**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Fluorescein 100 mg/ml Solution for injection
Fluorescein sodium
PA2273/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Fluorescein 100 mg/ml solution for injection, from Pharmargus Limited *for diagnostic use only. For fluorescein angiography of the ocular fundus.*

Fluorescein 100 mg/ml solution for injection was first authorised in Ireland on 27th August 2021 through a new national application for marketing authorisation, submitted in accordance with Article 10 (1) of Directive 2001/83/EC, a generic application. Following on from this, the HPRA acted as RMS for a mutual recognition procedure, IE/H/1215/MR, with Germany was a CMS. This MRP was completed 23rd November 2022.

The reference product cited in this application is Fluorescein Alcon 100 mg/ml solution for injection from Alcon Pharma GmbH (marketing authorisation number 6375757.00.00) first authorised in Germany on 11 March 2005, and thereafter by mutual recognition procedure (DE/H/0746/001; concluded 17 January 2007) in Czech Republic, Estonia, Lithuania, Poland and the Slovak Republic. Similar products are authorised in a number of other European member states. Fluorescein 100 mg/ml solution for injection has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as the reference product.

This product is for diagnostic use. It is subject to a prescription which may not be renewed, supplied through pharmacies only, with a condition of licence that it is subject to restricted medical prescription in that Fluorescein 100 mg/ml solution for injection should be used exclusively by qualified physicians with technical expertise in performing and interpreting fluorescence angiography (see Summary of Product Characteristics, section 4.2).

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

| | |
|---|---|
| Name of the product | Fluorescein 100 mg/ml Solution for injection |
| Name(s) of the active substance(s) (INN) | Fluorescein sodium |
| Pharmacotherapeutic classification (ATC code) | S01JA01- fluorescein |
| Pharmaceutical form and strength(s) | Solution for injection/100 milligrams/millilitre |
| Marketing Authorisation Number(s) in Ireland (PA) | PA2273/001/001 |
| Marketing Authorisation Holder | Pharmargus Limited |
| MRP/DCP No. | IE/H/1215/MR |
| Reference Member State | IE |
| Concerned Member State | DE |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Fluorescein 100 mg/ml Solution for injection of finished product.

### II.2 Drug substance

The active substance is Fluorescein sodium , an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

P.1 Composition

*1 ml solution contains 100 mg fluorescein (as 113.2 mg fluorescein sodium)*
*One 5 ml vial contains 500 mg fluorescein (as 566 mg fluorescein sodium)*

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Fluorescein 100 mg/ml Solution for injection

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance is a generic formulation of Fluorescein Alcon 100 mg/ml solution for injection from Alcon Pharma GmbH (marketing authorisation number 6375757.00.00) on the European market since first authorised in Germany on 11 March 2005. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

**III.2 Ecotoxicity/environmental risk assessment**

The applicant has not provided a full environmental risk assessment (ERA) in accordance with the guideline (CHMP/SWP/4447/00). Instead justification for the absence of a full ERA is supplied. Since Fluorescein 100 mg/ml solution for injection is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of fluorescein sodium are well known. As fluorescein sodium is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Fluorescein sodium is a well-known active substance with established efficacy and tolerability. The content of SmPC approved during the MR procedure is in accordance with that accepted for the reference product Fluorescein Alcon 100 mg/ml solution for injection marketed by the marketing authorisation holder Alcon Pharma GmbH.

For this generic application for Fluorescein 100 mg/ml solution for injection the applicant has not submitted a bioequivalence study and, in accordance with the EMA's 'Guideline on the investigation of bioequivalence' (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 Jan 2010), such studies are not required.

### IV.2 Pharmacokinetics

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

Biotransformation:
Fluorescein undergoes rapid metabolism to fluorescein monoglucuronide. After intravenous 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 intravenous 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 is essentially complete by 48 to 72 hours after administration of 500 mg fluorescein. Although a longer excretion rate in patients with renal impairment is possible, limited experience in renally impaired subjects (glomerular filtration rate below 20 ml/min) suggests that, in general, no dose adjustment is required.

### IV.3 Pharmacodynamics

Fluorescein is a fluorochrome used in medicine as a diagnostic stain. Fluorescein is used to make the blood vessels of the ocular fundus visible (angiography of the retina and choroid).

### IV.4 Clinical Efficacy

As this is a generic application no new clinical efficacy studies have been submitted. Efficacy is expected to be similar to the reference product Fluorescein Alcon 100 mg/ml solution for injection marketed by Alcon Pharma GmbH.

### IV.5 Clinical Safety

As this is a generic application no new clinical safety studies have been submitted. Safety is expected to be similar to the reference product Fluorescein Alcon 100 mg/ml solution for injection marketed by Alcon Pharma GmbH.

Risk Management Plan

The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fluorescein 100 mg/ml Solution for injection.
Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

Summary of safety concerns

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

**Periodic Safety Update Report (PSUR)**

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

## IV.6 Discussion on the clinical aspects

Fluorescein sodium is a well-known substance and has been widely marketed. As this is a generic application the need for repetitive tests on humans has been avoided and no new efficacy or safety clinical studies have been submitted. Efficacy and safety is expected to be similar to the reference product Fluorescein Alcon 100 mg/ml solution for injection marketed by Alcon Pharma GmbH.

Post marketing authorisation data has been submitted by the applicant on account of Pharmargus Limited's marketing authorisation for FLUOSINE 500MG/5 ML VIAL CONTAINING SOLUTION FOR I.V. INJECTION in Turkey.

The product information, SmPC and patient leaflet, are identical to those of the reference product.

## V. OVERALL CONCLUSIONS

Fluorescein100 mg/ml solution is a generic form of Fluorescein Alcon 100 mg/ml solution for injection marketed by Alcon Pharma GmbH. Fluorescein Alcon 100 mg/ml solution for injection marketed by Alcon Pharma GmbH is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The marketing authorisation holder (MAH) has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Fluorescein 100 mg/ml solution for injection is equivalent with the reference product and has a satisfactory risk/benefit profile, and therefore granted a marketing authorisation.

## VI. REVISION DATE

27 August 2026