Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluorescein 100 mg/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE 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)

Excipient with known effect:
Sodium (as fluorescein sodium and sodium hydroxide) 3.15 mmol dose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, red-orange solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
For fluorescein angiography of the ocular fundus.

4.2 Posology and method of administration

Adults, including elderly:
Inject 5 ml of Fluorescein 100 mg/ml Solution for injection rapidly into the antecubital vein after taking precautions to avoid extravasation. In cases when highly sensitive imaging systems e.g., scanning laser ophthalmoscope are used, the dose of this product should be reduced to 2 ml of Fluorescein 100 mg/ml solution for injection.

Paediatric population:
Fluorescein 100 mg/ml Solution for injection has not been studied in children and dose-adaptation data are not available. Therefore, Fluorescein 100 mg/ml Solution for injection should not be used in patients below 18 years as efficacy and safety in this group have not been established.

Patients with renal insufficiency (glomerular filtration rate below 20ml/min):
Limited experience in renally impaired subjects (glomerular filtration rate below 20 ml/min) suggests that, in general, no dose adjustment is required although a longer excretion rate in patients with renal impairment is possible (see section 5.2).
Dialysed patients: Reduce dose to 2.5 ml (half a vial).

Method of administration and fluorescence angiography

Fluorescein 100 mg/ml solution for injection should be used exclusively by qualified physicians with technical expertise in performing and interpreting fluorescence angiography.

This product should only be administered intravenously.

Flush intravenous cannulas with sterile sodium chloride solution (0.9%) before and after medicinal products are injected to avoid physical incompatibility reactions. The injection should be administered rapidly (1 ml per second is normally recommended) into the antecubital vein, after taking precautions to avoid extravasation using a 23-gauge butterfly needle for injection. Luminescence usually appears in the retina and choroidal vessels in 7 to 14 seconds.

For further instructions on the correct administration/use of this medicinal product, see sections 6.2 and 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Fluorescein 100 mg/ml Solution for injection should not be injected intrathecally or intra-arterially.

4.4 Special warnings and precautions for use

Fluorescein sodium can induce serious intolerance reactions.

In the event of serious intolerance reactions during a first angiography, the benefit of an additional fluorescein angiography should be balanced with the risk of severe hypersensitivity reactions (with fatal outcome in some cases).

These reactions of intolerance are always unpredictable but they are more frequent in patients who have previously experienced an adverse reaction after fluorescein injection (symptoms other than nausea and vomiting), in patients with history of allergy such as food or drug induced urticaria, asthma, eczema, allergic rhinitis or in patients with history of bronchial asthma.

Intradermal skin tests are not reliable in predicting these intolerance reactions and so their use can be dangerous. A specialized allergy consultation should be undertaken to make this diagnosis.

The benefit to risk of the angiography procedure should be considered in patients with pre-existing conditions such as cardiovascular disease, diabetes mellitus, and multiple concomitant drug therapies (in particular beta-blockers, see section 4.5).

Any pre-existing systemic condition(s) impacting renal function could pose additional risk to the subject. The physician must exercise medical judgement based on increased serum creatinine, patient's age, medical history, and current health status to determine potential risk vs benefit prior to use of Fluorescein.

Literature suggests Fluorescein Angiography (FA) may cause contrast-induced Nephropathy (CIN) based on increased serum creatinine. CIN is a possible risk factor for end-stage renal disease progression.

Detailed questioning of each patient must be carried out before the angiography to search for any history of cardiopulmonary disease or allergy or concomitant medications (such as beta- blocking agents, including eye-drops solutions) (see section 4.5). If the examination appears to be really necessary for a patient identified as being at risk of hypersensitivity reactions and for a patient treated with beta-blocking agents (including eye-drops solutions), this examination should be performed under the supervision of a physician experienced in intensive care (resuscitation). Beta-blocking agents could reduce the vascular compensation reactions to anaphylactic shock and reduce the effectiveness of adrenaline in the case of cardiovascular collapse. Before any fluorescein sodium injection, the physician should seek information about concomitant treatment with a beta-blocking agent.

Premedication can be undertaken. However, the risk of occurrence of severe adverse drug reactions still remains. Premedication includes mainly oral antihistaminic H1 drugs, followed by corticosteroids, before injection of fluorescein. Given the low incidence of these adverse reactions, such pre- medication is not recommended for all patients.

The risk of hypersensitivity reactions with fluorescein sodium requires:

- Close monitoring of the patient by the ophthalmologist performing the examination, throughout the examination and for at least 30 minutes after;
- Maintaining the infusion line for at least 5 minutes, to treat a possible severe adverse reaction without delay;
- To have at one's disposal appropriate material for emergency resuscitation which is based at first on the installation of a 2nd intravenous line, allowing the restoration of the plasma volume (aqueous solution polyionic or colloidal substitute of plasma) and the intravenous injection of adrenaline at the recommended dosage (see section 4.5).

Note:

Extravasation should be avoided due to the high pH of fluorescein solution which can result in severe local tissue damage (severe pain in the arm for several hours, sloughing of the skin; superficial phlebitis). The correct intravenous position of the

needle tip must be ascertained. When extravasation occurs, the injection should be immediately discontinued. Appropriate measures must be taken to treat damaged tissue and to relieve pain.

If an X-ray procedure is conducted within 36 hours of injection (maximum duration of fluorescein elimination from the body), the resultant high visibility of the excretory organs in the X-ray image may lead to misinterpretation.

This medicinal product contains 72.45mg sodium per 5ml unit, equivalent to 3.62% of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Fluorescein is a relatively inert dye and specific drug interaction studies have not been reported. There are few case reports on potential interactions with organic anion transporters and interference with certain laboratory tests. It is possible that fluorescein may influence certain blood and urine values for 3 to 4 days after application. Caution is advised when performing therapeutic drug monitoring for drugs with a narrow therapeutic window, e.g. digoxin, quinidine. Compounds that inhibit or compete with the active transport of organic anions (e.g. probenecid) may affect the systemic profile of fluorescein.

The concomitant use of Fluorescein 100 mg/ml Solution for injection with beta- blocking agents (including eye-drops solutions) may rarely provoke severe anaphylactic reactions.

Beta-blocking agents could reduce the vascular compensation reactions to anaphylactic shock and also reduce the effectiveness of adrenaline in the presence of cardiovascular collapse that may require intensive pharmacologic therapy and even resuscitative measures (see section 4.4).

Concomitant intravenous injection of other solutions or the mixing of Fluorescein 100 mg/ml Solution for injection with other solutions should be avoided as the possibility of interactions cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data available concerning the use of Fluorescein 100 mg/ml Solution for injection in pregnancy. Animal studies do not indicate teratogenic effects (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Fluorescein 100 mg/ml Solution for Injection during pregnancy.

Breast-feeding
Fluorescein sodium is excreted in human milk following systemic administration for up to 7 days. A risk to the suckling child cannot be excluded. Following fluorescein angiography, breast-feeding should therefore be discontinued for 7days and the milk should be pumped off and discarded during this period.

Fertility
Studies have not been performed to evaluate the effect of intravenous administration of fluorescein on fertility.

4.7 Effects on ability to drive and use machines

If mydriasis is necessary for the examination with fluorescence angiography visual acuity is influenced and thus affects the ability to react in traffic or use machinery. The patient must be made aware that after application and until visual acuity returns to normal, driving a vehicle or operating dangerous machinery is prohibited.

4.8 Undesirable effects

Summary of safety profile
The most frequently reported treatment related undesirable effects were nausea, vomiting, syncope and pruritus. Less frequent but more severe adverse reactions have been reported shortly after fluorescein injection such as: angioedema, respiratory disorders (bronchospasm, laryngeal oedema, and respiratory failure), anaphylactic shock, hypotension, loss of consciousness, convulsion, respiratory arrest, and cardiac arrest.

Tabulated list of adverse reactions

The following adverse reactions were assessed to be treatment-related and are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Term (v.16.0)**
Immune system disorders	*Uncommon*: hypersensitivity *Rare*: anaphylactic reaction *Very Rare*: anaphylactic shock
Nervous system disorders	*Common:* syncope *Uncommon*: dysphasia, paraesthesia, dizziness, headache *Very Rare*: convulsion *Not Known*: cerebrovascular accident, vertebrobasilar insufficiency, loss of consciousness, tremor, hypoesthesia, dysgeusia
Cardiac disorders	*Rare*: cardiac arrest *Very Rare*: angina pectoris, bradycardia, tachycardia *Not Known:* myocardial infarction
Vascular disorders	*Uncommon*: thrombophlebitis *Rare*: hypotension, shock *Very Rare*: hypertension, vasospasm, vasodilatation, pallor, hot flush
Respiratory, thoracic and mediastinal disorders	*Uncommon:* cough, throat tightness *Rare:* bronchospasm *Very Rare*: respiratory arrest, pulmonary oedema, asthma, laryngeal oedema, dyspnoea, sneezing, nasal oedema *Not Known:* throat irritation
Gastrointestinal disorders	*Very Common*: nausea *Common:* abdominal discomfort, vomiting *Uncommon*: abdominal pain *Not Known*: retching
Skin and subcutaneous tissue disorders	*Common*: pruritus *Uncommon*: urticaria *Not Known:* rash, cold sweat, eczema, erythema, hyperhidrosis, skin discolouration
General disorders and administration site conditions	*Common:* extravasation *Uncommon:* pain, feeling hot *Not Known*: chest pain, oedema, malaise, asthenia, chills

Description of selected adverse reactions

A yellowish discolouration of the skin could appear but usually disappears within 6 to 12 hours. Urine, which may also exhibit a bright yellow colouration, returns to its normal colour after 24 to 36 hours.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

No toxic effects are expected given the minimal risk of overdose with Fluorescein 100 mg/ml solution for injection.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: DIAGNOSTIC AGENTS, Colouring agents ATC code: S01JA01
Fluorescein sodium 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

5.2 Pharmacokinetic properties

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.

Elimination:
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.

5.3 Preclinical safety data

Non-clinical data for sodium fluorescein reveal no special hazard for humans based on studies of single dose toxicity.

Fluorescein did not show teratogenic effects in rats and rabbits. Fluorescein crosses the placental barrier. After the intravenous application of 500 mg/kg intense fluorescence was detectable both in the fetus and the amniotic fluid.

Studies on mutagenicity did not show any mutagenic effects of fluorescein sodium.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

To avoid physical incompatibilities, this product must not be administered simultaneously with other solutions for injection with acid pH (especially antihistamines) by the same intravenous route (see section 4.2 for information about cannulas).

6.3 Shelf life

Before opening: 5 years
After opening, the vial must be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not refrigerate or freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Glass (type I) vial with grey bromobutyl coated rubber stopper and aluminium seal with polypropylene flip-off cap.

Pack containing 1 vial or 12 vials of 5 ml injection solution.

6.6 Special precautions for disposal

The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles. .
For single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.
Do not use Fluorescein 100 mg/ml Solution for Injection if the vial is cracked or damaged in any way.

7 MARKETING AUTHORISATION HOLDER

Pharmargus Limited
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30 Upper Pembroke Street
Dublin
D02 EK84
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2273/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th August 2021

10 DATE OF REVISION OF THE TEXT

May 2023