

# NEW ZEALAND DATA SHEET

## FLUORESCEIN Novartis 500mg/5mL (fluorescein sodium)

### Name of the medicine

Active ingredient: fluorescein sodium

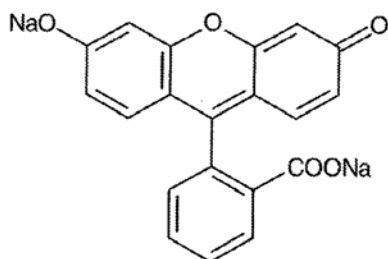
Chemical name: disodium 2-(3-oxo-6-oxido-3*H*-xanthen-9-yl)benzoate

Molecular formula: C<sub>20</sub>H<sub>10</sub>Na<sub>2</sub>O<sub>5</sub>

CAS number: 518-47-8

Molecular weight: 376.3

Structural formula:



### Description

Fluorescein Novartis 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 Novartis 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. After 15 min of intravenous administration, concentration of fluorescein glucuronide, metabolite of fluorescein which also has fluorescent properties, was higher when compared to fluorescein. Intravenous administration of 188mg fluorescein sodium resulted in C<sub>max</sub> 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 is 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 1/3 to 1/4 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.

### **Special populations**

**Renal impairment:** The plasma concentrations of free fluorescein and fluorescein glucuronide had been elevated in patients with renal insufficiency. Systemic fluorescein did not have influence in glomerular filtration rate in patients with chronic kidney disease, thus dose adjustments in patients with renal impairment are not warranted (see Dosage and administration).

**Hepatic impairment:** There is no study information on pharmacokinetics of fluorescein in patients with impaired hepatic function.

### **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 Novartis (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.

### **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 ~~shown~~ 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 ~~in the form of~~ beta-blocker eye-drops, as they may require more intensive resuscitation measures due to reduced efficacy of adrenaline and volume expansion.

### **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.

### **Women of Child-bearing Potential**

No specific recommendation for women of child-bearing potential. For information regarding the use of Fluorescein Novartis during pregnancy please refer to the next section.

### **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<sup>2</sup> 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 Novartis 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 4 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.

### **Other patient populations**

#### **Use in renal impairment:**

Limited experience in renally impaired subjects suggests that no dose adjustment is necessary in renal impaired patients.

#### **Use in Hepatic Impairment:**

Fluorescein undergoes hepatic metabolism to fluorescein glucuronide. Dose adjustment is not necessary in hepatic impaired patients.

### **Carcinogenicity and genotoxicity**

No carcinogenicity studies are available.

A standard set of *in vitro* and *in vivo* genotoxicity studies were negative (Ames bacterial mutagenicity, chromosomal aberration in CHO cells and chromosome aberration and micronucleus tests in mouse bone marrow).

Positive results were obtained in a mouse lymphoma cell thymidine kinase assay as well as in sister chromatid exchange studies *in vitro* (CHO cells) and *in vivo* (mouse bone marrow cells). ]. Using a weight of evidence approach for the evaluation of the data summarized above, it is concluded that fluorescein has no clinically relevant genotoxic potential.

Intravenous administration of fluorescein sodium did not produce embryotoxic and teratogenic effects in rats or rabbits at doses as high as 1,000, 500, and 31.3 mg/kg, respectively (approximately 100-, 50-, and 3.1-times the recommended human dose).

### **Effect on 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 Novartis 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).

#### **Organic anion transporter inhibitors**

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

For physical incompatibilities, see DOSAGE AND ADMINISTRATION Incompatibilities.

### **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 ( $\geq 10\%$ ): Nausea

Common ( $\geq 1\%$  and  $\leq 10\%$ ): Vomiting

Uncommon ( $\geq 0.1\%$  and  $\leq 1\%$ ): Abdominal pain

#### **General disorders and administration site conditions:**

Common ( $\geq 1\%$  and  $\leq 10\%$ ): extravasation

Uncommon ( $\geq 0.1\%$  and  $\leq 1\%$ ): dysphasia, feeling hot, pain.

#### **Nervous system disorders:**

Common ( $\geq 1\%$  and  $\leq 10\%$ ): Syncope

Uncommon ( $\geq 0.1\%$  and  $\leq 1\%$ ): Dizziness, paresthesia.

#### **Respiratory, thoracic and mediastinal disorders:**

Uncommon ( $\geq 0.1\%$  and  $\leq 1\%$ ): Cough, throat tightness.

#### **Skin and subcutaneous tissue disorders:**

Uncommon ( $\geq 0.1\%$  and  $\leq 1\%$ ): 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, 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 ( $\geq 10\%$ )

Common ( $\geq 1\%$  and  $\leq 10\%$ )

Uncommon ( $\geq 0.1\%$  and  $\leq 1\%$ )

Rare ( $\geq 0.001\%$  and  $\leq 0.1\%$ )

Very rare ( $\geq 0.001\%$ )

#### **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: convulsions

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

**Respiratory, thoracic and mediastinal disorders:**

Uncommon: cough, throat tightness

Rare: bronchospasm

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

**Gastrointestinal disorders:**

Very common: nausea

Common: abdominal discomfort, vomiting

Uncommon: abdominal pain

Not known: retching

**Skin and subcutaneous tissue disorders:**

Common: Urticaria, pruritus.

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

**Vascular disorder:**

Uncommon: thrombophlebitis

Rare: Shock, hypotension

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

**Dosage and administration****Dosage**

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

**Other patient populations**

**Use in renal impairment:** Limited experience in renally impaired subjects suggests that no dose adjustment is necessary in patients with renal impairment.

**Use in Hepatic Impairment:** Fluorescein undergoes hepatic metabolism to fluorescein glucuronide. Dose adjustment is not necessary in patients with hepatic impairment. **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 Novartis 500mg/5mL is used in children a dosage adjustment is recommended, e.g. 8 mg/kg.

**Method of Administration**

Fluorescein Novartis 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.

Product is for single use in one patient only. Discard any residue. Contains no antimicrobial agent.

Inject the contents of the vial rapidly into the antecubital vein after taking precautions to avoid extravasation. A syringe filled with Fluorescein Novartis 500mg/5mL is 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 Novartis 500mg/5mL.

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 immediately before any Fluorescein Novartis 500mg/5mL is administered. When assured that extravasation has not occurred, the room light may be switched off and the Fluorescein Novartis 500mg/5mL administration completed. Luminescence appears in the retina and choroidal vessels in 7 to 14 seconds and can be observed by standard viewing equipment. An emergency tray and oxygen should be present when administering this product (see PRECAUTIONS).

### **Special Precautions for Disposal**

Fluorescein Novartis is for single use only. 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.

### **Presentation and Storage Conditions**

Injection, 5 mL ampoule, in packs of 10 x 5 mL.

**Storage:** Store below 25°C.

### **Medicine classification**

Prescription Medicine

### **Distributed by**

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### **Date of preparation**

4 November 2011