SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Verdye 5 mg/ml Injection
25 mg / 50 mg, 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) or 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 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
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4.2 Posology and method of administration

Method of administration

Before administration the powder must be reconstituted with water for injection. For instructions on reconstitution of the medicinal product, see section 6.6.
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. Dissolved in water, indocyanine green shows no detectable decomposition at least for a few hours.

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.

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 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
  meperidine
  metamizol
  methadone
  morphium
  nitrofurantoin
  opium alkaloids
  phenobarbital
  phenylbutazone
- Medicinal products and substances that can increase absorption:
  cyclopropane
  probenicid
  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 cancerogenic 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.

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

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 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 MHRA, Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

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: Other diagnostic agents
ATC code: V04CX

The active substance in Verdye is 2-{7-[1,1-dimethyl-3-(4-sulfobutyl)-benz[e]indolin-2-ylidene]-1,3,5-heptatrienyl}-1,1-di¬methyl-3-(sulfobutyl)-1H-benz[e]-indolium hydroxide, inner salt, sodium salt).

The molecular formula is C43H47N2NaO6S2. The molecular weight is 774.96 daltons.

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.

Protein-binding

Following intravenous injection, indocyanine green is rapidly bound to plasma proteins, of which beta-apolipoprotein B is the principle carrier (95 %).

Metabolism

Indocyanine green is not metabolised.

Elimination

Plasma disappearance is biphasic, showing an initial elimination half-life t1/2 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: 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 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

Acute toxicity: the LD_{50} after single IV dose was 87mg/kg in rats, 60mg/kg in mice, and between 50mg/kg and 80mg/kg in rabbits. After dissolution in water for injections and administration by intraperitoneal injection in mice the LD_{50} was found to be 650mg/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 - 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The medicinal product does not contain excipients.

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 30ºC. Keep vials in the outer carton in order to protect from light.

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 25mg powder for solution for injection

5 vials, each with a content of 50mg powder for solution for injection

6.6 Special precautions for disposal

This medicinal product should be reconstituted immediately prior to use.

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

7 MARKETING AUTHORISATION HOLDER

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85609 Aschheim – Dornach
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 44791/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/10/2007

10 DATE OF REVISION OF THE TEXT

02/02/2016