Product Information
FLUORESCEIN SERB™ 500mg/5mL

(fluorescein sodium)

NAME OF THE MEDICINE

Active ingredient: fluorescein sodium

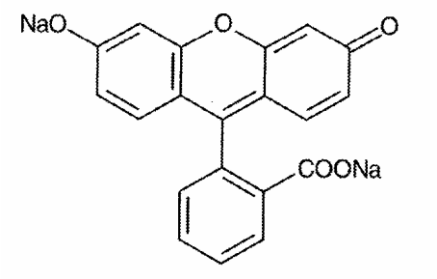
Chemical name: disodium 2-(3-oxo-6-oxido-3*H*-xanthen-9-yl)benzoate

Molecular formula: $C_{20}H_{10}Na_2O_5$

CAS number: 518-47-8

Molecular weight: 376.3

Structural formula:



DESCRIPTION

Fluorescein SERB 500mg/5mL is a sterile solution containing fluorescein sodium for intravenous injection. Each 1.0 mL of solution contains 100 mg fluorescein sodium. One ampoule of 5mL contains 500 mg fluorescein sodium.

Excipients: Sodium hydroxide for pH adjustment, water for injections.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Diagnostic agent, ATC code: SO1JA 01.

Mechanism of action

Fluorescein SERB 500mg/5mL is a diagnostic dye. When fluorescein sodium is stimulated by blue light (465 nm to 490 nm) it shows yellow-green (520 nm to 530 nm) fluorescence. The pattern of fluorescence facilitates diagnosis of pathological changes to the retinal blood circulation.

Pharmacokinetics

Absorption:

After intravenous injection, fluorescein is rapidly distributed throughout the body and appears in the retinal tissues within a few seconds. Intravenous administration of 188mg fluorescein sodium resulted in C_{max} of 10.9μg/mL and AUC 1350μg.min/mL. Fluorescein appears in the central artery of the eye, within 7 to 14 seconds after intravenous administration into the antecubital vein. The mean peak concentration for the 10% fluorescein sodium solution in the retinal artery amounted to 0.5mg/mL.

Distribution:

Fluorescein binds to albumin and red blood cells in a reversible fashion and the binding is moderate (~70-80%) during the first hour. About 15-17% is bound to erythrocytes.

Within a few minutes of intravenous administration of fluorescein sodium, a yellowish discolouration of the skin occurs, which begins to fade after 6 to 12 hours of dosing. Various estimates of volume of distribution indicate that fluorescein distributes well into interstitial space (0.5 to 0.8L/kg).

Metabolism:

Fluorescein undergoes rapid metabolism to fluorescein monoglucuronide. After intravenous administration of fluorescein sodium (14mg/kg) to 7 healthy subjects, approximately 80% of fluorescein in plasma was converted to glucuronide after a period of 1 hour post-dose, indicating relatively rapid conjugation. Fluorescein monoglucuronide is about ⅓ to ¼ as fluorescent as fluorescein, depending on the wavelength of excitation of the blue light. Terminal half-lives of fluorescein and fluorescein glucuronide in plasma are approximately 23.5 and 264 minutes, respectively. The glucuronide contributes almost all the plasma fluorescence after 4 to 5 hours. Fluorescein glucuronide is less bound to plasma than fluorescein. Diabetic and non-diabetic patients demonstrate similar fluorescein pharmacokinetics in the plasma.

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 was essentially complete by 48 to 72 hours after administration of 500mg fluorescein.

INDICATIONS

Fluorescein angiography of the fundus and of the iris vasculature.

This medicinal product is for diagnostic use only.

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients.
- Intrathecal or intra-arterial use.

PRECAUTIONS

NOT FOR INTRATHECAL USE – FOR OPHTHALMIC DIAGNOSTIC USE ONLY

Hypersensitivity Reactions

Hypersensitivity reactions, including rare cases of anaphylactic/anaphylactoid shock (some with fatal outcome), have been reported in patients receiving Fluorescein SERB 500mg/5mL (see **ADVERSE EFFECTS**). If serious hypersensitivity reactions have occurred during previous angiography with other diagnostic agents or there is a history of severe allergic reactions, the need for fluorescein angiography must be very carefully considered and the diagnostic importance balanced against the risk of a severe, possibly fatal (rate 1 in 220,000 angiographies as collected in a survey), allergic reaction.

Managing risk of hypersensitivity reaction with fluorescein angiography requires:

- The patient must be kept under close observation for at least 30 minutes after angiography.
- A protocol for management of anaphylaxis, and an emergency tray with appropriate resuscitation equipment such as adrenaline for intravenous or intramuscular use, intravenous fluids, oxygen, volume substitution and corticosteroids, should always be available in case of such reaction.

Cardiovascular Disease

Before administration, a complete medical history must be obtained, including history of allergy, history of cardio-pulmonary disease, concomitant medication (in particular beta blockers, including eye drops).

Patients with a history of cardiovascular disease require careful evaluation before undergoing an elective procedure with sodium fluorescein. Rarely, severe cardiovascular complications such as chest pain, myocardial infarction and death have occurred following administration of fluorescein sodium.

Caution is to be exerted in patients with a history of allergy or bronchial asthma.

Pre-existing conditions and concomitant medication

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 INTERACTIONS WITH OTHER MEDICINES).

Combination with Beta-blockers

Combination with beta-blockers may in rare cases cause lethal anaphylactic reactions. In patients identified as being at risk of hypersensitivity reactions, but in whom a fluorescein angiography is considered to be essential, the procedure must be carried out in the presence of a specialist in resuscitation, particularly when the patient is under beta-blocker therapy, including beta-blocker eye-drops, as they may require more intensive resuscitation measures due to reduced efficacy of adrenaline and volume expansion (see **INTERACTIONS WITH OTHER MEDICINES**)

Extravasation

Care must be taken to avoid extravasation during injection. The high pH of the fluorescein solution can result in severe local tissue damage. Complications from extravasation can cause severe pain, thrombophlebitis and an inflammatory reaction of the tissue leading to tissue necrosis. Before fluorescein is administered, precautions to avoid extravasation must be taken and the correct intravenous position of the needle tip must be ascertained. In case extravasation occurs, the injection must be stopped immediately and appropriate measures must be taken to treat damaged tissue and to relieve pain.

Special Instructions

The skin and urine may be coloured yellow but this is transient. Fluorescein sodium can stain skin, clothing and soft contact lenses on contact.

Effects on Fertility

There is no fertility data available.

Use in Pregnancy

Category B2. Embryofoetal toxicity studies in animals showed that doses of fluorescein associated with exposure levels approximately 9-times higher (rats) or the same (rabbits) as the human dose (on relative mg/m^2 body surface area basis) caused no foetal harm when administered iv during organogenesis.

There have been no adequate and well-controlled human studies on the safety of fluorescein sodium injection 10% during pregnancy. Avoid the use of Fluorescein SERB 500mg/5mL in patients who are pregnant unless considered absolutely necessary.

Use in Lactation

Fluorescein has been demonstrated to be excreted in human milk for up to 7 days. Following fluorescein angiography, breast-feeding should therefore be discontinued for at least 4 days and the milk should be pumped off and discarded during this period. Because of the potential for serious reactions in breastfed infants from fluorescein, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Based on the available data, extrapolation on excretion of fluorescein in breast milk suggests a complete removal of fluorescein may take approximately 2 weeks after intravenous administration.

Use in the Elderly

The benefit to risk of the angiography procedure should be considered in elderly patients with pre-existing conditions such as cardiovascular disease, diabetes mellitus and multiple concomitant drug therapies.

No overall difference in safety or effectiveness has been observed between elderly and other adult patients.

Use in Renal Impairment

Only limited experience in renally impaired subjects is available.

Carcinogenicity

No carcinogenicity studies are available.

Effect on Laboratory Tests

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.

Systemic concentration of fluorescein had been reported to interfere in the determination of digoxin and cortisol in serum when fluorescence polarization immunoassay based analysers are used. Caution is advised when performing therapeutic drug monitoring for drugs with a narrow therapeutic window, e.g. digoxin, quinidine.

Effects on Ability to Drive and Use Machines

No effects of Fluorescein SERB 500mg/5mL that would adversely influence the ability to drive are known. However, the mydriasis and cycloplegia required for the fluorescein angiography examination may affect vision. Patients should be advised that this might impair their ability to drive or to operate machinery.

INTERACTIONS WITH OTHER MEDICINES

Beta-blockers

Due to an interference of beta-blockers at the level of the beta-receptors, anaphylactic/anaphylactoid reactions may be more severe (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

Concomitant administration of other IV agents

Concomitant intravenous injection of other solutions or the mixing of fluorescein sodium with other solutions should be avoided as the possibility of interactions cannot be excluded (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

Organic anion transporter inhibitors

Compounds that inhibit the active transport of organic anions (e.g. probenecid) may affect the system profile of fluorescein.

ADVERSE EFFECTS

The occurrence of the following adverse reactions has been reported with use of fluorescein sodium injection 10% in clinical trials. A summary of treatment emergent adverse events and their estimate of frequencies (common, rare, very rare) in accordance with preferred term and system organ class (SOC) of any severity are listed below:

Gastrointestinal disorders:

Very common (≥ 10%): nausea

Common(≥ 1% and ≤ 10%): vomiting

Uncommon (≥ 0.1% and ≤ 1%): abdominal pain.

General disorders and administration site conditions:

Common(≥ 1% and ≤ 10%): extravasation

Uncommon (≥ 0.1% and ≤ 1%): dysphasia, feeling hot, pain.

Nervous system disorders:

Common(≥ 1% and ≤ 10%): syncope

Uncommon (≥ 0.1% and ≤ 1%): dizziness, paresthesia.

Respiratory, thoracic and mediastinal disorders:

Uncommon (≥ 0.1% and ≤ 1%): cough, throat tightness.

Skin and subcutaneous tissue disorders:

Uncommon (≥ 0.1% and ≤ 1%): urticaria.

Post-Marketing Experience

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 respiratory disorders (bronchospasm, laryngeal oedema), anaphylactic shock, hypotension, loss of consciousness, convulsion, respiratory and cardiac arrest.

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

A summary of treatment emergent adverse events and their estimate of frequencies (very common, common, uncommon, rare, very rare) in accordance with preferred term and system organ class (SOC) of any severity are listed below:

Very common (≥ 10%)

Common (≥ 1% and ≤ 10%)

Uncommon (≥ 0.1% and ≤ 1%)

Rare (≥ 0.001% ≤ 0.1%)

Very rare (≥ 0.001%)

Cardiac disorders:

Rare: cardiac arrest

Very rare: angina pectoris, bradycardia and tachycardia

Not known: acute myocardial infarction, shock.

General disorders and administration site conditions:

Common: extravasation

Uncommon: pain, feeling hot

Very rare: death

Not known: oedema, malaise, asthenia, chills, chest pain.

Immune system disorders:

Uncommon: hypersensitivity

Rare: anaphylactic reaction

Very rare: anaphylactic shock, anaphylactoid reaction, anaphylactoid shock.

Nervous system disorders:

Common: dysgeusia, syncope

Uncommon: headache, paraesthesia, dizziness

Very rare: seizures

Not known: vertebrobasilar insufficiency, loss of consciousness, tremor, hypoaesthesia, cerebrovascular accident, Dysgeusia.

Respiratory, thoracic and mediastinal disorders:

Uncommon: cough, throat tightness

Rare: bronchospasm

Very rare: dyspoea, sneezing, pulmonary oedema, asthma, respiratory arrest, hypoventilation, laryngeal oedema, nasal oedema.

Not known: throat irritation.

Skin and subcutaneous tissue disorders:

Common: urticaria, pruritus.

Not known: rash, cold sweat, eczema, erythema, hyperhidrosis, dermatitis.

Vascular disorders:

Uncommon: thrombophlebitis

Rare: shock, hypotension

Very rare: vasodilatation, hypertension, pallor, hot flush, peripheral vascular disorder, intermittent claudication, vasospasm.

Gastrointestinal disorders:

Very common: nausea

Common: abdominal discomfort, vomiting

Uncommon: abdominal pain

Not known: retching

DOSAGE AND ADMINISTRATION

Dosage

Adults: One single dose of 500 mg (1 ampoule of 5 mL).

Use in the elderly: There is no indication that dosage needs to be modified for the elderly.

Paediatric use: Studies in the paediatric population have not been performed. If Fluorescein SERB 500mg/5mL is used in children, a dosage adjustment is recommended, e.g. 5 mg/kg.

Method of Administration

Fluorescein SERB 500mg/5mL is given by intravenous (IV) injection.

Instructions for Use and Handling

Visually inspect ampoule for particulate matter and discolouration.

Do not mix or dilute with other solutions or drugs in syringe. Intravenous cannulas should be flushed before and after drugs are injected to avoid physical incompatibility reactions.

Fluorescein SERB 500mg/5mL contains no antimicrobial preservative and is for single use in one patient only.

Special Precautions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Drugs with acidic pH (especially antihistamines, e.g. promethazine) or citric acid may lead to precipitation of fluorescein and should not be given simultaneously through the same intravenous line.

OVERDOSAGE

No specific measures are known. In case of overdose with clinical signs, general supportive treatment should be provided.

Contact the Poisons Information Centre: **Australia 13 11 26** or **New Zealand 0800 POISON** or **0800 764766** for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Fluorescein SERB solution for injection ampoules contain 500mg of fluorescein sodium as the active ingredient.

A clear, orange-yellow solution with a yellowish green fluorescence.

Each 1.0 mL of solution contains 100 mg of fluorescein sodium.

5 mL type I clear glass ampoule, in packs of 1 x 5mL or 10 x 5 mL. (AUST R 124565)

Storage: Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Clinect Pty Ltd

120-132 Atlantic Drive
Keysborough VIC 3173
Australia

Free Call Australia: 1800 899 005

Free Call New Zealand: 0800 138 803

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

13 February 2007

DATE OF MOST RECENT AMENDMENT

8 March 2017

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