SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zyogreen 2.5 mg/mL, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 2.5 mg indocyanine green.

Each ampoule contains 25 mg indocyanine green in 10 mL of water for injections.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Deep emerald-green solution with a pH value between 5.5 and 7.5.

Osmolality is usually between 10 and 20 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only. It is indicated in:

- Oncology:

Intraoperative identification of the sentinel lymph node and visualisation of the lymphatic pathways in cases of breast cancer.

- Ophthalmic angiography diagnostics:

Measurement of perfusion of the choroid.

- Liver function diagnostics:

- Measurement of liver blood flow

- Measurement of excretory function of the liver.

- Cardiac, circulatory and micro-circulatory diagnostics:

- Measurement of cardiac output and stroke volume

- Measurement of circulating blood volumes

- Measurement of cerebral perfusion

4.2 Posology and method of administration

Single dose per measurement in adults, elderly, adolescents, children:

Intraoperative sentinel node location and visualisation of lymph ducts (oncology):

The dose varies from 5 to 10 mg (i.e. 2 to 4 mL of a 2.5 mg/mL solution).

Ophthalmic angiography :

0.1 to 0.3 mg/kg body weight as intravenous bolus injection

Liver function diagnostics:

0.25 to 0.5 mg/kg body weight as intravenous bolus injection

Cardiac, circulatory, micro-circulatory and tissue perfusion diagnostics as well as cerebral blood flow:

0.1 to 0.3 mg/kg body weight as intravenous bolus injection

The total dose injected should not exceed 0.5 mg/kg.

Method of administration

In oncology:

Subcutaneous route.

The injection is given intraoperatively via the subcutaneous route in the periareolar or peritumoral zone.

The injection is given approximately 10 minutes before the start of surgery. The breast is massaged for a few minutes after the injection.

Measurement of cardiac, circulatory and cerebral blood flow as well as liver function diagnostics and ophthalmologic angiography:

For cardiac, circulatory, microcirculatory and liver function diagnostics, as well as for ophthalmologic angiography, Zyogreen is intended for intravenous injection via an injection needle, a central or peripheral catheter or cardiac catheter.

The administration and site of Zyogreen are of critical importance for the quality of the measurements. In principle, for obtaining optimal quality first pass indicator dilution curves, the injection should be as close as possible to the vascular bed, organ or tissue of interest.

On peripheral intravenous injection, venipuncture should be done after application of a tourniquet. After release of the tourniquet, Zyogreen should be injected immediately and the arm should be raised. This ensures rapid transport of the dye from the site of injection and peripheral injection is then practically equivalent to central venous injection.

Areas under the first pass curve, transit time, half-life, plasma disappearance rate and retention rate of Zyogreen can be determined:

a. non-invasively by pulse dye densitometry or near infrared spectroscopy

b. invasively by fibre optic probes/catheters in suitable vessels

c. conventionally by determination of the concentration either by continuous withdrawal of heparinised blood through a cuvette densitometer or by collection of blood samples and measurement of the plasma concentration in a photometer

Evaluation of fundus perfusion in ophthalmic angiography

The perfusion of the fundus of the eye can be determined and quantified by ophthalmic fluorescence angiography.

Measurement of tissue perfusion

Tissue perfusion of the superficial tissue layers can be made visible and quantified by near infrared fluorescence video angiography.

4.3 Contraindications

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

Other contraindications include:

- patients with hyperthyroidism, patients with autonomic thyroid adenomas.
- in-vitro experiments have shown that indocyanine green displaces bilirubin from its protein binding. Zyogreen should not be used in premature infants or neonates in whom an exchange transfusion is indicated due to hyperbilirubinemia,
- if injection of Zyogreen was poorly tolerated in the past it must not be used again, since severe anaphylactic reactions might occur.
- patients with hypersensitivity to iodine.

4.4 Special warnings and precautions for use

- There is a risk of hypersensitivity reactions with Zyogreen irrespective of the route of administration and the dose administered.
- Serious allergic reactions (such as Quincke's oedema or anaphylactic reaction) have been reported very rarely after administration of indocyanine green alone or after concomitant administration of indocyanine green and fluorescein. This risk means that the patient must be monitored during and after the injection of these products. Zyogreen should only be administered under the supervision of a physician, and emergency resuscitation facilities should be available for immediate use. Patients should be monitored for at least an hour after

administration of indocyanine green for the occurrence of hypersensitivity reactions.

- The iodine content of Zyogreen can interfere with thyroid tests performed before or after administration of the dye. Therefore, radio-active iodine uptake studies should not be performed for at least a week following the use of Zyogreen.
- When Zyogreen is administered intradermally or subcutaneously, patients should be advised to avoid direct sun or UV radiation for at least 1 week, or until any greenish discoloration at the injection site has disappeared.
- Heparin preparations containing sodium bisulphite may reduce the absorption peak of indocyanine green in plasma and blood. Therefore heparin should not be used as an anticoagulant for the collection of samples for analysis.

4.5 Interaction with other medicinal products and other forms of interaction

The clearance of indocyanine green may be altered by medicinal products that interfere with liver function.

The absorption peak of indocyanine green is reduced by injectables containing sodium bisulphite (particularly in combination with heparin).

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number (242) of exposed pregnancies indicate no adverse effects of indocyanine green on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. No studies for reproduction, teratogenicity, or carcinogenic properties in animals are available. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women. Repeated applications on one day have to be avoided.

Lactation

It is not known whether this medicinal product is excreted in human milk. Because many medicinal products are excreted in human milk, caution should be exercised when indocyanine green is administered to a nursing woman.

Fertility

There are no data regarding the effect of indocyanine green on fertility.

4.7 Effects on ability to drive and use machines

Zyogreen has minor influence on the ability to drive and use machines. Impaired vision has been reported with Zyogreen when used in ophthalmology.

4.8 Undesirable effects

Immediate hypersensitivity reactions may occur. These reactions may include one or more of the following effects, occurring concomitantly or successively: cutaneous (urticaria, pruritus, facial oedema), respiratory (bronchospasm, laryngospasm, shortness of breath), gastrointestinal (nausea) and/or cardiovascular reactions (acceleration of heart rate, fall in blood pressure, cardiac arrest). Any of these effects may be a warning sign of an anaphylactic reaction.

Adverse reactions are listed in the following table by system organ class and frequency, according to the following categories: Very common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000, <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

System organ class	Undesirable effects	Frequency of undesirable effects
Immune system disorders	Anaphylactic reaction*	Very rare
	Hypersensitivity	Not known
Vascular disorders	Hot flushes	Rare
Gastrointestinal disorders	Vomiting	Uncommon
	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Rash	Rare
	Urticaria	Rare
	Skin reaction	Rare
	Pruritus	Rare
	Hyperhidrosis	Rare
	Angioedema	Very rare
	Alteration of skin colour**	Not known
General disorders and abnormalities at the administration site	Dizziness	Rare
	Staining at the injection site	Not known

*Anaphylactic reaction after administration of indocyanine green alone or after concomitant administration of indocyanine green and fluorescein.

**Temporary discolouration of the integuments observed in the event of accidental para-venous injection.

If, contrary to expectations, symptoms of anaphylaxis do occur, the following immediate measures should be taken:

- stop further administration of Zyogreen, leave injection catheter or cannula in the vein

- keep airways free

- inject 100-300 mg hydrocortisone or a similar preparation by rapid intravenous injection

- substitute volume with isotonic electrolyte solution

- give oxygen, monitor circulation

- slowly administer antihistamines intravenously

The following additional measures are indicated in cases of anaphylactic shock:

- place patient in recumbent position with legs raised

- rapidly substitute volume with e.g. isotonic electrolyte solution (pressure infusion), plasma expanders

- immediately administer 0.1-0.5 mg adrenaline (epinephrine) diluted to 10 ml with 0.9 % saline intravenously (repeat after 10 minutes if necessary)"

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 suspected adverse reactions via the Yellow Card Sheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

No cases of overdose have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostics, other diagnostics, ATC code: V04CX01

Mechanism of action

Indocyanine green is a dye with an absorption spectrum that peaks at around 805 nm and re-emits at 835 nm.

Pharmacodynamic effects

Zyogreen is a fluorescent diagnostic product with no conventional pharmacodynamic effect.

Clinical efficacy and safety

For indocyanine green used in breast cancer, the sentinel node detection rate analysed in 2,904 patients from literature data in 24 studies across the United Kingdom and the European Union is over 95.0% and the average number of nodes excised is between 2.0 and 2.7 nodes per patient.

Clinical safety data from 13,847 patients across 76 studies worldwide did not highlight any emerging safety issues in this clinical setting.

5.2 Pharmacokinetic properties

Absorption

After intravenous injection, Zyogreen binds to plasma proteins rapidly and strongly.

After subcutaneous injection, Zyogreen travels through the lymph ducts to the lymph nodes within a few minutes and is then drained into the bloodstream.

Distribution

Zyogreen remains in the intra-vascular compartment, allowing determination of cardiac or hepatic blood flow. In addition, the absence of dye leakage from the choroidal vessels means that they can be viewed using infrared ocular angiography.

Comparative studies of pigment concentration in the afferent and efferent circulation of various organs showed that uptake was negligible in the kidneys, lungs and cerebrospinal fluid.

Foetal blood samples showed no evidence of Zyogreen crossing the placental barrier.

Elimination

This chromogen is then taken up by the hepatocytes and eliminated unchanged entirely via the biliary route with no enterohepatic cycle.

The half-life of Zyogreen in healthy subjects is 3.4 ± 0.7 minutes.

Elimination is slower when the hepatocyte mass is reduced.

Furthermore, if the bile ducts are obstructed, the dye appears in the liver's lymphatic circulation.

5.3 Preclinical safety data

Acute toxicity: the LD50 after single IV dose was 87 mg/kg in rats, 60 mg/kg in mice, and between 50 mg/kg and 80 mg/kg in rabbits. After dissolution in water for injections and administration by intraperitoneal injection in mice the LD50 was found to be 650 mg/kg body weight. No macroscopic or histopathological changes were observed.

Genetic toxicity: indocyanine green was not found to be mutagenic in the tests performed (Ames test, gene mutation assay - thymidine kinase locus/TK+/- - in mouse lymphoma L5178Y cells, chromosome aberration test in Chinese hamster V79 cells).

No studies for reproduction, teratogenicity, or carcinogenic properties in animals are available, but decades of experience in humans have not revealed any incidence of these properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Ascorbate

Water for Injections

6.2 Incompatibilities

6.3 Shelf life

21 months.

From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

10 mL type I brown glass ampules. Pack of 5 ampoules.

6.6 Special precautions for disposal

This medicinal product is for single use only.

Do not use Zyogreen if the solution is discoloured.

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

7 MARKETING AUTHORISATION HOLDER

PROVEPHARM SAS

22 rue Marc Donadille

13013 Marseille

France

8 MARKETING AUTHORISATION NUMBER(S)

PL 40051/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2026

10 DATE OF REVISION OF THE TEXT

21/04/2026