SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fluoresceine SERB

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluorescein sodium 10g/100 ml of solution for injection.

One 5 mL ampoule contains 0.5g of fluorescein sodium.

One 5 mL ampoule contains 65.5 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For examination of the retina by fluorescent angiography.

4.2. Posology and method of administration

Posology

One 5-ml ampoule (10%) injected intravenously.

Patients with renal impairment

The limited experience with use of Fluorescein sodium in patients with renal impairment suggests that dose adjustment in these patients is not necessary required (see section 5.2).

Patients with hepatic impairment

No studies have been performed in patients with hepatic Impairment.

Paediatric population

The safety and the efficacy of Fluorescein SERB in children and adolescents below 18 years have not been established. Therefore, Fluorescein SERB should not be used.

Geriatrics (65 years old and over)

Experience in geriatric patients suggests that no dose adjustment is necessary.

Method of administration

Intravenous use.
Fluorescein SERB should not be mixed with other medicinal products (see section 6.2 and section 6.6) and should preferably be injected into the antecubital vein after taking precautions to avoid extravasation (see section 4.4).

4.3. Contraindications

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

Use by intrathecal or arterial routes.

4.4. Special warnings and precautions for use

A detailed medical history of each patient must be carried out before examination including any history of allergy, history of cardiopulmonary disease, diabetes mellitus or concomitant treatments (in particular beta-blocking drugs, including eye drops solutions). Beta-blocking agents can reduce the vascular compensation reactions and reduce the effectiveness of adrenaline in the case of cardiovascular collapse.

Special warnings

Hypersensitivity

Fluorescein sodium may induce severe hypersensitivity reactions.

The benefit of Fluorescein angiography must be carefully weighed against the risk of severe hypersensitivity reactions (sometimes with a fatal outcome).

These hypersensitivity reactions are always unforeseeable, 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 drug-induced urticaria, asthma, eczema, allergic rhinitis; these hypersensitivity 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 is proposed. However, it does not prevent the occurrence of severe accidents:

- premedication mainly includes H1 antihistamines administered orally, followed by corticosteroids before fluorescein injection,
- it is not currently considered necessary to administer the premedication to all patients given the low percentage of accidents.

The risk of hypersensitivity reactions to fluorescein sodium means that throughout the examination:

- fluorescein angiography must be performed only in facilities with staff trained in emergency resuscitation with the appropriate materials and equipment,
- close patient monitoring must be ensured by the ophthalmologist carrying out the examination throughout the duration of the examination and for at least 30 minutes following completion of the examination,
- the venous infusion line must be maintained for at least 5 minutes in order to treat any potential accident without delay,
- the materials required for emergency resuscitation must be available. This involves inserting a second intravenous line to enable vascular filling (polyionic solution or colloidal plasma substitute) and the intravenous injection of adrenaline in 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).

Pre-existing conditions and concomitant treatments

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.

Extravasation:

Due to the alkaline pH of the solution, care must be taken not to inject the fluorescein solution outside the vein. 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

The fluorescence may interfere with the analysis of blood and urinary parameters for a period of 3 to 4 days. Interference of fluorescein with serum concentration determination of digoxin and cortisol has

been reported. Caution is advised when performing therapeutic drug monitoring for drugs with a narrow therapeutic window.

Excipient with known effect

This medicinal product contains 65.5 mg of sodium per ampoule, equivalent to 3.3% of the maximum daily amount recommended by the WHO which is 2 g of sodium per adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

A few cases of potential interactions with organic anion transporters have been described. Compounds that inhibit or compete with active organic anion transport (e.g. probenecid) may affect the systemic profile of fluorescein.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no or limited data on the use of fluorescein sodium in pregnant women. Animal studies do not indicate any direct or indirect harmful effect on reproduction (see section 5.3).

As precautionary measure, it is preferable to avoid the use of fluorescein sodium during pregnancy.

Breast-feeding

Fluorescein sodium is excreted in breast milk. The effect of fluorescein sodium on infants/newborns is unknown.

Breast-feeding should be discontinued for 7 days after treatment with fluorescein sodium. The milk should be pumped off and discarded during this period.

Fertility

No human data on the effect of fluorescein on fertility are available. No animal studies have been performed to evaluate the effects of intravenously-administered 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. Therefore, it should be considered whether it is advisable to drive or operate machines in these circumstances.

4.8. Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are nausea and vomiting.

Less frequent, but more severe adverse reactions have been reported shortly after injection, in particular angioedema, respiratory disorders (bronchospasm, laryngeal oedema, respiratory disorders), anaphylactic shock, hypotension, loss of consciousness, respiratory arrest, and cardiac arrest.

Tabulated list of adverse reactions

The following adverse drug reactions have been described in connection with the use of fluorescein sodium. Frequencies are defined as: 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), or not known (cannot be estimated from the available data).

MedDRA System Organ Class	**MedDRA** Preferred Term (PT)	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Very rare

MedDRA System Organ Class	**MedDRA** Preferred Term (PT)	Frequency
Immune system disorders[1]	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 accident, aphasia	Not known
Cardiac disorders	Cardiac arrest, acute myocardial infarction, circulatory collapse, bradycardia, tachycardia	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 disorder, throat tightness	Not known
Gastrointestinal disorders	Vomiting, nausea	Uncommon
	Abdominal pain	Rare
	Salivary hypersecretion	Very rare
	Retching	Not known
Skin and subcutaneous tissue disorders	Rash, erythema, urticaria, pruritus	Uncommon
	Dermatitis, hyperhidrosis, skin discolouration[2]	Rare
	Cold sweat	Very rare
Renal and urinary ~~tract~~ disorders	Chromaturia[3]	Rare

MedDRA System Organ Class	**MedDRA** Preferred Term (PT)	Frequency
General disorders and administration site conditions	Extravasation[4], malaise	Uncommon
	Chest pain, oedema, asthenia, feeling hot, chills	Rare
	Infusion site thrombosis, 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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form */https://sideeffects.health.gov.il*

4.9. Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: **DIAGNOSTIC AGENTS, COLOURING AGENTS;** ATC code: **S01JA01**.

When exposed to blue light (465-490 nm) fluorescein sodium emits a yellow-green fluorescence (520-530 nm). This fluorescence allows the detection of pathological changes in the retinal circulation.

5.2. Pharmacokinetic properties

Distribution

After intravenous injection, fluorescein is quickly distributed and appears in the retinal tissue within 15-20 seconds.

Approximately 80% of fluorescein is bound to plasmatic proteins (mainly to albumin) and 15 to 17% to erythrocytes.

Biotransformation

After intravenous administration, fluorescein is quickly transformed into fluorescein glucuronide which also has fluorescent properties.

After 4 to 5 hours, almost all plasma fluorescence is due to fluorescein glucuronide.

Plasma pharmacokinetics of fluorescein are the same in diabetic and non-diabetic patients.

Elimination

Fluorescein is excreted in the urine, as unchanged fluorescein glucuronide metabolite, within 24-36 hours after administration. The urine may attain a bright yellow colour during this period.

Plasma elimination half-lives of fluorescein and fluorescein glucuronide are about 23.5 and 264 minutes respectively.

5.3. Preclinical safety data

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

In vitro and *in vivo* genotoxicity studies conducted with fluorescein sodium were negative in Ames test, in the chromosomal aberration test and in the micronucleus test in mice. In the mouse lymphoma assay, sister chromatid exchange test *in vitro* for CHO cells and *in vivo* for mouse bone-marrow cells are positive.

Fluorescein has not shown embryotoxic or teratogenic effects in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium hydroxide, water for injection.

6.2. Incompatibilities

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

Solutions for injections with an acid pH (in particular antihistamines) can induce fluorescein precipitation because of its alkaline pH and should not be injected simultaneously in the same intravenous line. It is recommended to avoid mixing fluorescein with other solutions or using it concomitantly with intravenous solutions. The physico- chemical incompatibility cannot be excluded.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 30ºC

6.5. Nature and contents of container

5 ml ampoule (colorless type I glass)

6.6. Special precautions for disposal and other handling

Check visually if there is any visible particulate matter or discoloration.

Do not mix or dilute with other solutions or medicines into the syringe.

The venous infusion line must be rinsed before and after the injection in order to avoid incompatibility reactions.

Fluoresceine SERB is intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

SERB SAS
40 AVENUE GEORGE V
75008 PARIS
FRANCE

8. MARKETING AUTHORISATION HOLDER

Tradis Gat Ltd.
32 Shacham St.
Petach Tikva.

9. MARKETING AUTHORISATION NUMBER(S)

- 113 59 25293

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