SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Verdye 5 mg/ml powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 mg indocyanine green (to be reconstituted with 5 ml of water for injections)
Each vial contains 50 mg indocyanine green (to be reconstituted with 10 ml of water for injections).

1 ml of the reconstituted solution for injection

contains 5 mg indocyanine green. For the full list of

excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection

Dark-green powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Diagnostic indications

Cardiac, circulatory and micro-circulatory diagnostics:
- measurement of cardiac output and stroke volume
- measurement of circulating blood volumes
- measurement of cerebral perfusion

Liver function diagnostics:
- measurement of liver blood flow
- measurement of excretory function of the liver

Ophthalmic angiography diagnostics:

- measurement of perfusion of the choroid

Intraoperative identification of sentinel lymph nodes and visualization of lymphatic pathways in breast cancer.

4.2 Posology and method of administration

Posology

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

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

Liver function diagnostics: 0.25 to 0.5 mg/kg body weight as intravenous bolus injection

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

Identification of sentinel lymph nodes and visualization of lymphatic pathways regardless of body weight:
5 to 10 mg per injection (intradermal, subcutaneous or peritumoral). This corresponds to 1 to 2 ml of the reconstituted 5 mg/ml solution. The volume per injection should not exceed 2 ml. If higher dilutions (<5 mg/ml) are used, larger volumes per injection can also be administered (e.g. to obtain an indocyanine green concentration of 2.5 mg/ml, the reconstituted solution can be further diluted with 5 ml or 10 ml water for injections depending on the vial size).

Total daily dose in adults, elderly, adolescents, children:

Adults, elderly, adolescents 11 - 18 years:
The total daily dose of Verdye should be kept below 5 mg/kg body weight.

Children 2 - 11 years:
The total daily dose should be kept below 2.5 mg/kg body weight.

Children 0 - 2 years:
The total daily dose should be kept below 1.25 mg/kg body weight.

Paediatric population
Single doses to be used in paediatrics are the same as for adults but the total daily dose should be kept below 2.5 mg/kg body weight in children 2 - 11 years and below 1.25 mg/kg body weight in children 0 - 2 years.

Patients with renal impairment
Verdye has not formally been studied in patients with renal impairment. No specific dose recommendations for this patient population are available. Patients with severe renal impairment should be carefully monitored for adverse reactions (see

section 4.4).

Patients with hepatic impairment
Verdye has not formally been studied in patients with hepatic impairment. No specific dose recommendations for this patient population are available. In patients with severe hepatic impairment (e.g. alcoholic or biliary cirrhosis), plasma clearance of indocyanine green may be reduced.

Identification of sentinel lymph nodes and visualization of lymphatic pathways
For the identification of sentinel lymph nodes and visualization of lymphatic pathways, the total daily dose of Verdye should not exceed 10 mg; the use in children and adolescents is not recommended due to insufficient data on safety and efficacy.

Method of administration
Before administration the powder must be reconstituted with water for injections. For instructions on reconstitution of the medicinal product before administration, see sections 6.2 and 6.6.
The reconstituted solution is clear and free from visible particles.

Verdye is administered by intravenous, intradermal, subcutaneous or peritumoral injection.

Methods of measurement
The absorption and emission maximum of indocyanine green are both in the near infrared range, the absorption maximum at 800 nm and the emission maximum for fluorescence measurement at 830 nm.
In *in-vitro*-tests indocyanine green remains stable in human serum for several days. Dissolved in water, indocyanine green shows no detectable decomposition at least for a few hours.

Diagnostic procedures with Verdye should be performed under the supervision of a physician.

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, Verdye is intended for intravenous injection via an injection needle, a central or peripheral catheter or cardiac catheter.

The administration and site of Verdye 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, Verdye 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 Verdye 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.

Identification of sentinel lymph nodes and visualization of lymphatic pathways
Because of the protein binding rate of [Nationally approved name] in the lymph fluid, the sentinel lymph nodes can be imaged by means of fluorescence angiography.

For the identification of sentinel lymph nodes and visualization of lymphatic pathways in breast cancer, Verdye is injected into a region that is upstream of the particular lymph nodes that are of interest and that is drained by these. The injection can be intradermal, subcutaneous (interstitial) or also peritumoral. It is possible to accelerate the transport of indocyanine green into the sentinel lymph nodes through a breast massage. Imaging may be started within 15 minutes after injection. Transcutaneous detection of sentinel lymph nodes is performed using a near-infrared fluorescence imaging system that visualizes the ICG fluorescence. The suitability of the near-infrared fluorescence imaging system for the detection of sentinel lymph nodes must be tested in advance.

4.3 Contraindications

Verdye is contraindicated for safety reasons:

- in patients with hypersensitivity to indocyanine green or to sodium iodide unless special precautions are taken,
- in patients with hypersensitivity to iodine,
- in patients with hyper-thyroidism, patients with autonomic thyroid adenomas,
- as *in-vitro* experiments have shown that indocyanine green displaces bilirubin from its protein binding, Verdye must not be used in premature infants or neonates in whom an exchange transfusion is indicated due to hyperbilirubinemia,
- if injection of Verdye was poorly tolerated in the past it must not be used again, since severe anaphylactic reactions might occur.

4.4 Special warnings and precautions for use

- Since severe anaphylactic reactions might occur after application of Verdye, it must

only be applied under 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.

- Due to an increased incidence of adverse reactions in patients with severe renal insufficiency, Verdye must only be applied after a careful benefit/risk assessment.
- Heparin preparations containing sodium bisulphite reduce the absorption peak of indocyanine green in plasma and blood and, therefore, should not be used as an anticoagulant for the collection of samples for analysis.
- Indocyanine green is stable in plasma and whole blood so that samples obtained in discontinuous sampling techniques may be read hours later. Sterile techniques have to be used in handling the dye solution.
- The iodine content of Verdye 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 Verdye.
- When Verdye is applied 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.
- The identification of sentinel lymph nodes and visualization of lymphatic pathways may be impaired if they are located in deeper tissue layers or are covered by fatty tissue. Similarly, in patients with pronounced obesity (BMI >40), the mapping of sentinel lymph nodes and visualization of lymphatic pathways may be impaired.

4.5 Interaction with other medicinal products and other forms of interaction

Regarding incompatibilities with solvents for dilution see section 6.6.

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

Probenecid and some of its metabolites may be secreted into the bile and may depress the biliary secretion of indocyanine green, which may result in an impaired indocyanine green liver function test.

Concomitant use of certain medicinal products and injectables can alter the absorption. The absorption is reduced by injectables containing sodium bisulphite (particularly in combination with heparin). The following gives an overview of interaction with other medicinal products:

- Medicinal products and substances that can reduce absorption:

  - anticonvulsants
  - bisulphite compounds
  - haloperidol
  - heroin
  - metamizole
  - methadone

- morphine
- nitrofurantoin
- opium alkaloids
- pethidine
- phenobarbital
- phenylbutazone

• Medicinal products and substances that can increase absorption:

- cyclopropane
- probenecid
- rifamycin

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

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency definitions:

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)
Not known (cannot be estimated from the available data)

Anaphylactic or urticarial reactions have been reported in patients with or without history of allergy to iodides. Also, in very rare cases coronary artery spasm has been

described. Furthermore, greenish reversible skin discoloration at the injection site following paravasal (intradermal, subcutaneous) application of indocyanine green has been reported.

It is known that injection of indocyanine green preparations can in very rare cases cause nausea and anaphylactoid or anaphylactic reactions (<1/10 000). In patients with terminal renal insufficiency the possibility of an anaphylactic reaction seems to be increased. Symptoms which should be mentioned are: unrest, feeling of warmth, pruritus, urticaria, acceleration of heart rate, fall in blood pressure and shortness of breath, bronchospasm, flush, cardiac arrest, laryngospasm, facial oedema, nausea. Together with the anaphylactoid reaction, hypereosinophilia may occur.

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

- stop further administration of Verdye, 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)

Urticarial reactions of the skin occurred very rarely (<1/10 000).

Tabulated list of undesirable reactions

System Organ Class	**Frequency**	**Undesirable reaction**
Immune system disorders	Very rare	Anaphylactoid reaction, Anaphylactic reaction
Cardiac disorders	Very rare	Coronary arteriospasm
Gastrointestinal disorders	Very rare	Nausea
Skin and subcutaneous tissue disorders	Very rare	Urticaria
General disorders and administration site conditions	Not known	Injection site discoloration

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 national reporting system*: Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard*. or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Up to now no case of medicinal product overdose or laboratory findings accompanying overdose of Verdye has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic agents, Other diagnostic agents
ATC code: V04CX01

The active substance in Verdye is indocyanine green.

The molecular formula is $C_{43}H_{47}N_2NaO_6S_2$. The molecular weight is 774.96 Dalton.

Indocyanine green has a sharply defined spectral peak absorption of near-infrared light at 800 nm in blood, plasma and lymph fluid. This is the same wavelength at which the optical density of oxygenated haemoglobin in blood approximately equals that of reduced haemoglobin. Therefore, this coincidental light absorption makes it possible to measure indocyanine green concentrations in blood, plasma, serum and lymph fluid in terms of its optical density at 800 nm, independent of variations in oxygen saturation level.

Indocyanine green permits recording of the indicator-dilution curves for both diagnostic and research purposes. Indocyanine green exhibits no pharmacological effects after intravenous, intradermal, subcutaneous or peritumoral administration. For the use of indocyanine green to identify sentinel lymph nodes in breast cancer, bibliographic data from 21 studies were analysed. In total 2168 patients underwent indocyanine green imaging procedures. The mean detection rate of sentinel lymph nodes was 97.4 % and the mean number of sentinel lymph nodes detected per patient generally ranged between 2.0 and 3.0. The clinical safety data from this patient population did not indicate any emerging safety concerns in this clinical setting.

5.2 Pharmacokinetic properties

Absorption
After intradermal, subcutaneous and peritumoral injection, indocyanine green enters the lymph nodes via the lymphatic vessels and is then drained into the bloodstream. No pharmacokinetic data are available for humans, but animal data indicate very low plasma concentrations of indocyanine green.

Distribution
After injection indocyanine green undergoes no significant extrahepatic or

enterohepatic circulation; simultaneous arterial and venous blood estimations have shown negligible renal, peripheral, or lung uptake of the dye. In healthy volunteers indocyanine green cannot be detected in either urine or cerebrospinal fluid. Indocyanine green does not cross the placental barrier. The volume of distribution corresponds to the blood volume. After oral or rectal administration indocyanine green is not absorbed from the gut.

Protein-binding
Following intravenous injection, indocyanine green is rapidly bound to plasma proteins, of which beta-apolipoprotein B is the principle carrier (95 %). In the lymph fluid and in the interstitium, indocyanine green preferentially binds to albumin.

Biotransformation
Indocyanine green is not metabolised.

Elimination
Following intravenous administration plasma disappearance of indocyanine green is biphasic, showing an initial elimination half-life $t_{1/2}$ of 3-4 min and a secondary phase with a dose-dependent $t_{1/2}$ of approximately 60-80 min. After intradermal, subcutaneous and peritumoral application, $t_{1/2}$ can be prolonged.

Indocyanine green is taken up from the plasma almost exclusively by the hepatic parenchymal cells with a maximum rate of uptake (transport maximum: T_m of about 0.1 mg/minute/kg) and is secreted unmetabolized and unconjugated entirely into the bile. The concentration maximum in bile is reached after about ½-2 hours depending on the amount injected.

After biliary obstruction, the dye appears in the hepatic lymph, independently of the bile, suggesting that the biliary mucosa is sufficiently intact to prevent diffusion of the dye, though allowing diffusion of bilirubin.

As indocyanine green is not reabsorbed in the intestine, there is no enterohepatic circulation.

5.3 Preclinical safety data

Acute toxicity: the LD_{50} 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 LD_{50} was found to be 650 mg/kg body weight. No macroscopic or histopathological changes were observed.

Genotoxicity: Indocyanine green was not found to be mutagenic in the tests performed (Ames test, gene mutation assay - thymidin 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.

Environmental Risk Assessment (ERA): It is not expected that indocyanine green poses a risk to the environment upon clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be diluted with solutions containing salts (saline, Ringer's solution etc.) as this can lead to precipitation of the dye. This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

5 years

After reconstitution, the solution should be used immediately, protected from light.

6.4 Special precautions for storage

Do not store above 30 °C.
Keep the vials in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Container: amber glass vial (type I)
Closure: rubber stopper (bromobutyl, grey) fixed by an aluminium cap covered by a blue polypropylene cap

Pack sizes:
5 vials, each with a content of 25 mg powder for solution for injection
5 vials, each with a content of 50 mg powder for solution for injection

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product should be reconstituted immediately prior to use.

This medicinal product is reconstituted by addition of 5 ml water for injections to the vial containing 25 mg of active substance or 10 ml water for injections to the vial containing 50 mg of active substance, respectively, giving in both cases a dark-green solution for injection with a concentration of 5 mg/ml (0.5 % w/v).

Visually inspect the reconstituted solution. If an incompatibility is noted in the form of an unclear solution, the reconstituted solution should be discarded.
Only use clear solutions free from visible particles. This medicinal product is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Diagnostic Green Limited
Athlone Business and Technology Park
Garrycastle, Athlone, Co. Westmeath
N37 F786, Ireland

T: +353 90 646 5499
Email: info@diagnosticgreen.com

8 MARKETING AUTHORISATION NUMBER(S)

PL 56699/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24.02.2003 / 15.10.2007

10 DATE OF REVISION OF THE TEXT

13/06/2025