

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-980**

**CHEMISTRY REVIEW(S)**

**NDA 21-980**

**FLUORESCITE (fluorescein injection, USP) 10%**

**Alcon, Inc.**

Appears This Way  
On Original

**Lin Qi, Ph.D.**  
**CDER-ONDQA-DPA-BRANCH IV**



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# Chemistry Review Data Sheet

1. NDA 21-980
2. REVIEW #: 1
3. REVIEW DATE: February 15, 2005
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

Sep 29, 2005

Amendment

Jan 17, 2006

Amendment

Jan 30, 2006

Amendment

Feb 15, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Alcon, Inc.

Address: P.O. Box 62  
Bosch 69  
CH-6331, Hunenberg  
Switzerland

Representative: Alcon Research, Ltd.  
6201 South Freeway  
Fort Worth, Texas 76134-2099

Telephone: 817-551-4325



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: FLUORESCITE
- b) Non-Proprietary Name (USAN): Fluorescein Injection
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: V & VII
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Filed under 505 (b)(2) of the Federal Food, Drug and Cosmetic Act

10. PHARMACOL. CATEGORY: Diagnostic aid for corneal trauma and ophthalmic angiography

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10% (w/v)/Normal adult dose is 500mg (100 mg/mL)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

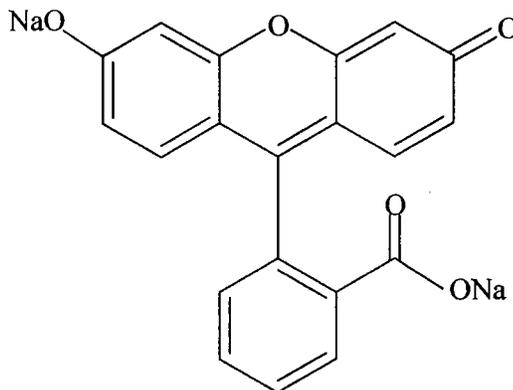
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: Spiro[isobenzofuran-1(3H), 9'-[9H]xanthene]-3-one, 3', 6'-dihydroxy, disodium salt

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

Structural formula:



376.27 MW

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------|
|       |      |        |                 |                   | Adequate            | 2/13/2006             |          |
|       |      |        |                 |                   | Adequate            | 11/03/2000            |          |
|       |      |        |                 |                   | Adequate            |                       |          |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| None     |                    |             |
|          |                    |             |
|          |                    |             |
|          |                    |             |

### 18. STATUS:

#### ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                                  | DATE    | REVIEWER       |
|-------------------------------|---|---------|----------------|
| Biometrics                    |   |         |                |
| EES                           | Acceptable<br>Alcon: Acceptable<br>IMS: Pending | 2/15/06 |                |
| Pharm/Tox                     |   |         |                |
| Biopharm                      |   |         |                |
| LNC                           |   |         |                |
| Methods Validation            |   |         |                |
| OPDRA                         |   |         |                |
| EA                            | Categorical Exclusion<br>Claimed                | 2/15/06 | Qi, Lin        |
| Microbiology                  | Pending   | 2/15/06 | Pawar, Vinayak |

# The Chemistry Review for NDA 21-980

## The Executive Summary

### I. Recommendations

- A. Recommendation and Conclusion on Approvability:** From the chemistry, manufacturing, and controls' perspective, this application is recommended for approval pending acceptable establishment evaluation results and acceptable findings in the microbiology review.
- B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:** None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, fluorescein, is a yellowish red powder insoluble in water and soluble in dilute alkali hydroxides. The drug substance is manufactured by \_\_\_\_\_  
The manufacturing procedure, process controls, release specification, batch analysis, container closure system and stability studies of the drug substance are provided in \_\_\_\_\_. In addition, the applicant provided additional information on the drug substance quality control. The applicant performed spectral studies \_\_\_\_\_, solid state studies \_\_\_\_\_, and physicochemical studies to establish the properties of fluorescein. The applicant also identified \_\_\_\_\_ fluorescein related substances. Based on their recent experience, \_\_\_\_\_ of these impurities have a higher potential of being present in fluorescein drug substance and are controlled in the drug substance acceptance specification. These are \_\_\_\_\_ and impurities \_\_\_\_\_ and \_\_\_\_\_. Based on the available stability results, the applicant proposed an initial \_\_\_\_\_ retest period for fluorescein.

Although Alcon has marketed 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 \_\_\_\_\_) was used in the current application. FLUORESCITE Injection, 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

## CHEMISTRY REVIEW

### Executive Summary Section

used to: \_\_\_\_\_ FLUORESCITE  
Injection, 10% is filled in 5 mL \_\_\_\_\_ clear molded glass vials with \_\_\_\_\_ grey  
chlorobutyl stoppers and \_\_\_\_\_ flip-off aluminum seals. \_\_\_\_\_  
\_\_\_\_\_ The proposed shelf-life of  
the drug product is: \_\_\_\_\_

#### **B. Description of How the Drug Product is Intended to be Used**

FLUORESCITE Injection, 10% contains fluorescein sodium (equivalent to fluorescein 10%) and is a sterile aqueous solution for use intravenously as diagnostic aid. It is indicated in diagnostic fluorescein angiography or angiography of the retina and iris vasculature. When administered intravenously, the yellowish-green fluorescence of the drug demarcates the vascular area under observation, distinguishing it from adjacent areas. Skin will attain a temporary yellowish discoloration. Urine will attain a bright yellow color. Discoloration of the skin will fade in 6 to 12 hours and discoloration in urine will fade in 24 to 36 hours.

#### **C. Basis for Approvability Recommendation**

Although the drug substance is manufactured by \_\_\_\_\_, 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 applicant responded to all comments appropriately during the review cycle.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

ChemistName/Date: Lin Qi, 2/15/06  
BranchChiefName/Date: Norman Schmuff, 2/15/06  
ProjectManagerName/Date

#### **C. CC Block**

54 Page(s) Withheld

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Deliberative Process

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/s/

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2/16/2006 02:03:47 PM  
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