HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYOGREEN safely and effectively. See full prescribing information for ZYOGREEN.

ZYOGREEN® (indocyanine green injection), for intravenous or interstitial use
Initial U.S. Approval: 1959

----------INDICATIONS AND USAGE----------

ZYOGREEN 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 (1.1)
- Fluorescence imaging of extrahepatic biliary ducts in adults and pediatric patients from birth to less than 1 year of age and 6 years of age 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
  - Pediatric patients less than 1 month of age: 0.15 mg/kg
  - Adults and pediatric patients 1 month of age and older: 1.25 mg to 5 mg by intravenous injection (2.2)
- Extremity perfusion visualization through the skin
  - Pediatric patients less than 1 month of age: 0.15 mg/kg
  - Pediatric patients 1 month of age and older: 1.25 mg to 5 mg
  - Adults: 3.75 mg to 10 mg by intravenous injection (2.2)
- Visualization of extrahepatic biliary ducts
  - Pediatric patients from birth to less than 1 year of age: 0.1 mg/kg (not to exceed 2.5 mg) 12 to 24 hours prior to surgery
  - Adults and pediatric patients 6 years of age and older: 2.5 mg by intravenous injection at least 45 minutes prior to surgery (2.3)
- Lymphatic mapping of cervical and uterine cancer in adults
  - 5 mg interstitially as four 1.25 mg injections.
  - See Full Prescribing Information for injection techniques. (2.4)
- Ophthalmic Angiography in adults and pediatric patients: doses up to 40 mg by intravenous injection. (2.5)
- The total dose must not exceed 2 mg/kg for all patients.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 25 mg per 10 mL (2.5 mg per mL) of indocyanine green as a ready-to-use solution in a single-dose ampule (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to indocyanine green (4)

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity reactions: 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 Sagent Pharmaceuticals at 1–800-625-1618 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 ZYOGREEN. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2026

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

ZYOGREEN 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.

1.2 Visualization of Extrahepatic Biliary Ducts

ZYOGREEN is indicated for fluorescence imaging of extrahepatic biliary ducts in adults and pediatric patients from birth to less than 1 year of age and 6 years of age and older.

1.3 Lymphatic Mapping of Cervical and Uterine Cancer

ZYOGREEN 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

ZYOGREEN is indicated for use in ophthalmic angiography in adults and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- ZYOGREEN is a ready-to-use solution, provided in ampules at a concentration of 2.5 mg per mL.
- Use immediately after opening ampule.
- Withdraw the contents of the ampule through a 5 micrometer or smaller straw/filter needle to ensure that the withdrawn solution contains no particulates.
- Visually inspect the withdrawn solution for particulate matter and discoloration prior to administration.
- Each ampule of ZYOGREEN is for a single dose. Discard any unused portion.

2.2 Recommended Dose, Administration and Imaging for Visualization of Vessels, Blood Flow and Tissue Perfusion

Dosing

- Administer the recommended initial dose of ZYOGREEN as a single intravenous injection. The recommended initial dose is based on patient age as shown in Table 1.
- Additional doses may be administered to obtain imaging sequences during the procedure.
- The maximum total dose for any patient, including all initial and additional doses combined, must not exceed 2 mg/kg.

Table 1. Recommended Dose of ZYOGREEN for Visualization of Vessels, Blood Flow and Tissue Perfusion by Age

Imaging	Patient Age	Recommended Dose
Visualization of vessels, blood flow and tissue perfusion (single imaging sequence)	Pediatric patients from birth to less than 1 month of age	0.15 mg/kg*
	Pediatric patients 1 month of age and older	1.25 mg to 5 mg
	Adults	
Extremity perfusion visualization through the skin (single imaging sequence)	Pediatric patients from birth to less than 1 month of age	0.15 mg/kg*
	Pediatric patients 1 month of age and older	1.25 mg to 5 mg
	Adults	3.75 mg to 10 mg

*Dose based on actual body weight

Administration

- Prior to the imaging procedure, draw the desired dose of ZYOGREEN into a syringe.
- For adults, prepare 10 mL of 0.9% Sodium Chloride Injection in a separate syringe for flushing.
- For pediatric patients, adjust the amount and type of flush for the individual patient to avoid volume and sodium overload.
- Administer via a central or peripheral venous line using a three-way stopcock.
- Inject ZYOGREEN as a tight bolus.
- Immediately switch the access on the stopcock and inject the prepared flush.

Imaging Instructions

- Use ZYOGREEN 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.

2.3 Recommended Dose, Administration and Imaging for Visualization of Extrahepatic Biliary Ducts

Dosing and Administration

- Administer the recommended dose of ZYOGREEN as a single intravenous injection. The initial dose and timing of administration are based on patient age as shown in Table 2.
- Additional doses may be administered to obtain imaging sequences during the procedure.
- The maximum total dose for any patient, including all initial and additional doses combined, must not exceed 2 mg/kg.

Table 2: Recommended Dose of ZYOGREEN for Visualization of Extrahepatic Biliary Ducts by Age

Patient Age	Recommended Dose	Timing of Administration
Pediatric patients from birth to less than 1 year of age	0.1 mg/kg* (Do not exceed 2.5 mg)	Administer 12 hours to 24 hours prior to surgery
Pediatric patients from 1 to less than 6 years of age	Not indicated	Not applicable
Pediatric patients 6 years of age and older	2.5 mg	Administer at least 45 minutes prior to surgery
Adults		

*Dose based on actual body weight

Imaging Instructions

- Use ZYOGREEN with an FDA-authorized imaging device that is intended to be used with indocyanine green for fluorescence imaging of extrahepatic biliary ducts.
- For patients 6 years of age and older, fluorescence is visible in the biliary tree within 45 minutes after injection.
- For patients less than 1 year of age, fluorescence is visible in the biliary tree between 12 hours and 24 hours after injection.

2.4 Recommended Dose, Administration and Imaging for Lymphatic Mapping of Cervical and Uterine Cancer

Dosing and Administration

- The recommended dose of ZYOGREEN for lymphatic mapping of cervical and uterine cancer in adults is 5 mg.
- Administer this dose interstitially as four separate 1.25 mg injections into the cervix, with each injection consisting of a 0.5 mL volume of the 2.5 mg/mL solution. The injections should be given at the 3 o'clock and the 9 o'clock positions of the cervix. At each of these two positions, one superficial injection (1 mm to 3 mm depth) and one deep injection (1 cm to 3 cm depth) are required to complete the dosing.

Imaging Instructions

- Use ZYOGREEN 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.

2.5 Recommended Dose and Administration for Ophthalmic Angiography

- Administer doses up to 40 mg of ZYOGREEN intravenously for ophthalmic angiography in adult and pediatric patients. The specific dose should be determined based on the imaging equipment and technique being used.
- The total dose must not exceed 2 mg/kg.
- For adults, administer a 5 mL bolus of 0.9% Sodium Chloride Injection immediately following the injection.
- For pediatric patients, adjust the amount and type of flush solution for the individual patient to avoid volume and sodium overload.
- The antecubital vein can be used for ZYOGREEN administration.

3 DOSAGE FORMS AND STRENGTHS

Injection: 25 mg per 10 mL (2.5 mg per mL) of indocyanine green as a deep emerald-green ready-to-use solution in a single-dose ampule.

4 CONTRAINDICATIONS

ZYOGREEN 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, the active ingredient in ZYOGREEN *[see Adverse Reactions (6)]*.

ZYOGREEN 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 ZYOGREEN 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, the active ingredient in ZYOGREEN. 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 ZYOGREEN 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 ZYOGREEN.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no adequate and well-controlled studies of ZYOGREEN 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 ZYOGREEN and any potential adverse effects on the breastfed infant from ZYOGREEN or from the underlying maternal condition.

8.4 Pediatric Use

Use in Pediatric Patients for Visualization of Vessels, Blood Flow and Tissue Perfusion
The safety and effectiveness of ZYOGREEN 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 have been established in pediatric patients. Use of ZYOGREEN for this indication in pediatric patients is supported by evidence from clinical trials in adults and published studies that demonstrated the utility of indocyanine green for blood vessel evaluation and assessment of tissue perfusion in 59 pediatric patients, including 6 neonates, during surgeries within the indicated surgical categories.

Use in Pediatric Patients for Visualization of Extrahepatic Biliary Ducts
The safety and effectiveness of ZYOGREEN for fluorescence imaging of extrahepatic biliary ducts have been established in pediatric patients from birth to less than 1 year of age and in those 6 years of age and older. Use of ZYOGREEN for this indication in these age groups is supported by evidence from clinical trials in adults and from the following published studies in pediatric patients.

For patients less than 1 year of age, supporting publications included two prospective observational studies and one retrospective case series evaluating a total of 34 pediatric patients (age range: 2 to 119 days) with jaundice undergoing Kasai portoenterostomy who received indocyanine green for fluorescence imaging of biliary structures.

For patients 6 years of age and older, a supporting publication consisted of a prospective, single institution case series in 31 pediatric patients (age range: 6 to 18 years) undergoing cholangiography with indocyanine green during laparoscopic cholecystectomy.

The safety and effectiveness of ZYOGREEN have not been established for fluorescence imaging of extrahepatic biliary ducts in pediatric patients 1 year to less than 6 years of age.

Use in Pediatric Patients for Ophthalmic Angiography
ZYOGREEN is indicated for ophthalmic angiography in pediatric patients.

Use in Pediatric Patients for Lymphatic Mapping of Cervical and Uterine Cancer
The safety and effectiveness of ZYOGREEN for fluorescence imaging of lymph nodes and lymphatic vessels during lymphatic mapping for cervical and uterine cancer have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects 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 subjects 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. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between elderly and younger patients.

Clinical studies of indocyanine green for visualization of extrahepatic biliary ducts did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

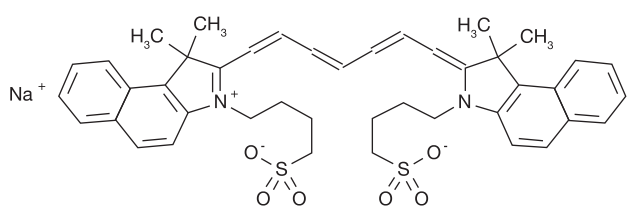
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

11 DESCRIPTION

ZYOGREEN (indocyanine green injection) is an optical imaging agent for intravenous or interstitial use.

The chemical name for indocyanine green is 1*H*-Benz[e]indolium, 2-[7-[1,3-dihydro-1,1-dimethyl-3-(4- sulfobutyl)-2*H*-benz[e]indol-2-ylidene]-1,3,5-hepta-trienyl]-1,1-dimethyl-3-(4-sulfobutyl)-, hydroxide, inner salt, sodium salt.

It has a molecular formula of $C_{43}H_{47}N_2NaO_6S_2$ and a molecular mass of 774.96 g/mol.
The structural formula is shown below.



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

ZYOGREEN is a sterile, ready-to-use solution. Each mL contains 2.5 mg of indocyanine green with not more than 0.125 mg sodium iodide and the following inactive ingredients: 1 mg sodium ascorbate and water for injection with a pH between 5.5 and 7.5.

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 is 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 cerebrospinal 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, ZYOGREEN 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 ZYOGREEN 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. 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 3 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 3: 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	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 4 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 4: 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
ZYOGREEN (indocyanine green injection) is a deep emerald-green ready-to-use solution in amber glass ampules supplied as follows:

NDC	ZYOGREEN® (indocyanine green injection) (2.5 mg per mL)	Package Factor
25021-841-10	25 mg per 10 mL Single-Dose Ampules	5 ampules per carton

Storage and Handling
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store in original carton to protect from light.
Do not refrigerate or freeze.
Use immediately after opening ampule. Discard unused portion.

Sterile, Nonpyrogenic, Preservative-free.
Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions
Advise patients to seek medical attention for reactions following injection of ZYOGREEN 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)]*.

sagent

Mfd. for SAGENT Pharmaceuticals
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Made in France

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