ATTACHMENT 1

CARDIO-GREEN® (CG®)

STERILE INDOCYANINE GREEN, USP

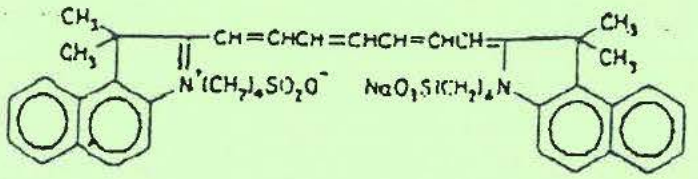
NAME OF THE DRUG

Indocyanine green

DESCRIPTION

Cardio-Green® (CG®) is a sterile, water soluble, tricarbocyan dye with a peak spectral absorption at 800 - 810 nm in blood plasma or blood. Cardio-Green contains not more than 5.0% sodium iodide. Cardio-Green is to be administered intravenously.

The molecular formula is $C_{45}H_{47}N_2NaO_6S_2$, the molecular weight 774.96. The structural formula is given below:



The Aqueous Solvent provided with this product, pH of 5.5 to 6.5, is a prepared Sterile Water for Injection used to dissolve CG.

PHARMACOLOGY

Following intravenous injection, CG is rapidly bound to plasma protein, of which albumin is the principal carrier (95%). CG undergoes no significant extrahepatic or enterohepatic circulation; simultaneous arterial and venous blood estimations have shown negligible renal, peripheral, lung or cerebro-spinal uptake of the dye. CG is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile. After bilary obstruction, the dye appears in the hepatic lymph, independently of the bile, suggesting that the bilary mucosa is sufficiently intact to prevent diffusion of the

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dye, though allowing diffusion of bilirubin. These characteristics make CG a helpful index of hepatic function.

INDICATIONS

For determining cardiac output, hepatic function and liver blood flow, and for ophthalmic angiography.

CONTRAINDICATIONS

CG contains sodium iodide and should be used with caution in patients who have a history of allergy to iodides.

WARNINGS AND PRECAUTIONS

Two anaphylactic deaths have been reported following CG administration during cardiac catheterisation. One of these was in a patient with a history of sensitivity to penicillin and sulfur drugs. CG contains no antimicrobial preservative. Therefore, it should be used as soon as practicable after reconstitution. If there is to be any dely in using the reconstituted product, it should be stored at 2 - 8 °C. Any residue should be discarded.

The Aqueous Solvent provided with this product, pH 5.5 to 6.5, which is especially prepared sterile Water for Injection, should be used to dissolve CG because there have been reports of incompatibility with some commercially available Water for Injection.

General Precautions: CG Powder and Solution: CG is unstable in aqueous solution and must be used within 10 hours, However, the dye is stable in plasma and whole blood so that samples obtained in discontinuous sampling techniques may be read hours later. Sterile techniques should be used in handling the dye solution as well as in the performance of the dilution curves.

CG powder may cling to the vial or lump together because it is freeze-dried in the vials. *This is not due to the presence of water* - the moisture content is carefully controlled.

Heparin preparations containing sodium bisulfite reduce the absorption peak of CG in blood and, therefore, should not be used as an anticoagulant for the collection of samples for analysis.

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The plasma fractional disappearance rate at the recommended 0.5 mg/kg dose has been reported to be significantly greater in women than in men, although there was no significant difference in the calculated value for clearance.

Radio-active iodine uptake studies should not be performed for at least a week following the use of CG.

Pregnancy Category C: Animal Reproduction studies have not been conducted with CG. It is also not known whether CG can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CG should be given to a pregnant woman only if clearly indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CG is administered to a nursing woman.

Drug Abuse and Dependence: CG is not known to lead to dependence or abuse.

ADVERSE REACTIONS

Anaphylactic or urticarial reactions have been reported in patients with or without history of allergy to iodides. If such reactions occur, treatment with the appropriate agents, e.g., adrenaline, antihistamines, and corticosteroids should be administered.

DOSAGE AND ADMINISTRATION

INDICATOR-DILUTION STUDIES:

CG permits recording of the indicator-dilution curves for both diagnostic and research purposes independently of fluctuations in oxygen saturation. In the performance of dye dilution curves, a known amount of dye is usually injected as a single bolus as rapidly as possible via a cardiac catheter into selected sites in the vascular system. A recording instrument (oximeter or densitometer) is attached to a needle or catheter for sampling of the dye-blood mixture from a systemic arterial sampling site.

Under sterile conditions, the CG powder should be dissolved with the Aqueous Solvent furnished, and the solution used within 10 hours after it is prepared. The amount of solvent to be used can be calculated from the dosage form which follows. It is recommended that the syringe used for injection of the dye be

rinsed with this diluent. Isotonic saline should be used to flush the residual dye from the cardiac catheter into the circulation so as to avoid hemolysis. With the exception of the rinsing of the dye injection syringe, saline is used in all other parts of the catheterisation procedure.

This matter of rinsing the dye syringe with distilled water may not be critical, since it is known that an amount of sodium chloride sufficient to make an isotonic solution may be added to dye *that has first been dissolved in distilled water.* This procedure has been used for constant-rate injection techniques without precipitation of the dye.

The usual doses of CG which have been used for dilution curves are as follows:

Adults:	5.0mg
Children:	2.5mg
Infants:	1.25mg

These doses of the dye are usually injected in a mL volume. An average of five dilution curves are required in the performance of a diagnostic cardiac catheterisation. The total dose of dye injected should be kept below 0.7mg/kg/hr.

Calibrating Dye Curves:

To quantitate the dilution curves, standard dilutions of CG in whole blood are made as follows. It is strongly recommended that the same dye that was used for the injections be used in the preparation of these standard dilutions. The most concentrated dye solution is made by accurately diluting 1mL of the 5mg/mL dye with 7mL of distilled water. This concentration is then successfully halved by diluting 4mL of the previous concentration with 4 ml of distilled water. [If a 2.5mg/mL concentration was used for the dilution curves, 1mL of the 2.5mg/mL dye is added to 3mL of distilled water to make the most concentrated "standard" solution. This concentration is then successively halved by diluting 2mL of the previous concentration with 2mL of distilled water.] Then 0.2mL portions (accurately measured from a calibrated syringe) of these dye solutions are added to 5mL aliquols of the subject's blood, giving final concentrations of the dye in blood beginning with 24.0 mg/liter, approximately (actual concentration depends on the exact volume of dye added). This concentration is, of course, successively halved in the succeeding aliquots of the subject's blood. These aliquots of blood containing known amounts of dye, as well as a blank sample of which 0.2mL of saline containing no dye has been added, are then passed through the detecting instrument and a calibration curve is constructed from the deflections recorded.

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HEPATIC FUNCTION STUDIES:

Due to its absorption spectrum, changing concentrations of CG in the blood can be monitored by ear densitometry or by obtaining blood specimens at timed intervals. The technique for both methods is as follows.

The patient should be studied in a fasting, basal state. The patient should be weighed and the dosage calculated on the basis of 0.5mg/kg of body weight.

Under sterile conditions, the CG powder should be dissolved with the Aqueous Solvent furnished. Exactly 5mL of aqueous solvent should be added to the 25mg vial or exactly 10mL of aqueous solvent should be added to the 50mg vial, giving 5mg of dye per mL of solution.

Inject the correct amount of dye into the lumen of an arm vein as rapidly as possible, without allowing the dye to escape outside the vein. *[If the photometric method is used, prior to injecting CG, withdraw 6mL of venous blood from the patient's arm for serum bland and standard curve construction, and through the same needle, inject the correct amount of dye.]*

Ear Densitometry:

Ear oximetry has also been used and makes it possible to monitor the appearance and disappearance of CG without the necessity of withdrawal and spectrophotometric analysis of blood samples for calibration. An ear densitometer which has a compensatory photo-electric cell to correct for changes in blood volume and hematocrit, and a detection photocell which registers CG levels has been described. This device permits simultaneous measurement of cardiac output, blood volume and hepatic clearance of CG and was found to provide a reliable index of plasma removal kinetics after single injections or continuous intrusions of CG. This technique was employed in newborn infants, healthy adults and in children and adults with liver disease. The normal subject has a removal rate of 18 - 24% per minute. Due to the absence of extra-hepatic removal, CG was found to be ideally suited for serial study of severe chronic liver disease and to provide a stable measurement of hepatic blood flow. In larger doses, CG has proven to be particularly valuable in detecting drug induced alterations of hepatic function and in the detection of mild liver injury.

Using the ear densitometer, a dosage of 0.5mg/kg in normal subjects gives the following clearance pattern.

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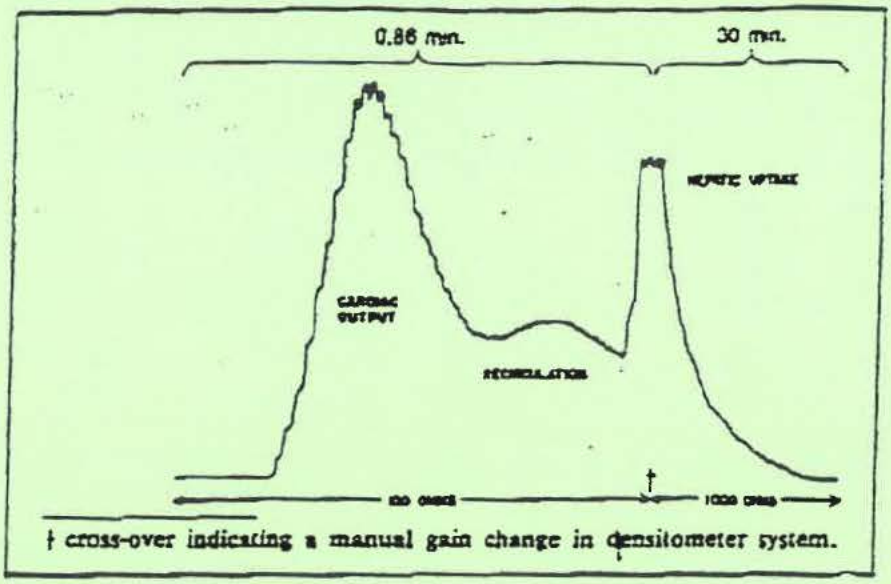

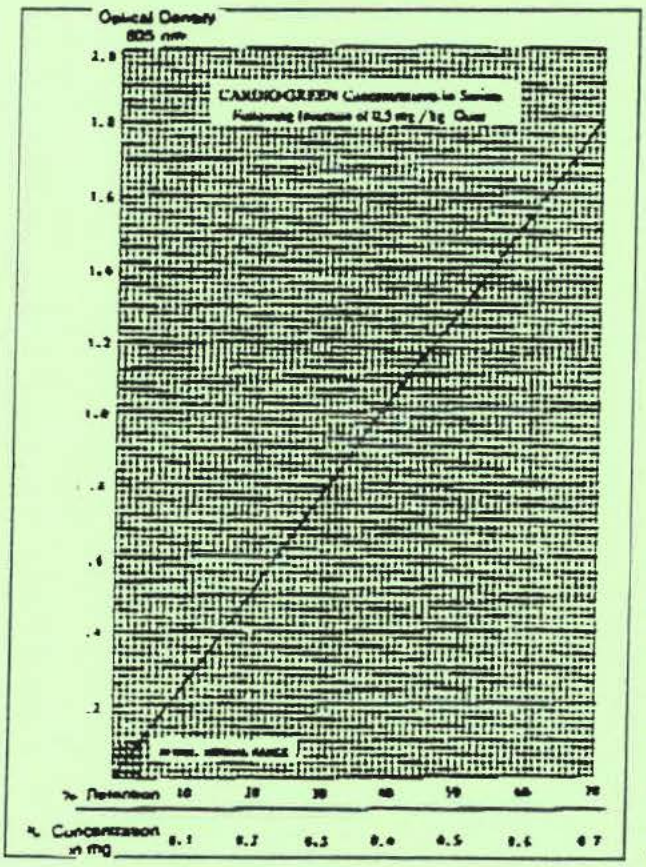

Photometric Method

Determination Using percentage Retention of Dye:

A typical curve obtained by plotting dye concentration versus optical density is shown opposite. Percent retention can be read from this plot.

If more accurate results are desired, a curve using the patients blood and the vial of CG being used in the determination can be constructed as follows:

1. Take 6mL of non-dye containing venous blood from the patient's arm. Place in a test tube and allow the blood to clot. The serum is separated by centrifugation.

2. Pipette 1mL of the serum into a microcuvette.

3. Add 1 lambda (λ) of the 5mg/mL aqueous CG solution to the serum, giving a dilution of 5mg/liter, the standard for 50% retention. [The addition of 2 lambda (λ) of the 5mg/mL CG solution would give 100% retention; however, this concentration cannot be read on the spectrophotometer.]

4. The optical density of this solution is read at 805 nm, using normal serum as the blank.

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5. Using graph paper similar to that used in the illustration, plot the 50% figure obtained in Step 4, and draw a line connecting this point with the zero coordinates.

Percentage Retention:
A single 20 minute sample (withdrawn from a vein in the opposite arm to that injected) is allowed to clot, centrifuged and its optical density is determined at 805 nm using the patients normal serum as the blank. Dye concentration is read from the curve above. A single 20 minute sample of serum in healthy subjects should contain no more than 4% of the initial concentration of the dye. The use of percentage retention is less accurate than percentage disappearance rate, but provides reproducible results. Hemolysis does not interfere with a reading.

Determination Using Disappearance Rate of Dye:
To calculate the percentage disappearance rate, obtain samples at 5, 10, 15 and 20 minutes after injecting the dye. Prepare the samples as in the previous section and measure the optical densities at 805 nm, using the patient's normal serum as the blank. The CG concentration in each timed specimen can be determined by using the concentration curve illustrated . Plot values on semilogarithmic paper.

Specimens containing CG should be read at the same temperature since its optical density is influence by temperature variations.

Normal Values:
Percentage disappearance rate in healthy subjects is 18-24% per minute. Normal biological half-time is 2.5 - 3.0 minutes.

OPHTHALMIC ANGIOGRAPHY STUDIES:
The excitation and emission spectra (Figure 1) and the absorption spectra (Figure 2) of CG make it useful in ophthalmic angiography. The peak absorption and emission if CG lie in a region (800-850 nm) where transmission of energy by the pigment epithelium is more efficient than in the region of visible light energy. CG also has the property of being nearly 98% bound to blood protein, and therefore, excessive dye extravasation does not take place in the highly fenestrated choroidal vasculature. It is, therefore useful in both absorption and fluorescence infrared angiography of the choroidal vasculature when using appropriate filters and film in a fundus camera.

A dosage of 40mg CG dye in 2mL of aqueous solvent has been found to give optimal results. In some patients, half of the volume has been found to produce angiograms of comparable resolution. The antecubital vein injected CG dye bolus should immediately be followed by 5mL bolus of normal saline. Dose should not exceed 0.7mg/kg up to a total dose of 40mg.

Clinically, angiograms of uniformly good quality can be assured only after taking care to optimise the contributions of all possible factors such as filter and film characteristics, film processing, camera focus, patient cooperation, and dye injection. The foregoing injection regimen is designed to provide delivery of a spatially limited dye bolus of optimal concentration to the choroidal vasculature following intravenous injection.

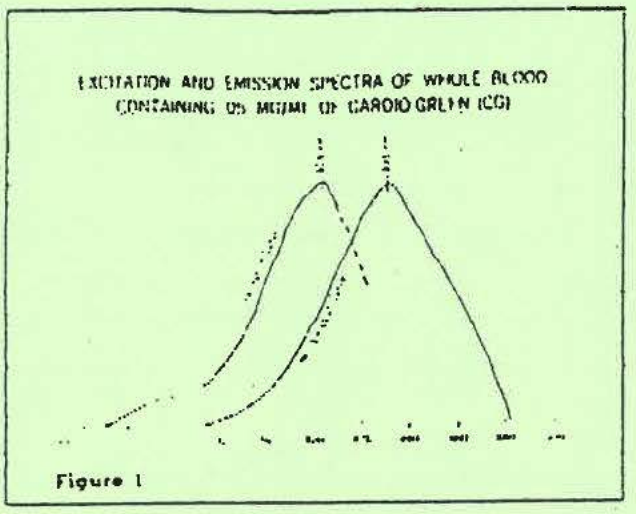

Figure 1

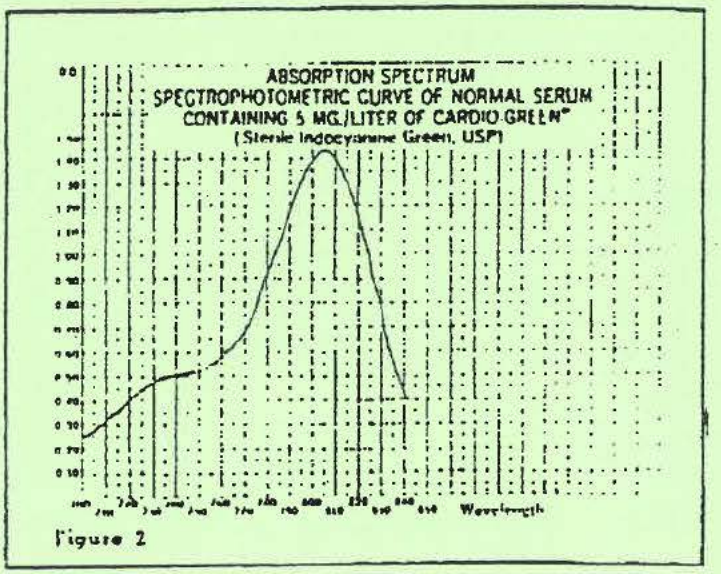

Figure 2

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OVERDOSAGE

There are no data available describing the signs, symptoms, or laboratory findings accompanying overdosage. The LD_{50} after intravenous administration ranges between 60 and 80mg/kg in mice, 50 and 70mg/kg in rats and 50 and 80mg/kg in rabbits.

PRESENTATION

Cardio-Green® (CG®), 25mg vial with two 10mL ampules aqueous solvent, NDC 0011-8361-20.

Cardio-Green, 50mg vial with two 10mL ampules aqueous solvent, NDC 0011-8362-55.

TGA APPROVAL

Pending

NAME AND ADDRESS OF THE SPONSOR

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AUSTRALIA

TECHNICAL INFORMATION

Telephone Technical Services, toll free (800) 638-8663

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