1 NAME OF THE MEDICINAL PRODUCT

Fluorescite™ Injection 10%

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

INJECTION

1 mL solution contains 100 mg fluorescein (as 113.2 mg fluorescein sodium)

One vial of 5 mL contains 500 mg fluorescein (as 566 mg fluorescein sodium)

Contains sodium (from fluorescein sodium and sodium hydroxide) at amounts up to 1.45% (approximately 3.15 mmol) per dose.

The active substance is fluorescein.

The other ingredients are sodium hydroxide and / or hydrochloric acid (used to adjust the pH of the solution) and water for injections.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, red-orange solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and Method of Administration

Use in adults, including the elderly:

- Inject 5 mL of Fluorescein 10% 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 10% solution for injection.

Use in paediatric patients:

- For children, the dose should be calculated on the basis of 35 mg for each 10 pounds of body weight (7.7 mg/kg body weight).

Use in patients with renal insufficiency (glomerular filtration rate below 20 mL/min):

- Limited experience in renally impaired patients (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.

- Dialyzed patients: Reduce dose to 2.5 mL (half a vial).

Administration

- Fluorescein 10% 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.
- 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 Fluorescein 10% solution 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.
- 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.
- Any unused product or waste material should be disposed of in accordance with local requirements.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients.

Intrathecal or intra-arterial use.

4.4 Special Warnings and Precautions for Use

Fluorescein sodium can induce serious intolerance reactions. 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. The benefit of the fluorescein angiography should be balanced with the risk of severe hypersensitivity reactions (with fatal outcome in some cases). Intradermal skin tests have limited predictive value for serious intolerance reactions to Fluorescein. Fluorescein intolerance reactions can occur following a negative intradermal skin test.

The benefit to risk of the angiography procedure should also 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). 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 evaluate any prior history of cardiopulmonary disease or allergy or concomitant medications (see Section 4.5).
- The risk of hypersensitivity reactions with fluorescein sodium requires:
    - Fluorescein should only be administered in facilities with personnel trained in resuscitation and with appropriate material and equipment for emergency resuscitation. Patients should be given a second intravenous line, allowing volume therapy and the intravenous injection of adrenaline and other standard resuscitation drugs (see Section 4.5).
    - Close monitoring of the patient by the ophthalmologist performing the examination, throughout the examination, and for at least 30 minutes thereafter;
    - Maintaining the infusion line for at least 5 minutes, to treat a possible severe adverse reaction without delay;
    - In addition, in patients identified as being at risk of hypersensitivity reactions, but in whom a fluorescein angiography is considered to be essential, it is recommended to carry out the procedure with the equipment and personnel trained in emergency resuscitation in the treatment room.
- 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.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

There are few case reports on potential interactions with organic anion transporters and interference with certain laboratory tests. The fluorescence may interfere with the analysis of blood and urinary parameters for a period of 3 to 4 days. 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., probenicid) may affect the systemic profile of fluorescein.

The concomitant use of Fluorescite™ Injection 10% 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.

Concomitant intravenous injection of other solutions or the mixing of Fluorescite™ Injection 10% with other solutions should be avoided as the possibility of interactions cannot be excluded.

4.6 Fertility, Pregnancy, and Lactation

Fertility

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

Pregnancy

There are insufficient data available concerning the use of Fluorescite™ Injection 10% during pregnancy. Studies in animals with fluorescein do not indicate harmful effects with respect to reproductive toxicity following systemic administration.

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 at least 7 days and the milk should be pumped off and discarded during this period.

4.7 Effects on Ability to Drive and Use Machines

The patient must be made aware that after application and until visual acuity returns to normal, driving a vehicle or operating dangerous machinery is not recommended.

4.8 Undesirable Effects

The following adverse reactions have been described with the use of Fluorescite™ Injection 10%. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (v 27.1)
Immune system disorders	anaphylactic shock, anaphylactic reaction, hypersensitivity
Nervous system disorders	cerebrovascular accident, syncope, loss of consciousness, convulsion, paraesthesia, hypoaesthesia, dizziness, headache, dysgeusia
Cardiac disorders	myocardial infarction, cardiac arrest, bradycardia, tachycardia
Vascular disorders	shock, thrombophlebitis, hypotension, hypertension, pallor
Respiratory, thoracic and mediastinal disorders	respiratory arrest, pulmonary oedema, asthma, laryngeal oedema, dyspnoea, cough, throat tightness, throat irritation, sneezing
Gastrointestinal disorders	vomiting, retching, diarrhoea, nausea, abdominal pain
Skin and subcutaneous tissue disorders	rash, cold sweat, erythema, urticaria, pruritus, hyperhidrosis, skin discoloration
General disorders and administration site conditions	chest pain, oedema, pain, malaise, asthenia feeling hot, chills

A yellowish discoloration of the skin could appear following administration, but usually disappears within 6 to 12 hours. Urine, which may also exhibit a bright yellow coloration, returns to its normal color after 24 to 36 hours.

4.9 Overdose

No toxic effects are expected given the minimal risk of overdose with Fluorescite™ Injection 10%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Ophthalmologic Diagnostic 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). 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.

Pediatric population

No overall differences in effectiveness have been observed between pediatric and adult patients when dosed based on the patient's body weight.

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).

Metabolism:

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 subjects with renal impairment (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, genotoxicity, and reproductive function.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium hydroxide and/or 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).

Once opened the vial must be immediately used.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and Contents of Container

Single-use 5 mL glass vial with grey FluroTec coated chlorobutyl (latex free) stopped and purple flip-off aluminum seal.

6.6 Instruction for use and Handling

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 in accordance with local requirements. Do not use Fluorescite 10% Injection if the vial is cracked or damaged in any way.

Date of Revision: <Update to the latest date>

(Alcon Logo)

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