SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorescein Sodium 100 mg/ml, Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 100mg fluorescein sodium (equivalent to 88.3 mg fluorescein anhydrous).

Excipient with known effect:
One 5 mL ampoule contains 2.84 mmol (65.5 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear red solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorescein angiography of the ocular fundus.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

Use in adults (18 years old and over), including the elderly

One 5 ml ampoule of fluorescein sodium 100 mg/ml to be injected intravenously into the antecubital vein after taking precautions to avoid extravasation.

Use in paediatric patients

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

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

There is limited data regarding the use of Fluorescein Sodium 100 mg/ml Solution for Injection in renally impaired patients (glomerular filtration rate below 20ml/min) and indicates, in general, no dose adjustment is required. Patients with renal impairment will exhibit a slower excretion rate (see section 5.2)

In dialysis patients: Reduce the dose to 2.5ml (half an ampoule) as an intravenous injection.

Method of administration and fluorescence angiography

Fluorescein Sodium 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 into the antecubital vein, after taking precautions to avoid extravasation using a 23 gauge butterfly needle for injection (see section 4.4). Luminescence usually appears in the retina and choroidal vessels in 15 to 20 seconds.

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

4.3 Contraindications

Hypersensitivity to fluorescein or to any of the excipients listed in section 6.1.

Fluorescein Sodium 100 mg/ml Solution for Injection should not be injected by the intrathecal or intra-arterial routes.

4.4 Special warnings and precautions for use

Special warning
Hypersensitivity reactions: Fluorescein sodium can trigger severe allergic reactions:

A detailed medical history of each patient must be carried out before examination including any history of allergy, cardiopulmonary disease diabetes mellitus or concomitant treatments (in particular beta-blocking drugs, including those in ophthalmic dosage forms). If the examination appears to be necessary for a patient taking beta-blocking drugs, then the examination should be performed under the supervision of a physician experienced in intensive care and resuscitation. Beta-blocking drugs can 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 check if the patient is treated with beta blocking drugs.

If serious allergic reactions occur during the first angiography, any further requirement for a fluorescein angiography must be carefully considered: the value of the diagnosis must be weighed with the risk of severe hypersensitivity which development is sometimes fatal.

These allergic reactions are most of the time unpredictable but they occur more frequently in patients who have poorly tolerated a previous injection of fluorescein sodium (other than by nausea and vomiting) or in patients who have displayed a history of allergy such as food-induced or iatrogenic urticaria, asthma, eczema, allergic rhinitis or in patients with history of bronchial asthma. These allergic reactions may not be detected by carrying out a specific intradermal skin allergy fluorescein test, whose results are unreliable and sometimes possibly dangerous. A specialised allergy consultation may provide a more precise diagnosis.

Premedication can be administered. However, it does not prevent the occurrence of severe adverse reactions. Premedication can include oral antihistamines, followed by corticosteroids before fluorescein is injected. Given the low percentage of adverse reactions, premedication may not be needed in all patients.

<u>The risk of hypersensitivity reactions to fluorescein sodium means that it is necessary throughout the examination:</u>

- to ensure close patient monitoring by the ophthalmologist carrying out the examination throughout the duration of the examination and for at least 30 minutes following completion of the examination. - to maintain the venous infusion line for at least 5 minutes, in order to treat any severe adverse drug reaction without delay;
- to have available the facilities required for emergency resuscitation, which are based on inserting a second intravenous line, permitting vascular filling (polyionic solution or colloidal plasma substitute) and the intravenous injection of adrenaline at an appropriate dose.

Cardiovascular complications

Severe cardiovascular complications such as chest pain, myocardial infarction and shock have occurred following administration of fluorescein sodium (see Section 4.8).

Extravasation

Due to the alkaline pH of the solution, care must be taken not to inject the fluorescein solution outside the vein as this can result in severe local tissue damage (severe pain in the arm for several hours, sloughing of the skin, superficial phlebitis). It is important to make sure that the needle is inserted properly into the vein before beginning to inject the fluorescein; if the product passes into the surrounding tissues (extravasation), the injection must be stopped immediately.

Laboratory tests

There are few case reports on potential interactions with organic anion transporters (e.g. probenecid) and interference with other diagnostic procedures.

Analytical interference is possible with blood and urine tests, due to the fluorescence, for up to 3 days after the procedure has been conducted.

Special warning

Each 5 ml ampoule of Fluorescein Sodium 100mg/ml Solution for Injection contains 65.5 mg sodium per ampoule, equivalent to 3.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. The amount of sodium should be taken into consideration by patients who are on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Fluorescein sodium 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 (e.g. probenecid).

Concomitant intravenous injections of other solutions, especially those with an acid pH (in particular antihistamines) may induce precipitation of fluorescein because of its alkaline pH. Therefore, concomitant use of, or the mixing of Fluorescein Sodium 100mg/ml Solution for Injection with other solutions should be avoided as the possibility of interactions cannot be excluded (see section 6.2 Incompatibilities).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Fluorescein Sodium 100 mg/ml Solution for Injection during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Animal studies demonstrate that fluorescein crosses the placental barrier (see section 5.3). The use of Fluorescein Sodium 100 mg/ml Solution for Injection should be avoided during pregnancy unless the benefit of the procedure is likely to exceed the risk.

Lactation

Fluorescein sodium is excreted in human milk for up to 7 days. Following fluorescein angiography, breast-feeding should therefore be discontinued for 7 days and the milk should be pumped off and discarded during this period.

Fertility

No human data on the effect of fluorescein on fertility are available. Animal studies have not been performed to evaluate the effect of fluorescein on fertility.

4.7 Effects on ability to drive and use machines

Due to the mydriasis induced by the angiography examination, visual acuity may be reduced and thus affects the patient’s ability to drive or use machinery. Therefore, the patient must be made aware and advised not to drive or operate machinery until visual acuity returns to normal.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The following undesirable effects have been observed to be treatment related and are classified according the convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (≥1/10,000). Within each frequency grouping, undesirable effects are presented by decreasing order of seriousness.

System Organ Classification	MedDRA Preferred Term (PT)	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Very rare
Immune system disorders	Anaphylactic shock, anaphylactic reaction, hypersensitivity	Uncommon
	Anaphylactoid reaction	Rare
Nervous system disorders	Loss of consciousness	Uncommon
	Coma, syncope, seizure, headache, dizziness, paraesthesia, dysgeusia, tremor	Rare
	Hypoaesthesia	Very rare
	Cerebrovascular event, aphasia	Not known
Cardiac disorders	Cardiac arrest, acute myocardial infarction, cardiovascular collapse, bradycardia, tachycardia	Rare
	Angina pectoris,	Very rare
Vascular disorders	Hypotension	Uncommon
	Shock, pallor, hot flush	Rare
	Thrombophlebitis, hypertension	Not known

Respiratory, thoracic and mediastinal disorders	Laryngeal oedema, asthma, dyspnoea, cough, throat irritation, sneezing, bronchospasm	Rare
	Respiratory arrest, pulmonary oedema	Very rare
	Respiratory distress, throat tightness	Not known
Gastrointestinal disorders	Abdominal discomfort	Common
	Vomiting, nausea	Uncommon
	Abdominal pain	Rare
	Salivary hypersecretion	Very rare
	Retching	Not known
Skin and subcutaneous tissue disorders	Rash, erythema, urticaria, pruritus, angioedema	Uncommon
	Dermatitis, hyperhydrosis, skin discolouration[2]	Rare
	Cold sweat	Very rare
Renal and urinary disorders	Chromaturia[3]	Rare
General disorders and administration site conditions	Extravasation, malaise	Uncommon
	Chest pain, oedema, asthenia, feeling hot, chills	Rare
	Infusion site thrombosis[4], pain	Not known

1 Hypersensitivity reactions including rare cases of anaphylactic/anaphylactoid shock which may have fatal outcome
2 A yellowish discoloration of the skin may appear following administration, but usually disappears within 6 to 12 hours.
3 Urine, which may also exhibit a bright yellow colouration, returns to its normal colour after 24 to 36 hours.
4 Extravasation of the solution which causes intense pain and may be followed by tissue necrosis (see Section 4.4 Special warnings and precautions for use

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: – DIAGNOSTIC AGENTS, COLOURING AGENTS

ATC code: S01JA

Fluorescein sodium is a fluorochrome and when exposed to blue light (465 to 490 nm) exhibits yellow-green fluorescence (520 to 530 nm). It is used in medicine as a diagnostic stain. The fluorescence exhibited under certain wavelengths of light makes it possible to detect pathological changes (angiography) in the retinal circulation (ocular fundus).

5.2 Pharmacokinetic properties

Distribution.

After intravenous injection into the antecubital vein, fluorescein is quickly distributed and appears in the retinal tissue within 15 to 20 seconds. It is rapidly distributed and distributes well into the interstitial space (volume of distribution estimated at 0.5 L/Kg). A yellowish discolouration of the skin appears within a few minutes which fades within 6 to 12 hours after dosing.

Approximately 80% of fluorescein is bound to plasma proteins (mainly to albumin), the remainder being the free salt.

Metabolism

After intravenous administration, fluorescein undergoes rapid metabolism to fluorescein monoglucuronide which has also fluorescent properties. Following intravenous administration approximately 80% of flourescein is conjugated within 1 hour. After 4 to 5 hours, almost all plasma fluorescence is due to fluorescein glucuronide.

Excretion

Fluorescein and its metabolites are eliminated in bile and urine, but mainly via renal excretion. Renal clearance of 1.75ml/min/Kg and hepatic clearance (due to conjugation) of 1.50 ml/min/kg have been estimated. Plasma elimination half-lives of fluorescein and fluorescein glucuronide are respectively about 23.5 and 264 minutes. 90% of elimination

occurs within 48 hours and is essentially complete within 72 hours. Fluorescein is detectable in urine for 24 to 36 hours post dose.

Plasma pharmacokinetics of fluorescein is the same with diabetic and non-diabetic patients.

There is limited data regarding the use of Fluorescein Sodium 100 mg/ml Solution for Injection in renally impaired patients (glomerular filtration rate below 20ml/min) and indicates, in general, no dose adjustment is required. Patients with renal impairment will exhibit a slower excretion rate

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Genotoxicity

In vitro and in vivo genotoxicity studies conducted with fluorescein sodium are negative in an Ames' test, in chromosomal aberration tests and in a micronucleus test in mice. In mouse lymphomas tests, in-vitro CHO cells and in-vivo mouse bone-marrow cells sister chromatids exchange tests are positive.

Neither embryotoxic nor teratogenic effects in rats and rabbits have been shown with fluorescein.

Reproductive and development toxicity

At exposures considered sufficiently in excess of the maximum human exposure, fluorescein did not show a teratogenic effect when administered orally to pregnant rats at doses up to 1500 mg/kg/day on days 6 to 19 of gestation, or to pregnant rabbits at doses up to 250 mg/kg/day on days 6 to 27 of gestation. A single intravenous administration of 500 mg/kg sodium fluorescein to pregnant rats or 140 mg to pregnant rabbits did not produce embryotoxic or teratogenic effects. Based on these results, fluorescein appears to have no teratogenic potential.

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.

Not all the conventional studies were conducted using the currently accepted standards for the evaluation of toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (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, Fluorescein Sodium 100mg/ml Solution for Injection should not be administered simultaneously with other solutions for injection, especially those with an acid pH (especially antihistamines) by the same intravenous route.

6.3 Shelf life

Before opening: 3 years.

After opening, the product must be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Glass (type 1 - colourless) 5ml ampoule packed in outer carton of 10 ampoules

6.6 Special precautions for disposal

For single use only. Any unused product or waste material should be disposed of in accordance with local requirements. Do not use Fluorescein Sodium 100mg/ml Solution for Injection if the ampoule is cracked or damaged or if there is any visible particulate matter or discolouration.

After drawing up the solution into a syringe, the solution should be inspected visually again for particulate matter prior to administration. The solution should only be used if the solution is clear and free from particles

Instructions to open the ampoule:

The ampoules are equipped with the OPC (One Point Cut) opening system and must be opened following the below instructions:

- Hold the bottom part of the ampoule between your thumb and index finger of one hand.
- Gently tab the top part of the ampoule with a finger of the other hand to get all liquid into the bottom part.

- Put the other hand on the top of the ampoule positioning the thumb above the coloured point.
- Press with light, even pressure. The ampoule should break with a clean snap.
- Using too much force can cause the ampoule to shatter. If the ampoule shatters or if the opened ampoule contains visible glass particles after opening, discard it and use a new ampoule.

7 MARKETING AUTHORISATION HOLDER

SERB SA
Avenue Louise, 480
1050 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

PL 43956/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/12/2024

10 DATE OF REVISION OF THE TEXT

24/12/2024