A Pilot Study to Determine the Efficacy of Fluorescein Visualization of the Uterus in Detecting Endometrial Cancer Invasion

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1. Table of Contents

2. *ABBREVIATIONS*

AE – adverse event

CCTO – Cancer Clinical Trials Office

CFR – Code of Federal Regulations

CRA – clinical research associate

CRF – case report form

CTCAE – Common Terminology Criteria for Adverse Events

FDA – Food and Drug Administration

GCP – good clinical practice

IRB – Institutional Review Board

IV – intravenously

mg – milligram

ml - milliliter

PI – principal investigator

PRMC – Protocol Review And Monitoring Committee

RSC – Research Support Center

SAE – serious adverse event

UAMS - University of Arkansas for Medical Sciences

UPIRTSO/UPR – unanticipated problems involving risk to subjects or others

3. PROTOCOL SUMMARY

Primary Objective: To determine if Fluorescein systemic injection during hysterectomy procedure can be useful in revealing the depth of endometrial cancer invasion.

Secondary Objectives: To compare depth of invasion as detected with fluorescein to that detected by frozen section and final pathology.

Exploratory Objectives: Can systemic fluorescein injection at time of hysterectomy provide an inexpensive and rapid determination of endometrial cancer invasion into the myometrium.

Study Population: Women with endometrial cancer who are undergoing hysterectomy.

Inclusion Criteria:
1. Known endometrial cancer and scheduled for hysterectomy as part of their treatment.
2. No known allergy to fluorescein dye.
3. Ability to understand and sign informed consent.
4. 18 year of age or older

Exclusion Criteria:
1. Prior hysterectomy.
2. Known sensitivity to fluorescein dye.

Investigational Product: Fluorescein dye injected systemically

Study Design: Pilot

4. STUDY SCHEMA

100 women with endometrial cancer who are scheduled for a hysterectomy as a part of their initial treatment

↓

Intravenous injection of 1 ampule (5 cc) of fluorescein dye prior to ligation of the uterine arteries during hysterectomy

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Uterus sent immediately to surgical pathology for opening, cross-sectioning, and exposure with Woods lamp to determine depth of invasion of endometrial cancer into the myometrium. Photograph taken of representative area and frozen section performed at same area

↓

Comparison of final pathology depth of invasion with frozen section depth of invasion and fluorescein dye detected depth of invasion to determine accuracy of procedure.

5. BACKGROUND

Endometrial cancer is a surgically staged disease. Staging involves removal of the uterus, tubes and ovaries as well as lymph nodes in the pelvic and aortic regions. In women with cancer that does not invade the uterine muscle or is of low grade and invades less than 50% of the muscle, removal of the lymph nodes is not mandatory. Intraoperative evaluation of the depth of invasion of the cancer is critical, therefore, in determining which patients require lymphadenectomy. Gross visualization is highly inaccurate. It is more sensitive to obtain a pathological frozen section on the uterus to accurately diagnose depth of invasion. However, frozen section increases the operative time and incurs an additional expense for the procedure. A rapid and accurate intraoperative assessment of invasion which could be performed in the operating room would reduce the time and expense of a frozen section. We propose to utilize fluorescein dye given intravenously prior to the hysterectomy to aid in visually determining the depth of invasion. If this assessment correlates well with the pathologic depth of invasion, then this could represent a valuable intraoperative tool to determine which patients require lymphadenectomy.

Fluorescein is approved by the FDA for angiography of the retinal vessels. There are many procedures that utilize fluorescein beyond its FDA indication. It is commonly used during surgery to assess the vascular viability of tissue, most particularly the viability of the intestines when there is concern. In this situation, fluorescein is injected intravenously and the intestines are examined using a Woods lamp to detect the areas of fluorescence. Areas of poor vascularity will not fluoresce. It is also commonly used to detect the boundaries of skin lesions. For example, in assessment of vulvar Paget's disease fluorescein injection and visualization of the vulva with Woods lamp can detect the extent of the lesion that would otherwise not be detectable by the naked eye.

6. TRIAL OBJECTIVES

a. Primary Objective: To determine if Fluorescein systemic injection during hysterectomy procedure can be useful in revealing the depth of endometrial cancer invasion

b. Secondary Objectives: To compare depth of invasion as detected with fluorescein to that detected by frozen section and final pathology

c. Exploratory Objectives: Can systemic fluorescein injection at time of hysterectomy provide an inexpensive and rapid determination of endometrial cancer invasion into the myometrium

7. PATIENT POPULATION

Women with documented endometrial cancer who are scheduled for a hysterectomy as part of their initial cancer staging.

Eligibility Criteria: Subjects are eligible for the study if the following inclusion and exclusion criteria are met:

Inclusion Criteria:
1. Documented endometrial cancer and scheduled for hysterectomy as part of their treatment.
2. No known allergy to fluorescein dye
3. Ability to understand and sign informed consent
4. 18 year of age or older

Exclusion Criteria:
1. Prior hysterectomy
2. Known sensitivity to fluorescein dye

8. INVESTIGATIONAL AGENT – Fluorecein dye for intravenous injection

a. General Description: Fluorescein is a synthetic organic compound with a dark orange color that is dissolved in water. It is supplied in a glass ampule with 500 mg of fluorescein sodium in 5 mL of water. The dye is injected intravenously and is stimulated by blue light (Woods lamp) in the range of 465 to 490 nm. Under the blue light, it will fluoresce as a bright yellow-green color.

b. Manufacturing and Formulation: Fluorescein 500mg/5mL is a sterile solution containing fluorescein sodium for intravenous injection. It is manufactured by multiple companies including Alcon Chemical (Fluorescite). Each 1.0 mL of solution contains 100 mg fluorescein sodium. One ampoule of 5mL contains 500 mg fluorescein sodium.
Excipients: Sodium hydroxide for pH adjustment, water for injections.

c. Preparation: Comes packaged as a single ampule containing 5 cc of fluorescein dye.

d. Dosing Administration or Utilization: One ampule (5 cc) injected intravenously prior to ligation of the uterine arteries.

e. Storage and Disposition: Fluorescein ampules should be stored between 5ºC to 25ºC.

f. Label Information: See Appendix I: Manufacturer's label

g. Agent Ordering: Fluorescein dye will be purchased by Pharmacy for this study, and the Division of Gynecologic Oncology will reimburse pharmacy as subjects complete the study.

h. Agent Accountability: UAMS Pharmacy Department

9. TREATMENT PLAN

a. On-Study Evaluation:

After signing the IRB-approved informed consent form, research participants will be registered by a clinical research associate (CRA) in the Cancer Clinical Trials Office (CCTO). Upon registration, surgery will be scheduled at the next available surgery time slot. All research participants will receive fluorescein injection through their existing intravenous line during their operative procedure for endometrial cancer staging. This will consist of one ampule (5 cc) injected intravenously prior to ligation of the uterine arteries. After the uterus is removed it will be sent to surgical pathology for evaluation as per routine care. The pathologist will open the uterus and evaluate the endometrium. He or she will then cut into the myometrium in an area most suspicious for invasion. The cross section of the myometrium and endometrium will be photographed while exposed to a Woods lamp. The normal myometrium will have a yellow fluorescent appearance under the Woods lamp. The cancerous tissue will have minimal fluorescence. The measurement will be taken estimating the depth of invasion of the cancer into the myometrium on the basis of its physical appearance under the Woods lamp. Cross-sectioning of the uterus is routine procedure by pathology for the intra-operative evaluation of endometrial cancer. This information routinely is provided in order to determine if lymph node staging is necessary.

The area that was measured and photographed will then be prepared for a frozen section to document depth of invasion. This is the standard procedure performed during an endometrial staging. The depth of invasion on the frozen section will be recorded. This same area will undergo histologic confirmation by permanent pathology to determine depth of invasion. The frozen section is part of routine standard of care in evaluation of endometrial cancer.

Subjects will be informed prior to participation in this study that they will have a bright yellow discoloration of their urine and possibly a mild yellow discoloration of their skin for up to 24 hours after the procedure.

b. Dose Assignment: This is a single arm study. A single dose of Fluorescein will be administered to all subjects in this study.

c. Specimen Handling: The uterus will be sent to pathology immediately after its removal from the patient. The study pathologist will be informed when to expect a subject specimen and will prepare the lab for Woods lamp evaluation, measurement and photography. The remainder of the specimens from the procedure will be processed in the usual manner for routine pathology evaluations.

Visit Breakdown

1. Informed consent will be obtained at the pre-operative surgery appointment.

2. Urine Pregnancy test (only for women of child bearing potential and only if a previous urine pregnancy exam has not been performed within 28 days of consent as standard of care)

3. Injection with the fluorescent dye will occur approximately 5 to 10 min. prior to ligation of the uterine vessels during the hysterectomy.

4. The uterus will be sent to pathology immediately after its removal where Woods lamp evaluation, measurement and photography will be performed.

d. Prohibited Medications: none

e. Dose Limiting Criteria: none

10. STUDY CALENDAR

TEST/EVENT	**VISITS**	
	Pre-Operative visit	Surgery
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Urine Pregnancy exam	X	
Flourescent dye injection		X
Pathology review		X
Adverse Event Assessment		X

11. RISKS AND TOXICITIES TO BE MONITORED

Potential Toxicities, Risks and Precautions

a. G.I. Nausea can occur in up to 10% of patients however vomiting is uncommon and abdominal pain is rare.

b. Nervous system. Syncope has been reported between 1 and 10% of patients. There have been very rare reports of convulsions.

c. Allergic reaction. Hypersensitivity reactions can occur after injection and may be as severe as anaphylaxis. Fatal anaphylactic reaction is reported in 1 of 220,000 angiographies.

d. Skin. Urticaria and pruitis can frequently occur after injection.

The above side effects will be unlikely to occur given that the injection is done while the patient is under general anesthesia. If there is any evidence of hypersensitivity, the anesthesiologists can utilize antihistamine agents to reduce the duration and severity of the hypersensitivity.

Benefits

There will be no direct benefit to the patient for participation in this study. However, this study may help to identify a less expensive and more rapid method of detecting the extent of endometrial cancer invasion at the time of staging. This could be a benefit in the future for determining which women require lymphadenectomy in which do not.

12. DATA HANDLING AND RECORD KEEPING

a. Registration Procedures: After consent has occurred and eligibility criteria has been completed, subjects must be registered with the CCTO before enrollment to the study. Patients are registered by the Research staff calling the CCTO Office Monday through Friday, 8:00 AM - 4:30 PM. Prior to registration, eligibility criteria must be confirmed by the research staff.

b. Confidentiality and De-Identification of Data: Upon registration, the subject will be assigned a unique identifying code or number to which the subject will be identied by. All subject related materials will be identified by that subject's unique identifying code or number. Only the Research staff will have access to the code/number and information that identifies the subject in this study.

c. Methods for Data Collection and Data Collection Tools: Data will be entered into OpenClinica through electronic web-based case report forms (CRFs). OpenClinica is a secure open source system for electronic data capture and clinical data management. Data will be stored electronically on encrypted computers. Data collection from this study will be limited to the pathologic findings at the time of endometrial cancer staging.

d. Storage of Study Related Items : This study's documents will be retained for a minimum of three years after study completion.

13. SPECIMEN STORAGE AND DISPOSAL

Solid tissues will be embedded into paraffin and are stored at room temperature as part of standard pathology evaluation. There will not be a study-specific specimen retained. Photographs of the stained endometrial cancer and myometrium will be retained for purposes of comparison in this study.

14. STATISTICAL CONSIDERATIONS

a. Sample Size and Study Duration: 100 subjects will be entered into this pilot study. It is estimated that this study will be completed in less than one year.

b. Study Endpoints: Invasion depth as determined using each of three methods: Systemic Fluorescein Injection (SFI), Frozen Section (FS), and Permanent Section (PS).

c. Data Analysis Plan: The primary objective is basically to determine whether the SFI method works. Provided that it works, the analysis plan in support of the Secondary Objective is as follows: For each study subject, the paired difference in invasion depths determined using the SFI versus FS methods will be calculated and expressed as a percentage of the FS-based invasion depth. Likewise, the paired difference in invasion depths determined using the SFI versus PS methods will be calculated and expressed as a percentage of the PS-based invasion depth. Each type of paired difference will be summarized as the mean and standard deviation. Because PS is considered the definitive "gold standard" of determining invasion depth, the mean of the paired differences between SFI and PS methods will be compared against equivalence limits of –25% and +25% via theTwo One-Sided Tests (TOST) procedure using an alpha=0.10 significance level. If this mean is significantly "in between" both equivalence limits, then this will indicate that the discrepancy in invasion depths between SFI and PS is significantly less than 25%, and we will accordingly consider further investigation of the SFI method of determining invasion depth.

Sample Size and Power: When two methods are equivalent, the mean of their paired difference will be 0%. The power of the TOST procedure to declare that a mean of 0% is significantly "in between" equivalence limits of –25% and +25% depends heavily on the standard deviation of the paired difference when the sample size is fixed at 20 subjects. A simulation study using 1,000,000 simulations in PASS 12 software indicates that 20 subjects gives the TOST procedure >90% power at 10% alpha to declare a mean of 0% to be significantly "in between" the above-stated equivalence limits provided that the standard deviation of the paired differences is less than 37%. This power calculation shows that, if SFI agrees well with PS, then 20 subjects should provide our study with sufficient power to demonstrate that fact.

d. Missing, Unused and Spurious Data: Missing data will be treated as missing, and will not be imputed. Spurious data will be corrected at the source document. Any data documented as spurious that is unable to be corrected at the source will be treated as missing.

15. ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with FDA regulations for the conduct and monitoring of clinical investigations. The following also represents sound research practice. All study personnel must have completed training in good clinical practice (GCP) and protection of human subjects.

a. Recruitment and Informed Consent: Patients with endometrial cancer will be identified in the UAMS gynecologic cancer clinic during routine clinic appointments by their providers. Upon identification, the patient will be informed of the study by their physician along with the research staff. The patient will be allowed to review the IRB-approved informed consent form, and if they would like to participate in the study, they will be presented the informed consent form. During the consent process, the patient will be clearly informed of the fact that participation in this study is voluntary and that the decision to not participate in the study will have no effect on future clinical care. The patient will be encouraged to have family or

friends participate in any or all of the process. The patient will be provided sufficient time to ask questions, and will be questioned to be ensure they understand the information. If the patient agrees to proceed, they will sign consent. The consent process will be documented in the medical record. A copy of the informed consent document will be given to the research paricipant, and additional copies will be sent to the medical records department. The original informed consent will be filed with the subject file in CCTO. The principles of informed consent are described by the Federal Regulatory Guidelines: Code of Federal Regulations (*21CFR50*) and the Office for Human Research Protections: Protection of Human Subjects (*45CFR46*). These principles must be followed to comply with Food and Drug Administration (FDA) regulations for the conduct and monitoring of clinical investigations.

b. Institutional Review: This study will be approved by the UAMS Institutional Review Board (IRB) as defined by Federal Regulatory Guidelines *21CFR56* and the Office for Human Research Protections: Protection of Human Subjects *45CFR46*. This study will also undergo scientific review by the Cancer Institute's Protocol Review and Monitoring Committee (PRMC). Approval by both the IRB and PRMC is required before the clinical trial can be activated.

c. Investigational Agent Accountability: Fluroescein for this study will be stored in the main inpatient pharmacy and will be ordered from there and sent to the operating room pharmacy for pick up. Fluorescein dye will be purchased by Pharmacy for this study, and the Division of Gynecologic Oncology will reimburse pharmacy as subjects complete the study.

16. ADVERSE EVENTS

a. Expedited Reporting:

- The Principal Investigator (PI) must be notified within 24 hours of learning of any serious adverse events (SAEs), regardless of attribution, occurring during the study.
- The UAMS IRB must be notified within 10 business days of "any unanticipated problem involving risk to subject or others (UPR/UPIRTSO)."
- For UPR/UPIRTSO, see UAMS IRB Policy 10.2.

b. Routine Reporting: All other AEs, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported annually as part of regular data submission.

17. MONITORING

a. Medical Monitor: The Medical Monitor, Principal Investigator and study staff will meet quarterly, once the PI has monitored the data, to review safety data (adverse events, serious adverse events and other scientific observations).

b. Data Monitor: The study will be monitored by the Principal Investigator to ensure that the rights and well-being of human subjects are protected, that the data are accurate, complete

and verifiable from source documents and that the trial is conducted in compliance with currently approved protocol/amendments.

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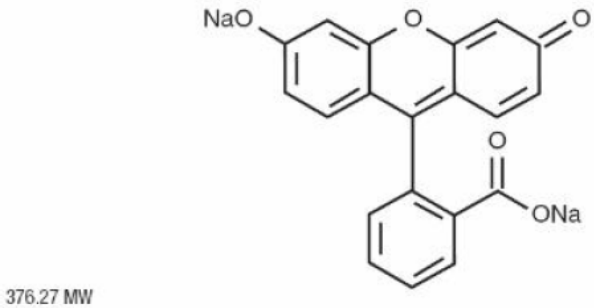
APPENDIX I

FLUORESCITE - fluorescein sodium injection, solution
Alcon, Inc.

DESCRIPTION

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:



376.27 MW

FLUORESCITE® (fluorescein injection, USP) 10% is supplied as a sterile, unpreserved, single-use aqueous solution, that has a pH of 8.0 - 9.8 and an osmolality of 572-858 mOsm/kg.
Active ingredient: fluorescein sodium
Inactive Ingredients
Sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection.

CLINICAL PHARMACOLOGY

Mechanism of Action
Fluorescein sodium responds to electromagnetic radiation and light between the wavelengths of 465-490 nm and fluoresces, i.e., emits light at wavelengths of 520-530 nm. Thus, 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 by the camera. In the fundus, the fluorescence of the dye demarcates the retinal and/or choroidal vasculature under observation, distinguishing it from adjacent areas/structures.

Pharmacokinetics
Distribution:
Within 7 to 14 seconds after IV administration into antecubital vein, fluorescein usually 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).
Metabolism:
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.
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 500 mg fluorescein.

INDICATIONS AND USAGE:

FLUORESCITE® (fluorescein injection, USP) 10% is indicated in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

CONTRAINDICATIONS

FLUORESCITE® (fluorescein injection, USP) 10% is contraindicated in patients with known hypersensitivity to fluorescein sodium or any other ingredients in this product.

WARNINGS

FOR INTRAVENOUS USE

Care must be taken to avoid extravasation during injection as the high pH of fluorescein solution can result in severe 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. Rare cases of death due to anaphylaxis have been reported (See PRECAUTIONS).

PRECAUTIONS

General

Caution is to be exercised in patients with a history of allergy or bronchial asthma. An emergency tray should be available in the event of possible reaction to **FLUORESCITE®** (fluorescein injection, USP) 10%. Use only if the container is undamaged.

Information for Patients

Skin will attain a temporary yellowish discoloration. Urine attains a bright yellow color. Discoloration of the skin usually fades in 6 to 12 hours and usually fades in urine in 24 to 36 hours.

Laboratory Information

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been no long-term studies done using fluorescein in animals to evaluate carcinogenic potential.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Adequate animal reproduction studies have not been conducted with fluorescein sodium. It is also not known whether fluorescein sodium can cause fetal harm when administered to a pregnant woman. Fluorescein sodium should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Fluorescein sodium has been demonstrated to be excreted in human milk. Caution should be exercised when fluorescein sodium is administered to a nursing woman.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have been established.

GERIATRIC USE

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS (SEE WARNINGS AND PRECAUTIONS)

Nausea, vomiting, gastrointestinal distress, headache, syncope, hypotension, and symptoms and signs of hypersensitivity have occurred. Cardiac arrest, basilar artery ischemia, severe shock, convulsions, thrombophlebitis at the injection site, and rare cases of death have been reported. Extravasation of the solution at the injection site causes intense pain at the site and a dull aching pain in the injected arm (see WARNINGS). Generalized hives and itching, bronchospasm and anaphylaxis have been reported. A strong taste may develop after injection.

DOSAGE 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).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not mix or dilute with other solutions or drugs. Flush intravenous cannulas before and after drugs are injected to avoid physical incompatibility reactions.

Inject the dose rapidly (1 mL per second is normally recommended) into the antecubital vein, after taking precautions to avoid extravasation. A syringe, filled with **FLUORESCITE®** (fluorescein injection, USP) 10%, may be attached to transparent tubing and a 23 gauge butterfly needle for injection. Insert the needle and draw the patient's blood to the hub of the syringe so that a small air bubble separates the patient's blood in the tubing from the fluorescein. With the room lights on, slowly inject the blood back into the

vein while watching the skin over the needle tip. If the needle has extravasated, the patient's blood will be seen to bulge the skin and the injection should be stopped before any fluorescein is injected. When assured that extravasation has not occurred, the room light may be turned off and the fluorescein injection completed. Luminescence usually appears in the retina and choroidal vessels in 7 to 14 seconds and can be observed by standard viewing equipment.
Reduction in dose from 5 ml to 2 ml of **FLUORESCITE®** (fluorescein injection, USP) 10% may be appropriate in cases when a highly sensitive imaging system e.g., scanning laser ophthalmoscope is used.

HOW SUPPLIED
FLUORESCITE® (fluorescein injection, USP) 10% is supplied in a single-use 5 mL glass vial with a gray FluroTec coated chlorobutyl (latex free) stopper and purple flip-off aluminum seal. It contains a sterile, red-orange solution of fluorescein sodium.
NDC 0065-0092-65
Storage
Store at 2°- 25°C (36°- 77°F).
Do Not Freeze
Rx Only
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA
Printed in USA

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PRINCIPAL DISPLAY PANEL
NDC 0065-0092-65 1 Dozen 5 mL Vials
Fluorescite® 10%
(fluorescein injection, USP) 10%
STERILE
100 mg/ml Fluorescein
Rx Only
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Store at 2° - 25° C (36° - 77°F)
Do Not Freeze

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