. Nonclinical safety issues relevant to clinical use

There are no drug-related safety issues relevant to clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

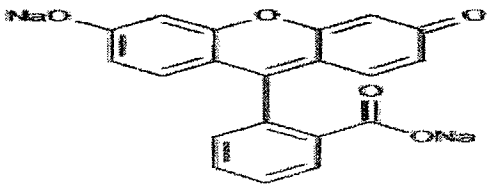
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 21-980
Review number: 000
Sequence number/date/type of submission: 000/September 28, 2005/Commercial
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Alcon Research, Ltd., Mail Code R7-18, 6201 South Freeway, Fort Worth, TX 76134-2099
Manufacturer for drug substance: [redacted]

Reviewer name: Zhou Chen, Ph.D.
Division name: Division of Anti-Infective and Ophthalmology Products
HFD #: 520
Review completion date: January 30, 2006

Drug:

Trade name: **FLUORESCITE®**
Generic name: Fluorescein, fluoresecin sodium
Code name: AL-39325, AL01088
Chemical name: Spiro[isobenzofuran-1(3H), 9'-[9H]xanthene]3-one, 3'6'-dihrdroxy, disodium salt
CAS registry number: 2321-07-5 for fluorescein and 518-47-8 for fluorescein sodium
Molecular formula/molecular weight: $C_{20}H_{10}O_5.2Na$, MW: 376.27
Structure:



Relevant INDs/NDAs/DMFs: DMF [redacted] and DMF [redacted]

Drug class: Diagnostic agent, angiographic agent

Indication: Diagnostic fluorescein angiography or angioscopy of retina and iris vasculature

Composition of Fluorescite Injection, 10%:

Component	[redacted]	Function	Compendial status
Fluorescein	[redacted]	Active ingredient	USP
NaOH or HCl	[redacted]	pH adjustment	NF
Water for injection	[redacted]	Vehicle	USP

Route of administration: Intravenous injection

Proposed use: For normal adults: 500 mg/5 ml of Fluorescite® Injection 10% (100 mg/ml, 10 mg/kg for a 50 kg person); for children: 7.7 mg/kg

Studies reviewed within this submission:

Pharmacology: No primary pharmacodynamics, secondary pharmacodynamics and safety pharmacology studies were conducted with Fluorescite®.

PK: No pharmacokinetic studies were conducted with Fluorescite®.

Toxicology:

Single dose studies

Effect of volume on the LD_{50} value of [redacted] odium fluorescein)
Acute systemic toxicity evaluation of 10% Fluorescite exposed to rubber plunger of syringe
LD_{50} determination of 10% Fluorescite syringes prepared by [redacted]
LD_{50} determination of 10% Fluorescite prepared from sodium fluorescein synthesized by [redacted]

Acute toxicity evaluation of 10% Fluorescite (Complaint Lot #W600) in mice and dogs

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

No pharmacology studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No study reports and tabulated summary were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

No PK studies were submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Neither study reports nor tabulated summary were provided.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Fluorescite® has been marketed in the US and other countries for many years and clinical safety of the drug has been established. Several single dose toxicity studies were submitted in this NDA package. The results obtained from these studies indicate that the intravenous LD_{50} values for fluorescein in mice were not affected by volume changes and 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} values and clinical signs.

2.6.6.2 Single-dose toxicity

Effect of volume on the LD_{50} value of AL01088 (sodium fluorescein)

Key study findings: The intravenous LD_{50} values for fluorescein in mice were not affected by volume changes.

Report N°: TR047:7320:72/73
Compound: 5%, 10% and 25% Fluorescite (Alcon, Lot #s: SI-655, SI-656, SI-659, and SI-660) and 10% and 25% sodium fluorescein ([redacted], Lot #s: 080671 and AE0012)
Dosing regimen: Single dose
Route: Intravenous injection, 0.1 ml/sec
Animal: Swiss albino mice, 5/sex/group
Study site: Not indicated
Study initiation: Not indicated (Reporting date: 2/13/1973)
GLP: No
Study design:

Formulation	Lot number	Volume (ml/kg)	Concentration (mg/ml)	Dosage (mg/kg)
Fluorescite 5% with $NaHCO_3$	SI-655	16-30	[redacted]	800-1500
Fluorescite 10% with $NaHCO_3$	SI-659	6-12		600-1200
Fluorescite 10% without $NaHCO_3$	SI-660	3-12		300-1200
10% sodium fluorescein	080671	10-12		1000-1200
Fluorescite 25% without $NaHCO_3$	SI-656	3.2-5.0		800-1250
25% sodium fluorescein	AE0012	3.6-5.0		900-1250
Vehicle for SI-655		30		0
Vehicles for SI-659, SI-660, 080671, and AE0012		12.0		0

The purpose of this study was to determine if the LD_{50} values of sodium fluorescein for mice was affected by dosing volume. After dosing, the animals were observed frequently for four hrs and at 24 hr intervals for 7 days thereafter. The LD_{50} values were calculated using the method of Finney.

Results:

General appearance and behavior: Drug-treated animals showed rapid respiration, lethargy, and fluorescent skin, urine and feces immediately after dosing. Prostration and lethargy frequently preceded death. In general, surviving mice were normal 24 hrs after dosing with all evidence of body fluorescein gone at 48 hr.

Mortality: Mortality was noted in all treated groups in a dosage-dependent manner. Similar incidences were noted in both males and females. The majority of deaths occurred within the first 24 hrs after dosing. The LD_{50} values for each formulation group, summarized in the table below, were generally comparable, suggesting that the LD_{50} values were not affected by the volume changes. In conclusion, the intravenous LD_{50} values for fluorescein in mice, which were determined by the dosage, were not affected by volume changes.

Comparison of LD_{50} values

Formulation	Lot number	LD_{50} (mg/kg)
Fluorescite 5% with $NaHCO_3$	SI-655	1327
Fluorescite 10% with $NaHCO_3$	SI-659	799
Fluorescite 10% without $NaHCO_3$	SI-660	943
Fluorescite 25% without $NaHCO_3$	SI-656	899
10% sodium fluorescein	080671	1043
25% sodium fluorescein	AE0012	958

Acute systemic toxicity evaluation of 10% Fluorescite exposed to rubber plunger of syringe

Key study findings: The intravenous LD_{50} values for fluorescein in mice were not affected by the exposure to the rubber plunger.

Report N^{o}: TR075:7320:72/73
Compound: 10% Fluorescite exposed to the plunger (Lot #: TI-273), 10% Fluorescite not exposed to the plunger (Lot #: TI-274)
Dosing regimen: Single dose
Dosage: 0.8, 0.9, 1.0, and 1.1 g/kg at 10 or 11 ml/kg
Route: Intravenous injection
Animal: Swiss albino mice, 16-28 g, 5/sex/group
Study site: Not indicated
Study initiation: Not indicated (Reporting date: 3/16/1973)
GLP: No
Study design:

Group	Lot number	Volume (ml/kg)	Concentration (mg/ml)	Dosage (mg/kg)
Fluorescite 10% exposed	TI-273	10 or 11	[redacted]	800-1100
Fluorescite 10% unexposed	TI-274	10 or 11	[redacted]	800-1100
vehicle	TI-275	10		0

The purpose of this study was to determine if the LD_{50} value for 10% Fluorescite was changed when the drug was exposed to the [redacted] black plunger by placing a number of rubber plungers in the drug solution in a quantity equal to the surface area of the syringe [redacted] After dosing, the animals were observed frequently for four hrs and at 24 hr intervals for 14 days thereafter. The LD_{50} values were calculated using the method of Finney.

Results:

General appearance and behavior: The same clinical signs were noted in both drug-treated groups including lethargy and fluorescent skin. Prostration and lethargy frequently preceded deaths. In general, surviving mice were normal 24 hrs after dosing with all evidence of body fluorescein gone at 48 hr. No abnormal findings were noted in the vehicle group.

Mortality: Mortality was noted in both treated groups in a dosage-dependent manner. Similar incidences were noted in both males and females. The majority of deaths occurred within the first 24 hrs after dosing. The LD_{50} values for both treated groups, summarized in the table below, were comparable and statistically equivalent, suggesting that the LD_{50} values were not affected by the exposure to the rubber plunger. In conclusion, the intravenous LD_{50} values for fluorescein in mice were not affected by the exposure to the rubber plunger.

Comparison of LD_{50} values

Formulation	Lot number	LD_{50} (mg/kg)
Fluorescite 10% exposed	TI-273	1025
Fluorescite 10% unexposed	TI-274	978

LD_{50} determination of 10% Fluorescite syringes prepared by ———

Key study findings: The 10% Fluorescite syringes prepared by ——— was equivalent to 10% Fluorescite formulations prepared at Alcon regarding acute toxicity.

Report Nº: TR024:7320:73/74
Compound: The syringe unit of 10% Fluorescite (Lot #: TI-275)
Dosing regimen: Single dose
Dosage: 800, 1000, and 1200 mg/kg, at 8, 10 or 12 ml/kg
Route: Intravenous injection
Animal: Swiss albino mice, 20 g, 5/sex/group
Study site: Not indicated
Study initiation: Not indicated (Reporting date: 6/22/1973)
GLP: No

The purpose of this study was to determine the LD_{50} value of 10% Fluorescite in syringe units prepared by ——— After dosing, the animals were observed frequently for four hrs and at 24 hr intervals for 7 days thereafter. The LD_{50} values were calculated using the method of Finney.

Results:

General appearance: All drug-treated animals showed piloerection. MD and HD animals showed lethargy. Prostration and convulsion were seen in animals that died after dosing. Surviving mice were normal 24 hrs after dosing and continued for 7 days. No abnormal findings were noted in vehicle group.

Mortality: Mortality was noted in MD (2f/3m) and HD (3f/3m) groups only. The LD_{50} value was 1088 mg/kg, similar to the LD_{50} values obtained from other studies (799-1113 mg/kg). It is concluded that the fluorescein in the syringe unit prepared at ——— is comparable to 10% Fluorescite formulations prepared at Alcon with respect to acute toxicity.

LD_{50} determination of 10% Fluorescite prepared from sodium fluorescein synthesized by ———

Key study findings: The 10% Fluorescite prepared from sodium fluorescein synthesized by ——— was equivalent to 10% Fluorescite formulations prepared previously at Alcon regarding acute toxicity.

Report Nº: TR037:7320:73/74
Compound: 10% Fluorescite (Lot #: TI-377)
Dosing regimen: Single dose
Dosage: 800, 1000, and 1200 mg/kg, at 8, 10 or 12 ml/kg
Route: Intravenous injection

Animal: Swiss albino mice, 5/sex/group
Study site: Not indicated
Study initiation: Not indicated (Reporting date: 7/9/1973)
GLP: No

The purpose of this study was to determine the LD_{50} value of 10% Fluorescite prepared with sodium fluorescein by [redacted] After dosing, the animals were observed frequently for four hrs and at 24 hr intervals for 7 days thereafter. The LD_{50} values were calculated using the method of Finney.

Results:

General appearance: All drug-treated animals showed piloerection, transient paralysis of the hind quarters, rapid respiration, and slight lethargy. MD and HD animals showed lethargy. Prostration and convulsions were seen in animals prior to deaths. Surviving mice were normal 24 hrs after dosing and continued for 7 days. Animals treated with vehicle alone showed only piloerection.

Mortality: Mortality was noted in drug-treated animals in a dose-dependent manner. Similar incidences were seen in both males and females. The LD_{50} value was 964 mg/kg, similar to the LD_{50} values obtained from other studies (799-1113 mg/kg). No mortality was seen in control animals. It is concluded that the sodium fluorescein synthesized by [redacted] was bioequivalent to 10% Fluorescite formulations prepared previously at Alcon with respect to acute toxicity.

Acute toxicity evaluation of 10% Fluorescite (Complaint Lot #W600) in mice and dogs

Key study findings: 10% Fluorescite Lot W600 (complaint) had acute toxicity potential similar to that of two other lots of 10% Fluorescite (W601 and V600) and a [redacted] product.

Report Nº: TR012:7320:76/77
Compound: 10% Fluorescite (Lot #s: W600, W601, and V600), fluorescein sodium 10% (a [redacted] product, Lot R56681)
Dosing regimen: Single dose
Dosage: 10 mg/kg at 0.1 ml/kg for Clinical Dose Study, and 800, 1200, and 1400 mg//kg at 20 ml/kg for LD_{50} Study
Route: Intravenous injection
Animal: Swiss albino mice, 5/sex/group and Mongrel dogs, 1 sex/group (Only mice were used in LD_{50} study.)
Study site: Alcon Laboratories, Inc., Fort Worth, Texas
Study initiation: Not indicated (Reporting date: July 1976)
GLP: No

A complaint was sent to the sponsor on 10% Fluorescite Lot W600. The purpose of this study was to determine the LD_{50} value of the complaint lot of 10% Fluorescite (Lot W600) in comparison to other 10% Fluorescite lots and a competitor product (fluorescein sodium 10%, [redacted]) after iv administration to mice (LD_{50} Study). A second part of the study was the iv administration of the clinical

dose (10 mg/kg) of 10% Fluorescite and other test materials in dogs and mice (Clinical Dose Study). **[Reviewer's comments**: It is not appropriate to directly compare 10 mg/kg in mice and dogs with 10 mg/kg in humans. The dose of 10 mg/kg in animals is not really a "clinical dose."] After dosing, the animals were observed for 7 days. The LD_{50} values were calculated using the method of Finney.

Results:

Clinical Dose Study:

All animals appeared normal. No mortality occurred during the 7-day observation period.

LD_{50} Study:

General appearance: Drug-treated animals showed transient (15 sec) paralysis of the hind quarters and lethargy. High incidence was seen with higher doses.

Mortality: Mortality was noted in all drug-treated groups in a dose-dependent manner. Similar incidences were seen in both males and females. The LD_{50} values were 1202.90 mg/kg, 1169.34 mg/kg, 1605.07 mg/kg, and 1205.55 mg/kg for Lots W600, W601, V600, and for [redacted] product, respectively. The values were biologically equivalent for all test materials. No mortality was seen in vehicle control animals. It was concluded that 10% Fluorescite Lot W600 had acute toxicity potential similar to that of two other lots of 10% Fluorescite (W601 and V600) and a marketed competitor [redacted] product.

2.6.6.3 Repeated-dose toxicity

No studies were submitted.

6.6.6.4 Genetic toxicology

No studies were submitted.

2.6.6.5 Carcinogenicity

No studies were submitted.

2.6.6.6 Reproductive and developmental toxicology

No studies were submitted. The sponsor submitted two publications for reproductive studies in rats and rabbits to address the toxicological and teratogenic potential of the drug. Both papers were published in the 1970s. When compared to the guidance within ICH documents, these studies are not adequate regarding animal numbers, dosage, or measured parameters (e.g., no skeletal examinations).

In studies[1] conducted in Charles River (CD) rats, fluorescein at the iv dose 500 mg/kg during gestation Day 1, 6, 12, or 18 caused no teratogenic effects. No statistically significant differences in the average length and weight of pups were noted between treated and control groups. However, the number of

pups/litter from dams treated on gestation Day 1 or 6 (8.3 ± 1.3/litter and 7.8 ± 2.4/litter, respectively) was lower than that of the control groups (11.5 ± 1.0/litter and 11.3 ± 0.5/litter, respectively). It was not clear if this was toxicologically significant because no other reproductive parameters were examined, no historical data were available and the author indicated that the differences were not statistically significant. No difference was noted in animals injected on gestation Day 12 or 18. Examination of pregnant animals showed that the amniotic fluid and fetuses from dams treated on gestation Day 12 or 18 exhibited yellow fluorescence at 1, 2, and 4 hr after injection. At 24 and 48 hr after injection, fetuses did not exhibit fluorescence.

In rabbit study(2), fluorescein at the iv dose of 140 mg/animal (31 mg/kg) during gestation Days 5, 6 and 8 or during gestation Days 13, 15 and 16 caused no teratogenic effects.

(1): Salem, H., et.al, Evaluation of the toxicologic and teratogenic potentials of sodium fluorescein in the rat. Toxicology. 1979 Feb; 12(2):143-50.
(2): McEnerney, J., et.al, Evaluation of the teratogenicity of fluorescein sodium. Am. J. Ophthalmol. 1977 Dec; 84(6):847-50.

2.6.6.7 Local tolerance

No studies were submitted.

2.6.6.8 Special toxicology studies

No studies were submitted.

2.6.6.9 Discussion and Conclusions

Fluorescite® has been marketed in the US and throughout the world for over 30 years. The drug product submitted in this NDA is the currently marketed drug. 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. Only five single dose toxicity studies and several publications were submitted in this NDA package. The results obtained from these studies indicated that the intravenous LD_{50} values for fluorescein in mice were not affected by volume changes and 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. From reproductive toxicity studies described in two publications included in the package, fluorescein at the iv dose of 140 mg/animal (about 31 mg/kg) in rabbits and 500 mg/kg in rats during different time periods (gestation Days 6 to 8 and 13 to 16 for rabbits and gestation Day 1, 6, 12, or 18 for rats) caused no teratogenic effects. The drug freely crossed the placenta barrier. The reviewer also checked several clinical and nonclinical publications suggesting that fluorescein angiography does not offer a high rate of birth anomalies or complications during pregnancy. However, [redacted] a category C is proposed. In conclusion, there are no specific concerns from the pharmacology/toxicology viewpoint regarding clinical use of Fluorescite®.

2.6.7 TOXICOLOGY TABULATED SUMMARY

No tabulated summary was submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Fluorescite® has been marketed as a single diagnostic use in the US and other countries for many years and clinical safety of the drug has been established. Fluorescein angiography is a routine procedure in research and clinical practice. Clinical experience indicated that fluorescein dye is nontoxic and nonirritating to the eye. There are no specific concerns from the pharmacology/toxicology viewpoint regarding clinical use of Fluorescite®.

Unresolved toxicology issues (if any): No

Recommendations:

An "approval" is recommended for this NDA application.

Suggested labeling:

Several modifications of labeling are recommended in the "Pregnancy" section.

Pregnancy

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

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/s/

Zhou Chen
2/16/2006 12:40:28 PM
PHARMACOLOGIST

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2/16/2006 12:43:19 PM
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