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

SPY AGENT® GREEN (indocyanine green for injection), for intravenous, interstitial, or intradermal use
Initial U.S. Approval: 1959

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.4)	06/2023
Dosage and Administration (2.4)	06/2023

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

SPY AGENT GREEN is an optical imaging agent indicated for use with a fluorescence imaging device for:

- Visualization of vessels (micro- and macro-vasaculature), 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)
- Visualization of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older. (1.2)
- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in adults with cervical and uterine cancer. (1.3)
- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in adults with breast cancer. (1.4)

----------DOSAGE AND ADMINISTRATION----------

- Visualization of vessels, blood flow and tissue perfusion (2.5 mg/mL solution)
  - 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.
  - 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.
  - 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)
  - 2.5 mg by intravenous injection at least 45 minutes prior to surgery.
  - 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)
  - 5 mg interstitially as four 1 mL injections.
  - See Full Prescribing Information for injection techniques. (2.3)
- Lymphatic mapping of breast cancers in adults (2.5 mg/mL solution)
  - 0.25 mg per breast intradermally as two 0.05 mL peri-areolar injections.
  - A subsequent peri-tumoral dose of 0.375 mg per breast (three 0.05 mL injections) may be administered intradermally.
  - See Full Prescribing Information for injection techniques. (2.4)
- See Full Prescribing Information for reconstitution instructions. (2.5).

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

For injection: 25 mg 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----------

Lymphatic mapping of breast cancers: Most common adverse reactions were skin and injection site discoloration in two patients (1.4%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Stryker Corp. at 1-800-624-4422 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 a week following the use of SPY AGENT GREEN. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Visualization of Vessels, Blood Flow and Tissue Perfusion

SPY AGENT 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

SPY AGENT 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

SPY AGENT 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 Lymphatic Mapping of Breast Cancer

SPY AGENT GREEN is indicated for fluorescence imaging of lymph nodes and delineation of lymphatic vessels during lymphatic mapping in adults with breast cancer for which this procedure is a component of intraoperative management.

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 SPY AGENT 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, USP.

Pediatric patients aged 1 month and older:

The recommended dose of SPY AGENT 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 SPY AGENT GREEN solution into appropriate syringes and prepare a 10 mL syringe of 0.9% Sodium Chloride Injection, USP.

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 SPY AGENT GREEN into the line as a tight bolus. Immediately switch the access on the stopcock and inject the prepared flush.

Imaging Instructions
SPY AGENT GREEN may be used with either the SPY® Elite or PINPOINT® Fluorescence Imaging Systems or with a FDA cleared or approved imaging device that is specifically indicated for use 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 SPY AGENT 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
SPY AGENT GREEN may be used with the PINPOINT® Fluorescence Imaging System or with a FDA cleared or approved imaging device that is specifically indicated for use 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 SPY AGENT 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
SPY AGENT GREEN may be used with the PINPOINT® Fluorescence Imaging System or with a FDA cleared or approved imaging device that is specifically indicated for use 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, Administration and Imaging for Lymphatic Mapping of Breast Cancer

Dosing and Administration
The recommended dose of SPY AGENT GREEN for lymphatic mapping of breast cancer in adults is 0.25 mg per breast administered intradermally as two 0.05 mL injections of a 2.5 mg/mL solution into the peri-areolar area at the 12 o'clock and the 9 o'clock positions for the right breast or at the 12 o'clock and 3 o'clock positions for the left breast.

If lymphatic flow towards the axillary lymph nodes is not visualized, a subsequent peri-tumoral dose of 0.375 mg (three 0.05 mL injections intradermally at the 12 o'clock, 3 o'clock and 9 o'clock positions) is recommended.

Imaging Instructions
SPY AGENT GREEN may be used during open field surgery with the SPY Portable Handheld Imaging (SPY-PHI®) System or with a FDA cleared or approved imaging device that is specifically indicated for use with indocyanine green for fluorescence imaging of lymph nodes and delineation of lymphatic vessels during lymphatic mapping of breast cancer.

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

2.5 Reconstitution Instructions

General
- Prepare SPY AGENT GREEN under sterile conditions prior to surgery.
- 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 and Lymphatic Mapping of Breast Cancer
Dissolve SPY AGENT GREEN with 10 mL Sterile Water for Injection, USP to form a concentration of 2.5 mg indocyanine green/mL.

Lymphatic Mapping of Cervical and Uterine Cancer
Dissolve SPY AGENT GREEN with 20 mL Sterile Water for Injection, USP to form a concentration of 1.25 mg indocyanine green/mL.

3 DOSAGE FORMS AND STRENGTHS

For injection: 25 mg of indocyanine green as a sterile, lyophilized, green powder for reconstitution provided in a 20 mL or a 25 mL single-patient-use vial.

4 CONTRAINDICATIONS

SPY AGENT 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 (6.2)].* SPY AGENT 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 SPY AGENT GREEN contains iodine, 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)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Lymphatic Mapping of Breast Cancer

In an open-label, single arm, clinical trial, 151 patients with breast cancer received a single dose of 0.25 mg SPY AGENT GREEN intradermally into the peri-areolar area. Five patients received a subsequent peri-tumoral injection of 0.375 mg intradermally in addition to the peri-areolar dose of 0.25 mg *[see Clinical Studies (14.2)]*.

Skin discoloration including injection site discoloration were reported in two patients (1.4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of indocyanine green products including SPY AGENT 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 SPY AGENT GREEN contains iodine, 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 SPY AGENT GREEN.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.4 Pediatric Use

Use of SPY AGENT 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, 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 SPY AGENT GREEN for visualization of vessels, blood flow and tissue perfusion has not been established in pediatric patients aged less than 1 month.

Use of SPY AGENT 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 SPY AGENT GREEN for visualization of extrahepatic biliary ducts has not been established in pediatric patients aged less than 12 years.

The safety and efficacy of SPY AGENT GREEN for visualization of lymph nodes and lymphatic vessels during lymphatic mapping for cervical and uterine cancer and breast cancer have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of patients in clinical studies of SPY AGENT GREEN in 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 SPY AGENT GREEN in 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. Of the total number of patients in clinical studies of SPY AGENT GREEN in visualization of lymph nodes and lymphatic vessels during lymphatic mapping of breast cancer, 38% were 65 and over, while 8% were 75 and over.

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.

Clinical studies of SPY AGENT GREEN in 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. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

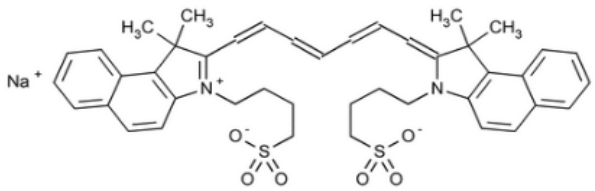
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

11 DESCRIPTION

SPY AGENT GREEN (indocyanine green for injection, USP) is a water soluble, optical imaging agent which is reconstituted with Sterile Water for Injection, USP, for intravenous, interstitial or intradermal use. Each vial contains a sterile, lyophilized, green powder containing 25 mg of indocyanine green with not more than 5% sodium iodide. Hydrochloric acid or sodium hydroxide may be used to adjust the pH prior to lyophilization.

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-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-, hydroxide, inner salt, sodium salt.

Molecular Formula: $C_{43}H_{47}N_2NaO_6S_2$; Molecular Mass: 774.96 g/mol, with the following structural formula:



Indocyanine green has a peak spectral absorption at 805 nm in blood. SPY AGENT GREEN has a pH of 5.5 to 7.5 when reconstituted with Sterile Water for Injection, USP.

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 relevant 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 or intradermal injections, 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.

Elimination

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

14 CLINICAL STUDIES

14.1 Lymphatic Mapping of Cervical and Uterine Cancer

The FILM Study (NCT 02209532) 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. SPY AGENT 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 SPY AGENT GREEN followed by blue dye or blue dye followed by SPY AGENT GREEN. Four 1 mL injections of a 1.25 mg/mL solution of SPY AGENT 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 the PINPOINT® Fluorescence Imaging System and standard light, followed by excision of tissues identified by SPY AGENT 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 SPY AGENT GREEN and the PINPOINT® Fluorescence Imaging System 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 SPY AGENT 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 SPY AGENT GREEN or blue dye in the modified intent-to-treat population (mITT). Among the confirmed lymph nodes identified, 93% were identified using SPY AGENT 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 SPY AGENT GREEN or Blue Dye (BD)

Analysis Population	Nodes (n)	All Lymph Nodes Detected with SPY AGENT GREEN	All Lymph Nodes Detected with BD	Lymph Nodes Detected with SPY AGENT 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 SPY AGENT GREEN or blue dye. With SPY AGENT 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 SPY AGENT GREEN or Blue Dye (BD)

Analysis Population	Patients (n)	Patients with All Lymph Nodes Detected with SPY AGENT GREEN	Patients with All Lymph Nodes Detected with BD	Patients with Lymph Nodes Detected with SPY AGENT 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

14.2 Lymphatic Mapping of Breast Cancer

The FILM-B Study (NCT 03200704) was a single-arm, prospective, multi-center, open-label, non-inferiority study in 151 patients with early stage breast cancer with clinically negative nodal status who were scheduled for surgery that included clinically indicated sentinel lymph node biopsy with approved Tc 99m-labeled active comparators.

Patients were administered SPY AGENT GREEN at the beginning of the operative procedure and an active comparator the day before or the day of surgery. There were no patients with bilateral breast cancer, therefore, a single index breast was injected in all patients. Two 0.05 mL injections of a 2.5 mg/mL solution of SPY AGENT GREEN for a total dose of 0.25 mg were administered intradermally into the peri-areolar region of the index breast at the 12 o'clock and 9 o'clock positions for the right breast and at the 12 o'clock and 3 o'clock positions for the left breast. Five patients received a subsequent peri-tumoral dose consisting of three intradermal injections of 0.05 mL each at the 12 o'clock, 3 o'clock and 9 o'clock positions for a total dose of 0.375 mg. Three of these five patients had unsuccessful lymphatic mapping and received a full axillary lymph node dissection. Lymphatic mapping was performed intraoperatively using the SPY-PHI® System followed by use of a handheld gamma probe as well as the surgeon's visual and palpation examination. The resected tissues were evaluated by histopathology to confirm presence of lymph nodes.

The mean age of the 151 patients was 60 years (range: 25 to 84 years); distribution by race and ethnicity was 81% White, 7% Black or African American, 5% Asian, 3% Hispanic/Latino and 3% other.

The efficacy of SPY AGENT 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 SPY AGENT GREEN followed by use of a gamma probe.

Table 3 shows the percentage of resected, confirmed lymph nodes and the percentage of patients with at least one resected, confirmed lymph node detected by SPY AGENT GREEN.

Table 3: Detection of Resected, Confirmed Lymph Nodes by SPY AGENT GREEN at the Node-Level and the Patient-Level

Lymph Nodes/ Patients (n)	Number (Percentage) of Lymph Nodes Detected with SPY AGENT GREEN	Number (Percentage) of Patients with at Least One Lymph Node Detected with SPY AGENT GREEN
406[†]/151	360 (89%)	145 (96%)

[†]Lymph nodes resected by using the SPY-PHI System and a handheld gamma probe as well as the surgeon's visual and palpation examination.

SPY AGENT GREEN met the prespecified noninferiority margin of 5% relative to active comparator at the node-level.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPY AGENT GREEN (indocyanine green for injection, USP) is supplied as 25 mg of lyophilized powder in a 20 mL (NDC 66259-146-01) or 25 mL (NDC 66259-146-02) single-patient-use vial in the following configurations:

	Components
Spy Elite Kit NDC 66259-306-13 Kit for use with SPY Elite System For visualization of vessels, blood flow and tissue perfusion	• One 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vial, • One 10 mL Sterile Water for Injection, USP plastic vial, • One ND8000 sterile drape
Spy Elite Pack NDC 66259-306-23	6 SPY Elite kits: • Six 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vials, • Six 10 mL Sterile Water for Injection, USP plastic vials, • Six ND8000 sterile drapes
SPY-PHI Kit NDC 66259-903-14 Kit for use with SPY-PHI System For visualization of vessels, blood flow and tissue perfusion For lymphatic mapping	• One 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vial, • One 10 mL Sterile Water for Injection, USP plastic vial, • One SPY-PHI (HH2000) sterile drape
SPY-PHI Pack NDC 66259-903-24	6 SPY-PHI kits: • Six 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vials, • Six 10 mL Sterile Water for Injection, USP plastic vials, • Six SPY-PHI (HH2000) sterile drapes

SPY Minimally Invasive Surgery (SPY-MIS) Kit NDC 66259-936-15 Kit for use with Advanced Imaging Modality (AIM) and PINPOINT Systems For visualization of vessels, blood flow and tissue perfusion For visualization of extrahepatic biliary ducts	• One 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vial, • One 10 mL Sterile Water for Injection, USP plastic vial, • Two 3 mL syringes (sterile), • Two 10 mL syringes (sterile), • Two 18G, 1 inch needles (sterile), • Labels for syringes
SPY Minimally Invasive Surgery (SPY-MIS) Pack NDC 66259-936-25	6 SPY-MIS kits: • Six 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vials, • Six 10 mL Sterile Water for Injection, USP plastic vials, • Twelve 3 mL syringes (sterile), • Twelve 10 mL syringes (sterile), • Twelve 18G, 1 inch needles (sterile), • Labels for syringes
SPY Lymphatics Kit NDC 66259-937-16 Kit for use with the Advanced Imaging Modality (AIM) L10 and L11 Light Sources and 1688 Camera System, and the PINPOINT System For lymphatic mapping	• One 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vial, • Two 10 mL Sterile Water for Injection, USP plastic vials, • One 10 mL syringe (sterile), • One luer-lock 10 mL syringe with controlled handle (sterile), • Two spinal needles 22G, 3.5 inch (sterile), • Labels for syringes
SPY Lymphatics Pack NDC 66259-937-26	6 SPY Lymphatics kits: • Six 25 mg SPY AGENT GREEN (indocyanine green for injection, USP) vials, • Twelve 10 mL Sterile Water for Injection, USP plastic vials, • Six 10 mL syringes (sterile), • Six luer-lock 10 mL syringes with controlled handle (sterile), • Twelve spinal needles 22G, 3.5 inch (sterile) • Labels for syringes

NDC 63323-185-10 (or NDC 0409-4887-10) Sterile Water for Injection, USP, 10 mL fill in 10 mL plastic vials.

STORAGE: Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions
Advise patients to seek medical attention for reactions following injection of SPY AGENT 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.
Ferentino (FR) or Monza (MB), Italy

Distributed by:
Novadaq Technologies ULC
8329 Eastlake Drive, Unit 101,
Burnaby, BC, Canada V5A 4W2

Sterile Water for Injection, USP is manufactured by:
Fresenius Kabi USA, LLC
Grand Island, NY 14072 U.S.A.
or
Hospira, Inc.
Rocky Mount, NC 27804 U.S.A.

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