CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-980

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	21-980
PRODUCT	Fluorescite® (fluorescein injection, USP) 10%
FORMULATION	Sterile, unpreserved aqueous solution
SUBMISSION DATES	September 28, 2005
SUBMISSION TYPE	505(b)(2) application
SPONSOR	Alcon, Inc.
OCP DIVISION	Division of Clinical Pharmacology IV
MEDICAL DIVISION	Division of Anti-infective and Opthamologic Drug Products
REVIEWER	Jeffrey J. Tworzyanski, Pharm.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.

CLINICAL PHARMACOLOGY REVIEW

1 EXECUTIVE SUMMARY

Alcon Inc. submitted a 505(b)(2) NDA for Fluorescite Injection 10%. This is an existing Alcon product that has been marketed in the USA for over 30 years, without the requirement of an NDA filing. The proposed indication is in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature. The proposed adult dose of Fluorescite Injection 10% is 500mg (100mg/ml) via intravenous administration. Fluorescein angiography is a routine procedure in research and clinical practice. Fluorescein dye is useful in evaluating both normal physiology and diseases of the anterior and posterior segments of the eye. 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 520-530 nm). The improvement in the quality of fluorescein dye and improvement in imaging equipment that has occurred in recent years has been helpful in advancing the understanding of the pathophysiology and treatment of diseases of the choroids and retina.

The sponsor did not submit any clinical pharmacology studies in the NDA. However, several literature articles describing the pharmacokinetics of intravenous fluorescein were submitted. Even though the source data from these articles were not submitted for review, the pharmacokinetic characteristics are consistent across multiple peer reviewed articles. Therefore, the pharmacokinetic information submitted in the form of published peer reviewed articles can be considered as evidence of demonstration of bioavailability of fluorescein to meet the regulatory requirement of CFR 320.21.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology IV (OCP/DCP IV) has reviewed NDA 21-980. The submission is acceptable from a Clinical Pharmacology point of view. The labeling comments in section 3 should be communicated to the sponsor.

1.2 PHASE IV COMMITMENTS

No phase IV commitments are recommended.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The sponsor did not submit any clinical pharmacology studies in the NDA. However, several literature articles were submitted to support the proposed clinical pharmacology section of the labeling. The literature articles submitted in the NDA reported the following pharmacokinetic results.

Within seven to 14 seconds after IV administration of fluorescein into the antecubital vein, the dye appears in the central artery. The plasma profile of fluorescein has been described by a two-compartment model. The initial disposition phase is thought to be due to distribution of fluorescein from the central compartment (including plasma) to an apparent peripheral compartment in conjunction with simultaneous elimination from the central compartment because of hepatic glucuronidation. The second phase may represent fluorescein redistribution to the central compartment and elimination from the body. Fluorescein appears to be bound to albumin and red blood cells, but this binding appears to be moderate and reversible. The protein binding ranged from 70 to 80% within four hours after intravenous administration. Various estimates of the volume of distribution indicate that fluorescein distributes well into interstitial fluid (0.5 L/kg). Fluorescein undergoes rapid metabolism to form fluorescein monoglucoronide, which is about 1/3 to 1/34 as fluorescent as fluorescein. The extent to which fluorescein glucoronide contributes to ocular fluorescence after a systemic dose may be minimal. Fluorescite and its metabolites are reported to be mainly eliminated via renal excretion. A renal clearance of 1.75 ml/min/kg and a hepatic clearance of 1.50 ml/min/kg have been reported.

Jeffrey J. Tworzyanski, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology IV

RD/FT Initialed by Venkat R. Jarugula, Ph.D.,_____
Team Leader

cc:
Division File: NDA 21-980
HFD-520 (CSO/Rodgers)
HFD-520 (MO/Boyd)
HFD-880 (Division File, Lazor, Selen, Jarugula, Tworzyanski)
CDR (Clin. Pharm./Biopharm.)

2 QUESTION BASED REVIEW

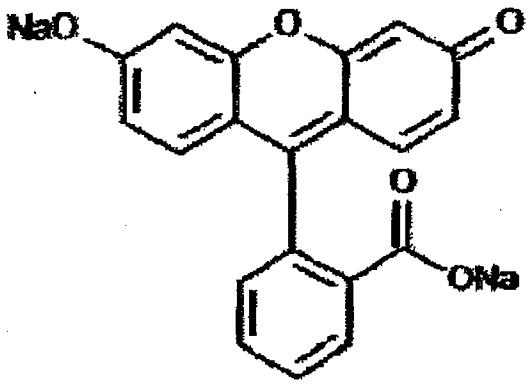
Since this is a 505b(2) NDA for a diagnostic agent that has been used for more than 30 years, only relevant questions from the QBR are addressed below.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug as they relate to clinical pharmacology and biopharmaceutics review?

Fluorescite® (fluorescein injection, USP) 10% is a sterile solution for use intravenously as a diagnostic aid. Its chemical name is spiro[isobenzofuran-1(3*H*),9'-[9H]xanthene]-3-one, 3'6'-dihydroxy, disodium salt. The active ingredient is represented by the chemical structure in Figure 1.

Figure 1. Chemical Structure of Fluorescite.



Molecular Weight: 376.27 daltons

Fluorescite® (fluorescein injection, USP) is supplied as a sterile, unpreserved, pyrogen free, buffered, unit dose, aqueous solution, that has a pH of 8.0-9.8 and an osmolality of 572-858 mOsm/kg. The active ingredient is fluorescein sodium. The inactive ingredients are sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The sponsor states that fluorescein sodium responds to electromagnetic radiation or light between the wavelengths of 465-490 nm. The hydrocarbon is excited by blue light and emits light that appears yellowish-green. Following intravenous injection of fluorescein sodium in an aqueous solution, the unbound fraction of the fluorescein can be excited with a blue light flash from a fundus camera as it circulates through the ocular vasculature, and the yellowish green fluorescence of the dye is captured on film. The sponsor believes that, in the fundus, the fluorescence of the dye demarcates the retinal

and/or choroidal vasculature under observation which distinguishes it from adjacent areas/structures.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

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 35mg for each ten pounds of body weight (7.7 mg/kg body weight).

2.2 General clinical pharmacology

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Pharmacokinetics – The following pharmacokinetic information has been obtained from peer-reviewed, published literature sources. The information contained in italics is what the sponsor has claimed in the proposed label.

2.2.5.3 What are the characteristics of drug absorption?

1. *Within 7 to 14 seconds after IV administration into antecubital vein, fluorescein appears in the central artery of the eye."*

In a study that was conducted by Barry, et al. 1985, fluorescein was administered intravenously to healthy subjects. Plasma samples were drawn at numerous time points in the study to determine the drugs concentration. The investigators conducted a pharmacokinetic analysis of fluorescein and reported the area under the concentration-time curve (AUC), volume of distribution (Vd), and systemic bioavailability. Table 2 shows the pharmacokinetic parameters that were reported in this study.

Table 2. Mean fluorescein pharmacokinetic parameters after IV Administration in healthy subjects (N=10)

Parameter	Intravenous (188mg)*
C_{max} (µg/ml)	10.9
$AUC_{0\text{-}10h}$ (µg·min/ml)	1350
Cl_{total} (ml/min)	139
$t_{½\alpha}$ (min)	38
$t_{½\beta}$ (min)	182
V_d (L/70kg)	36.8

*Standard deviation or coefficient of variation is not reported.

In a study by Van den Biesen, et al 1997, the investigators analyzed the angiography of six subjects injected with flourescein. The arm-to-retina time for six subjects ranged from 7.5 to 13.5 seconds.

equivalent to the adult dose based on the body weight (500 mg/70kg) and appears to be based on clinical practice.

2.2.2.5 Renal Impairment:

Larsen et al. (1988) reported slightly higher plasma concentrations of free fluorescein and markedly elevated plasma concentrations of fluorescein glucuronide in a diabetic subject with renal insufficiency compared to a healthy subject following IV injection of 37μM/kg fluorescein. Fluorescein has been in use as a diagnostic agent with single dose administration for over 30 years. Dose adjustment in special population is not warranted.

2.3.2.6 Hepatic Impairment:

The sponsor did not submit any information regarding pharmacokinetics of fluorescein in subjects with hepatic impairment. However, as noted in the previous question, no dosage adjustment is warranted in patients with hepatic impairment.

2.3.2.7 Nursing Mothers:
"Fluorescein has been demonstrated to be excreted in human milk. .

Maguire et al., conducted a study in which they measured fluorescein concentrations in the breast milk of a female subject after being administered a standard injection of 5ml 10% fluorescein sodium for diagnostic angiography. The authors reported that fluorescein was detectable in breast milk samples up to 76 hours after administration of fluorescein IV solution. A peak concentration of 372 ng/ml was measured at the first collection, six hours after intravenous injection. Seventy-six hours after injection a concentration of 170 ng/ml was determined in breast milk samples.

2.4 Extrinsic factors
2.4.2 Drug-Drug Interaction:

Cunha-Vaz et al, conducted a study on the permeability of the retinal capillaries on adult pigmented rabbits. Under local anesthesia, fluorescein was injected into the vitreous body

2.2.5.4 What are the characteristics of drug distribution?
"Within a few minutes of IV administration of fluorescein sodium, a yellowish discoloration of the skin occurs, which began to fade after 6 to 12 hours of dosing. Various estimates of volume of distribution indicate that fluorescein distributes well into interstitial space (

Dollery, et al., reported that IV administration of three 250mg doses of fluorescein caused a yellowish discoloration of the skin in patients. The investigators stated that the dye is rapidly excreted in the urine which becomes a bright yellow color during the first few hours after injection. The discoloration of the skin fades in six to twelve hours, but the urine remains slightly fluorescent for 24 to 36 hours. In one subject from this study, the fluorescein volume of distribution was reported to be four times that of I-131 labeled albumin in 10 minutes after dosing. In a study by Grotte, et al., one subject was estimated to have a volume of distribution of 0.13 L/kg for a central compartment and 0.55 L/kg for a peripheral compartment following IV administration of 10mg/kg fluorescein. In a study by Barry and Behrendt, fluorescein 188mg was administered IV to ten healthy subjects and they obtained a mean Vd of approximately 0.5 L/kg. Thus, various estimates from literature suggest that fluorescein distributes well into interstitial space with a volume of distribution of approximately 0.5 L/kg.

2.2.5.6 What are the characterisitics of drug metabolism?
"Fluorescein undergoes rapid metabolism to fluorescein monoglucuronide. After IV administration of fluorescein sodium (14mg/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.

Multiple published studies have shown that fluorescein undergoes rapid metabolism to fluorescein monoglucuronide (Chen et al. 1980, Chahal et al. 1985b, Grotte et al. 1980). Chahal et al. (1985), conducted a study in which they gave fluorescein intravenously (14 mg/kg) to seven normal subjects and eight diabetic subjects. Plasma samples taken during 60 minutes were subjected to microfiltration, from which aliquots of ultrafiltrate were incubated with beta-glucoronidase. The samples were subjected to high-performance liquid chromatography, and fluorescence activity was measured in the eluent. All of the subjects showed an additional fluorescence peak to that of fluorescein in plasma and ultrafiltrate five minutes after fluorescein administration and increased thereafter. When samples of ultrafiltrate were incubated with beta-glucuronidase, the additional peak was abolished. It was therefore assumed to be due to the formation of fluorescein glucuronide. At 60 minutes, 80% of the fluorescein was present as glucuronide and contributed to 20% of the total fluorescence in the ultrafiltrate. McLaren et al. (1986) reported that fluorescein glucoronide is 1/3 to 1/34 as fluorescent as fluorescein depending on the wavelength of excitation. At the wavelengths of 465nm to 490nm (used for fluorescein angiography), the glucoronide is approximately 25 times less fluorescent than fluorescein. Fluorescein angiography is typically done within minutes of IV administration. Therefore,

the extent to which fluorescein glucoronide contributes to ocular fluorescence may be minimal.

2.2.5.7 What are the characterisitics of drug excretion?
"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 500mg fluorescein."

Barry et al,, conducted a study in ten healthy male volunteers aged 22 to 24 years in which they were administered oral and IV doses of fluorescein. Plasma and urine samples were collected and test results showed that fluorescein excretion occurs in the urine up to 24 hours but the vast majority of the fluorescein which is eliminated by the kidney is eliminated within twelve hours of administration. In a study by Dollery et al., after injection of three 250 mg doses of fluorescein, the dye is rapidly excreted in the urine, which becomes a bright yellow color during the first few hours after injection. The urine remains slightly fluorescent for 24 to 36 hours. Grotte et al., reported in their study the estimated PK parameters of IV fluorescein to be a renal clearance of 1.75 ml/min/kg and a hepatic clearance (due to conjugation) of 1.50 ml/min/kg. In a study by Willerson et al., the serum clearance of fluorescein 25% was essentially complete in 48 to 72 hours following injection. These results are somewhat consistent with the total clearance (139 ml/min) and the terminal elimination half-lives (3 and 4.5 hrs following intravenous and oral administration, respectively) reported in the Barry et al study.

2.3 Intrinsic Factors
2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually)?

2.2.3.1 Geriatric Use:
"No overall differences in safety or effectiveness have been observed between the elderly and other adult patients."

No information to support this statement was submitted in the Clinical pharmacology section. Refer to the Clinical Review.

2.3.2.2 Pediatric Use:

[redacted]

Saine et al., notes in his textbook, "Opthalmic Photography", that the dose of Fluorescein when administered to children is 3.5mg per pound of body weight. This is equal to 7.7 mg/kg of body weight in children. The proposed dose in pediatrics is

through a 30 gauge needle. They found that inhibitors (e.g., Benemid) in the vitreous body inactivated the transport mechanism for fluorescein. The sponsor didn't submit any clinical information to support the statements regarding potential interaction with organic anion transporters.

3 Detailed Labeling Recommendations

The sponsor has provided references with this submission to support statements made in the proposed package label. The sponsor refers to a ——— of Fluorescite which does not pertain to this NDA for an intravenous formulation. It is recommended that the sponsor remove from the proposed label, all statements which pertain to ———

The following detailed labeling changes are recommended. The strike out sentences/words should be deleted and the underlined sentences/words should be added.

Pharmacokinetics- The following pharmacokinetic information has been obtained from published literature sources.

Distribution:

Metabolism:

Excretion:

Nursing Mothers:

Dosage and Administration:
"The normal adult dose of FLUORESCITE® Injection 10% is 500mg (100 mg/ml) via intravenous administration."

"For children, the dose should be calculated on the basis of 35mg for each ten pounds of body weight (7.7 mg/kg body weight)."

REFERENCES

Barry RE, Behrendt WA. Studies on the pharmacokinetics of fluorescein and its dilaurate ester under the conditions of the fluorescein dilaurate test. Arzneimittelforschung 1985;35(3):644-8.

Chahal PS, Neal MJ, Kohner EM. Metabolism of fluorescein after intravenous administration. Invest Opthalmol Vis Sci 1985;26(5):764-8 (a).

Chen SC, Nakamura H, Tamura Z. Studies on the metabolites of fluorescein in rabbit and human urine. Chem Pharm Bull 1980;28(5):1403-7.

Cunha-Vaz JG, Maurice DM. The active transport of fluorescein by the retinal vessels and the retina. J Physiol 1967;191:467-86.

Dollery CT, Hodge JV, Engel M. Studies of the retinal circulation with fluorescein. Brit Med J 1962;2:21 110-5.

Grotte, D, Mattox, V, Brubaker, R. Fluorescent, physiological and pharmacokinetic properties of fluorescein glucoronide. Exp Eye Res 1985 Jan;40(1):23-33.

Larsen M, Loft S, Hommel E, Lund-Andersen H. Fluorescein and fluorescein glucuronide in plasma after intravenous injection of fluorescein. Acta Opthalmol 1988 Aug;66(4):427-32.

Maguire AM, Bennett J. Fluorescein elimination in breast milk. Arch Opthalmol 1988;106:718-719.

McLaren JW, Brubaker RF. Measurement of fluorescein and fluorescein monoglucoronide in the living human eye. Invest Opthalmol Vis Sci 1986;27(6):966-74.

Saine, PJ, Tyler, ME Opthalmic Photography: A Textbook of Fundus Photography, Angiography, and Electronic Imaging. Twin Chimney Publishing, Newton, Maine, USA, 1997.

Van den Biesen PR, Hermens WT, Slaaf DW. Dye extravasation and the nature of background fluorescence in sodium fluorescein angiography. Retina 1997;17(6):540 6.

Willerson D, Tate GW Jr, Baldwin HA, Hearnsberger PL. Clinical evaluation of fluorescein 25%. Ann Opthalmol 1976;8(7):833-4, 837-41.

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