▼ This medicinal product is subject to additional monitoring in Australia due to approval of an extension of indications. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – VERDYE (INDOCYANINE GREEN) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Indocyanine green.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 mg indocyanine green (to be reconstituted with 5 mL of water for injections)

1 mL of the reconstituted solution for injection contains 5 mg indocyanine green, a lyophilised sterile dark green powder. The reconstituted solution is clear and free from visible particles.

This product contains no more than 5% sodium iodide

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder 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

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of administration

Before administration the powder must be reconstituted with water for injection.

The reconstituted solution is clear and free from visible particles.

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

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 injection the injection should be made immediately after application of tourniquet and the arm should be raised after release of tourniquet. This ensures rapid transport of the dye from the site of injection and peripheral injection is then practically equivalent to central venous injection.

Dosage

Single dose per measurement in adults, elderly, 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 bolus injection

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

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

Total daily dose:

***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.

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.

Measurement of cardiac, circulatory, and cerebral blood flow and liver function
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 fiberoptic 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.

Instructions for use and handling
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, giving in a dark-green solution for injection with a concentration of 5 mg/mL (0.5 % w/v).

If an incompatibility is noted in the form of unclear solution then the reconstituted solution should be discarded.

Visually inspect the reconstituted solution. Only use clear solutions free from visible particles.

This medicinal product is for single use only.

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,
• patients with hypersensitivity to iodine,
• 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 should not be used in premature infants or neonates in whom an exchange transfusion is indicated due to of 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.
- 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Regarding incompatibilities with solvents for dilution, see section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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
  - pethidine
  - metamizole
  - methadone
  - morphine
  - nitrofurantoin
  - opium alkaloids
  - phenobarbital
  - phenylbutazone
- Medicinal products and substances that can increase absorption:
  - cyclopropane
  - probenicid
  - rifamycin

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies examining the effects of VERDYE on fertility have been conducted.

Use in 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 fetus/newborn child. To date, no other relevant epidemiological data are available.

No embyrofetal development studies in animals are available. The potential risk for humans is unknown.

Caution should be exercised when prescribing to pregnant women. VERDYE should be given to a pregnant woman only if clearly indicated. Repeated applications on one day have to be avoided.

Use in 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.

No post-natal developmental studies in animals were conducted with indocyanine green.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

It is known that injection of indocyanine green preparations can in very rare cases cause nausea and anaphylactoid or anaphylactic reactions (<1/10000). In patients with terminal renal insufficiency the possibility that an anaphylactic reaction occurs 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 (<1/10000).

Two anaphylactic deaths have been reported following indocyanine green administration during cardiac catheterization. One of these was in a patient with a history of penicillin and sulfa allergy. Deaths due to anaphylaxis occurred in less than 1/330000 (estimate) including single reports.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other diagnostic agents

ATC code: V04CX

Indocyanine green has a sharply defined spectral peak absorption of near-infrared light at 800 nm in blood plasma or blood. 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 and serum 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 when administered intravenously.

5.2 PHARMACOKINETIC PROPERTIES

Distribution
After intravenous 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.

Following intravenous injection, indocyanine green is rapidly bound to plasma proteins (98%) and is largely confined to the intravascular compartment.

Metabolism
Indocyanine green is not metabolised.

Excretion
Plasma disappearance is biphasic, showing an initial elimination half-life $t_{1/2}$ of 3-4 min and a secondary phase with a dose-dependent t1/2 of approximately 60-80 min.

Indocyanine green is taken up from the plasma almost exclusively by the hepatic parenchymal cells with a maximum rate of uptake (transport maximum: Tm 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 1/2–2 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

Genotoxicity

Indocyanine green was not found to be mutagenic or clastogenic in three *in vitro* tests (a bacterial reverse mutation assay (Ames test), gene mutation assay in mouse lymphoma L5178Y cells and an *in vitro* chromosome aberration test in Chinese hamster V79 cells).

Carcinogenicity

No studies have been performed with indocyanine green to evaluate carcinogenicity.

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 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After reconstitution, the solution should be used immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25° C.

Keep the vials in the outer carton.
Once the solution for injection is prepared, it must be used immediately. Products not administered immediately after preparation should be discarded.

Product is for single use in one patient only. Discard any residue.

Only use solution if free from visible particles.

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

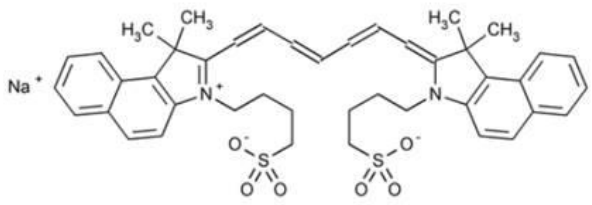
5 vials, each with a content of 25 mg powder for solution for injection.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number: 3599-32-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Non-scheduled

8 SPONSOR

Clinect Pty Ltd
120-132 Atlantic Drive
Keysborough, VIC 3173
Australia
Telephone: 1800 899 005

9 DATE OF FIRST APPROVAL

21 February 2024

10 DATE OF REVISION

5 September 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	New Sponsor details