HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INDOCYANINE GREEN for injection safely and effectively. See full prescribing information for INDOCYANINE GREEN for injection.

INDOCYANINE GREEN for injection, for intravenous or interstitial use
Initial U.S. Approval: 1959

RECENT MAJOR CHANGES

Indications and Usage, For determining Cardiac Output, Hepatic Function, and Liver Blood Flow (1.1)	12/2024 Removed
Indications and Usage (1.1, 1.2, 1.3)	12/2024
Dosage and Administration, Indicator-Dilution Studies and Hepatic Function Studies (2.1, 2.2)	12/2024 Removed
Dosage and Administration (2.1, 2.2, 2.3, 2.5)	12/2024

INDICATIONS AND USAGE
Indocyanine Green for injection is an optical imaging agent indicated for:
- Fluorescence imaging of vessels (micro- and macro-vasculature), blood flow and tissue perfusion before, during and after vascular, gastrointestinal, organ transplant, plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures, in adults and pediatric patients aged 1 month and older (1.1)
- Fluorescence imaging of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older (1.2)
- Fluorescence imaging of lymph nodes and lymphatic vessels during lymphatic mapping in adults with cervical and uterine cancer (1.3)
- Ophthalmic angiography in adults and pediatric patients (1.4)

DOSAGE AND ADMINISTRATION
- Visualization of vessels, blood flow and tissue perfusion (2.5 mg/mL solution)
  - o 1.25 mg to 5 mg by intravenous injection is recommended for a surgical procedure in adults and pediatric patients aged 1 month and older.
  - o 3.75 mg to 10 mg by intravenous injection is recommended for visualization of perfusion in extremities through the skin for plastic, micro- and reconstructive surgeries in adults.
  - o Additional doses may be administered. Do not exceed a total dose of 2 mg/kg. (2.1)
- Visualization of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older (2.5 mg/mL solution)
  - o 2.5 mg by intravenous injection at least 45 minutes prior to surgery.
  - o Additional doses may be administered. Do not exceed a total dose of 2 mg/kg. (2.2)
- Lymphatic mapping of cervical and uterine cancer in adults (1.25 mg/mL solution)
  - o 5 mg interstitially as four 1 mL injections.
  - o See Full Prescribing Information for injection techniques. (2.3)
- Ophthalmic Angiography
  - o Doses up to 40 mg in 2 ml of Sterile Water for Injection by intravenous injection. (2.4)
- See Full Prescribing Information for reconstitution instructions. (2.5).

DOSAGE FORMS AND STRENGTHS
For injection: 25 mg of indocyanine green as a lyophilized, green powder for reconstitution in a single-patient-use vial (3)

CONTRAINDICATIONS
Hypersensitivity to indocyanine green (4)

WARNINGS AND PRECAUTIONS
Hypersensitivity reactions: Hypersensitivity reactions including anaphylaxis and urticaria have occurred. Always have cardiopulmonary resuscitation personnel and equipment readily available and monitor patients. (5.1)

ADVERSE REACTIONS
The most common adverse reactions reported are anaphylaxis and urticaria. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Diagnostic Green LLC at 1-844-424-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Interference with Thyroid Radioactive Iodine Uptake Studies: Do not perform radioactive iodine uptake studies for at least one week following the use of Indocyanine Green. (7)

See 17 for PATIENT COUNSELING INFORMATION
Revised: 01/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Visualization of Vessels, Blood Flow and Tissue Perfusion
Indocyanine Green is indicated for fluorescence imaging of vessels (micro- and macro- vasculature), blood flow and tissue perfusion before, during and after vascular, gastrointestinal, organ transplant, plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures in adults and pediatric patients aged 1 month and older.

1.2 Visualization of Extrahepatic Biliary Ducts
Indocyanine Green is indicated for fluorescence imaging of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older.

1.3 Lymphatic Mapping of Cervical and Uterine Cancer
Indocyanine Green is indicated for fluorescence imaging of lymph nodes and delineation of lymphatic vessels during lymphatic mapping in adults with cervical and uterine cancer for which this procedure is a component of intraoperative management.

1.4 Ophthalmic Angiography
Indocyanine Green is indicated for use in ophthalmic angiography in adults and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose, Administration and Imaging for Visualization of Vessels, Blood Flow and Tissue Perfusion
Dosing
Adults:
The recommended dose of Indocyanine Green for a single image sequence for visualization of vessels, blood flow and tissue perfusion in adults is 1.25 mg to 5 mg administered intravenously as 0.5 mL to 2 mL of a 2.5 mg/mL solution.

For visualization of perfusion in extremities through the skin in adults, the recommended dose is 3.75 mg to 10 mg administered intravenously as 1.5 mL to 4 mL of a 2.5 mg/mL solution.

Immediately flush with a 10 mL bolus of 0.9% Sodium Chloride Injection.

Pediatric patients aged 1 month and older:
The recommended dose of Indocyanine Green for a single image sequence for visualization of vessels, blood flow and tissue perfusion in pediatric patients aged 1 month and older is 1.25 mg to 5 mg administered intravenously as 0.5 mL to 2 mL of a 2.5 mg/mL solution. Lower doses may be administered in younger patients and in those with lower body weight. Adjust the amount and type of flush to avoid volume and/or sodium overload.

In both adults and pediatric patients aged 1 month and older, additional doses may be administered to obtain imaging sequences during the procedure. Do not exceed the maximum total dose of 2 mg/kg.

Administration
Prior to the imaging procedure, draw up the desired dose of Indocyanine Green solution into appropriate syringes and prepare a 10 mL syringe of 0.9% Sodium Chloride Injection.

Administer via a central or peripheral venous line using a three-way stopcock attached to an injection port on the infusion line. Inject the prepared Indocyanine Green into the line as a tight bolus. Immediately switch the access on the stopcock and inject the prepared flush.

Imaging Instructions
Indocyanine Green may be used with an FDA-authorized imaging device that is intended to be used with indocyanine green for fluorescence imaging of vessels, blood flow and tissue perfusion.

A fluorescence response should be visible in blood vessels within 5 seconds to 15 seconds after injection.

2.2 Recommended Dose, Administration and Imaging for Visualization of Extrahepatic Biliary Ducts
Dosing and Administration
The recommended dose of Indocyanine Green for visualization of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older is 2.5 mg administered intravenously as 1 mL of a 2.5 mg/mL solution at least 45 minutes prior to surgery.

Additional doses may be administered to obtain imaging sequences during the procedure.

Do not exceed a total dose of 2 mg/kg.

Imaging Instructions
Indocyanine Green may be used with an FDA-authorized imaging device that is intended to be used with indocyanine green for fluorescence imaging of extrahepatic biliary ducts.

Fluorescence is visible in the biliary tree within 45 minutes after injection.

2.3 Recommended Dose, Administration and Imaging for Lymphatic Mapping of Cervical and Uterine Cancer
Dosing and Administration
The recommended dose of Indocyanine Green for lymphatic mapping of cervical and uterine cancer in adults is 5 mg administered interstitially as four 1 mL injections of a 1.25 mg/mL solution into the cervix, at the 3 o' clock and the 9 o'clock positions with a superficial (1 mm to 3 mm) and a deep (1 cm to 3 cm) injection at each position.

Imaging Instructions
Indocyanine Green may be used with an FDA-authorized imaging device that is intended to be used with indocyanine green for fluorescence imaging of lymph nodes and delineation of lymphatic vessels during lymphatic mapping of cervical and uterine cancer.

Fluorescent lymphatic vessels and lymph nodes should begin to be visible within 1 minute after injection.

2.4 Recommended Dose and Administration for Ophthalmic Angiography
Dosing and Administration
Doses up to 40 mg Indocyanine Green in 2 mL of Sterile Water for Injection depending on the imaging equipment and technique used should be administered intravenously and immediately followed by a 5 mL bolus of 0.9% Sodium Chloride Injection. The antecubital vein can be used for Indocyanine Green administration.

2.5 Reconstitution Instructions
General
- Prepare Indocyanine Green for injection using aseptic techniques prior to procedure.
- Inspect the reconstituted solution for particulate matter. The reconstituted solution should be a clear, green solution.
- Use the prepared solution within 6 hours.
- Discard any unused product.

Visualization of Vessels, Blood Flow, Tissue Perfusion and Extrahepatic Biliary Ducts
Dissolve 25 mg of Indocyanine Green with 10 mL Sterile Water for Injection to form a concentration of 2.5 mg/mL indocyanine green.

Lymphatic Mapping of Cervical and Uterine Cancer
Dissolve 25 mg of Indocyanine Green with 20 mL Sterile Water for Injection to form a concentration of 1.25 mg/mL indocyanine green.

Ophthalmic Angiography
Dissolve doses up to 40 mg of Indocyanine Green with 2 mL Sterile Water for Injection.

3 DOSAGE FORMS AND STRENGTHS
For injection: 25 mg of indocyanine green as a sterile, lyophilized, green powder for reconstitution provided in a 25 mL single-patient-use vial.

4 CONTRAINDICATIONS
Indocyanine Green is contraindicated in patients with a history of hypersensitivity to indocyanine green. Reactions have included anaphylaxis *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions including anaphylaxis, urticaria and deaths due to anaphylaxis have been reported following intravenous administration of Indocyanine Green *[see Adverse Reactions (6)]*. Indocyanine Green is contraindicated in patients with a history of hypersensitivity to indocyanine green *[see Contraindications (4)]*. Always have cardiopulmonary resuscitation personnel and equipment readily available and monitor all patients for hypersensitivity reactions.

5.2 Interference with Thyroid Radioactive Iodine Uptake Studies

Because Indocyanine Green contains sodium iodide, the iodine-binding capacity of thyroid tissue may be reduced for at least one week following administration *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*.

The following adverse reactions have been identified during post-approval use of Indocyanine Green. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylaxis, urticaria

7 DRUG INTERACTIONS

Interference with Thyroid Radioactive Iodine Uptake Studies

Because Indocyanine Green contains sodium iodide, the iodine-binding capacity of thyroid tissue may be reduced for at least one week following administration. Do not perform radioactive iodine uptake studies for at least one week following administration of Indocyanine Green.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of Indocyanine Green in pregnant women. Available data from a very small number of scientific literature studies with indocyanine green use in pregnant women over several decades have not reported any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Data from one small study in which indocyanine green was administered intravenously to pregnant women during labor suggest there is no placental transfer of the drug. Animal reproduction studies have not been conducted with indocyanine green.

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Seventeen cases of indocyanine green use in lactating women have been reported in the scientific literature with no adverse events observed in the breastfed infant. However, there are no data on the presence of indocyanine green in human milk or the effects on milk production. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Indocyanine Green and any potential adverse effects on the breastfed infant from Indocyanine Green or from the underlying maternal condition.

8.4 Pediatric Use

Use of Indocyanine Green for visualization of vessels, blood flow and tissue perfusion has been established in pediatric patients aged 1 month and older. Pediatric use is supported by published data in 49 pediatric patients who received indocyanine green for assessment of blood flow and tissue perfusion in cardiovascular, vascular, and plastic, micro- and reconstructive surgical procedures, and by clinical trials in adults. No overall differences in safety or effectiveness have been observed between pediatric patients and adults. The dose range was similar to the effective dose range in adults *[see Dosage and Administration (2.1)]*. The use of Indocyanine Green for visualization of vessels, blood flow and tissue perfusion has not been established in pediatric patients aged less than 1 month.

Use of Indocyanine Green for visualization of extrahepatic biliary ducts has been established in pediatric patients aged 12 years and older. Pediatric use is supported by clinical trials in adults in addition to clinical use in pediatric patients. No overall differences in safety or effectiveness have been observed between pediatric patients and adults. The dose range was similar to the effective dose range in adults *[see Dosage and Administration (2.2)]*. The use of Indocyanine Green for visualization of extrahepatic biliary ducts has not been established in pediatric patients aged less than 12 years.

Use of Indocyanine Green for visualization of lymph nodes and lymphatic vessels during lymphatic mapping for cervical and uterine cancer have not been established in pediatric patients.

Use of Indocyanine Green for ophthalmic angiography has been established in pediatric patients. Pediatric use is supported by evidence from the published literature.

8.5 Geriatric Use

Of the total number of patients in clinical studies of indocyanine green for visualization of vessels, blood flow and tissue perfusion, 7% were 65 and over, while 1% were 75 and over. Of the total number of patients in clinical studies of indocyanine green for visualization of lymph nodes and lymphatic vessels during lymphatic mapping of cervical and uterine cancer, 9% were 65 and over, while 2% were 75 and over. Clinical studies of indocyanine green for visualization of extrahepatic biliary ducts did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

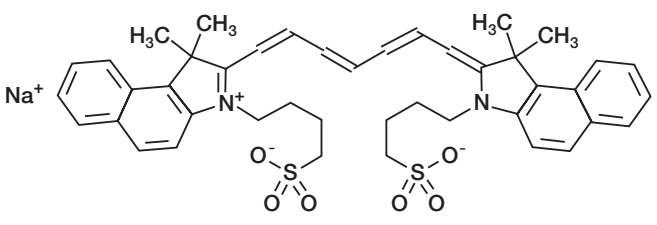
11 DESCRIPTION

Indocyanine Green for injection is an optical imaging agent for intravenous or interstitial use.

Each vial contains 25 mg of indocyanine green with not more than 5% sodium iodide as a sterile, lyophilized, green powder. Indocyanine Green has a pH of 5.5-7.5 when reconstituted with Sterile Water for Injection, USP.

The chemical name for Indocyanine Green is 1 HBenz[e]indolium, 2-[7-[1,3-dihydro-1,1-dimethyl-3-(4- sulfobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-, hydroxide, inner salt, sodium salt.

Molecular Formula: C43H47N2NaO6S2; Molecular Mass: 774.96 g/mol, with the following structural formula:



Indocyanine green has a peak spectral absorption at 805 nm in blood.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

When bound to proteins in plasma or in lymph fluid, indocyanine green absorbs light in the near-infrared region with peak absorption at 805 nm and emits fluorescence (light) at a slightly longer wavelength, with peak emission at 830 nm. Fluorescence imaging devices provide external energy as near infrared light for indocyanine green to absorb, resulting in excitation of the indocyanine green, and the emitted light (fluorescence) is transferred from the field of view to an image on a monitor. These optical properties of indocyanine green are utilized in fluorescence imaging of the micro- and macro-vasculature, blood flow and tissue perfusion, the extrahepatic biliary ducts, and for lymphatic mapping of lymph nodes and lymphatic vessels.

12.2 Pharmacodynamics

There are no pharmacodynamic data.

12.3 Pharmacokinetics

Distribution

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

Following interstitial injection, indocyanine green binds to proteins in lymph fluid and the interstitial space, is taken up by the lymphatic vessels, and drains to the lymph nodes.

Since excessive dye extravasation does not take place in the highly fenestrated choroidal vasculature, Indocyanine Green is useful in both absorption and fluorescence infrared angiography of the choroidal vasculature when using appropriate filters and film in a fundus camera.

Elimination

Indocyanine green is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to evaluate the potential for carcinogenicity, mutagenicity, or impairment of fertility by indocyanine green.

14 CLINICAL STUDIES

14.1 Lymphatic Mapping of Cervical and Uterine Cancer

The effectiveness of Indocyanine Green for fluorescence imaging of lymph nodes and delineation of lymphatic vessels during lymphatic mapping in adults with cervical and uterine cancer has been established based on a study of another formulation of indocyanine green for injection. Below is a description of the FILM Study (NCT 02209532).

The study was a randomized, prospective, multi-center, open-label study in patients with early stage uterine or cervical cancer and no known regional nodal or metastatic disease by standard clinical evaluation. Indocyanine green and a blue dye comparator were injected into the cervix of patients at the beginning of the operative procedure.

A total of 176 patients were randomized to receive either indocyanine green followed by blue dye or blue dye followed by indocyanine green. A total of four 1 mL injections of a 1.25 mg/ml solution of indocyanine green for a total dose of 5 mg were administered interstitially into the cervix at the 3 o'clock and 9 o'clock positions with a superficial (1 mm to 3 mm) and a deep (1 cm to 3 cm) injection at each position.

Lymphatic mapping was performed intraoperatively using a fluorescence imaging device and standard light, followed by excision of tissues identified by indocyanine green, blue dye, or the surgeon's visual and palpation examination. The resected tissues were evaluated by histopathology to confirm presence of lymph nodes. The efficacy of indocyanine green in the detection of lymphatic vessels and lymph nodes during lymphatic mapping procedures was determined by the number of histology-confirmed lymph nodes detected by indocyanine green and/or the blue dye comparator.

The mean age of the 176 patients was 63 years (range: 31 to 88 years); distribution by race and ethnicity was 79% White, 4% Black or African American, 3% Asian, 13% Hispanic/Latino and 1% other.

Table 1 shows the distribution of resected, confirmed lymph nodes detected by indocyanine green or blue dye in the modified intent-to-treat population (mITT). Among the confirmed lymph nodes identified, 93% were identified using indocyanine green, and 43% were identified using blue dye, a difference of 50% [95% confidence interval 39% to 60%].

Table 1: Distribution of Resected, Confirmed Lymph Nodes Detected by Indocyanine Green or Blue Dye (BD)

Analysis Population	Nodes (n)	All Lymph Nodes Detected with Indocyanine Green	All Lymph Nodes Detected with BD	All Lymph Nodes Detected with Indocyanine Green Only	Lymph Nodes Detected with BD Only	Lymph Nodes Detected with Neither
mITT	513	(476/513) 93%	(220/513) 43%	(262/513) 51%	(6/513) 1%	(31/513) 6%

Table 2 shows the number of patients with at least one resected, confirmed lymph node and the number of patients with at least one bilateral lymph node pair detected by indocyanine green or blue dye. With indocyanine green, approximately 97% of patients had at least one resected, confirmed lymph node detected and 73% had at least one bilateral lymph node pair detected, compared with 68% and 28%, respectively, with blue dye (p-values for each analysis <0.0001).

Table 2: Distribution of Patients with at Least One Confirmed Unilateral Lymph Node/ Bilateral Pair Detected by Indocyanine Green or Blue Dye (BD)

Analysis Population	Patients (n)	Patients with All Lymph Nodes Detected with Indocyanine Green	Patients with All Lymph Nodes Detected with BD	Patients with Lymph Nodes Detected with Indocyanine Green only	Patients with Lymph Nodes Detected with BD only	Patients with Lymph Nodes Detected with Neither
mITT Unilateral*	172	(167/172) 97%	(118/172) 68%	(51/172) 30%	(2/172) 1%	(3/172) 3%
mITT Bilateral**		(126/172) 73%	(49/172) 28%	(79/172) 46%	(2/172) 1%	(44/172) 26%

*: patients with at least one resected confirmed lymph node detected unilaterally
**: patients with at least one resected confirmed lymph node detected bilaterally

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Indocyanine Green for injection is supplied as a kit (NDC 70100-424-02) containing the following:

- Six 25 mL single-patient-use vials of Indocyanine Green (25 mg each) as a sterile, lyophilized green powder for reconstitution NDC 70100-424-01
- Six single-dose vials of Sterile Water for Injection (10 mL each) NDC 63323-185-10 or NDC 0409-4887-17 or NDC 0641-6147-01.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F).

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise patients to seek medical attention for reactions following injection of Indocyanine Green such as difficulty breathing, swollen tongue or throat, skin reactions including hives, itching and flushed or pale skin, low blood pressure, a weak and rapid pulse and other symptoms or signs of an anaphylactic reaction *[see Warnings and Precautions (5.1)]*.

Manufactured by:
Patheon Italia S.p. A.
20052 Monza (Milano) ITALY
or
LYOCONTRACT GmbH
38871 Ilsenburg, GERMANY

Distributed by:
Diagnostic Green LLC
Farmington Hills, MI 48331

Sterile Water for injection, USP
is manufactured by:
Fresenius Kabi USA, LLC
Grand Island, NY 14072
or
Hospira, Inc.
Rocky Mount, NC 27804
or
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

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