

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211580Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 26, 2018
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 211580
Product Name and Strength:	Indocyanine green for Injection 25 mg/ vial
Applicant/Sponsor Name:	Novadaq Technologies ULC. (now part of Stryker)
FDA Received Date:	November 21, 2018
OSE RCM #:	2018-185-03
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMORANDUM

Division of Medical Imaging Products (DMIP) requested that we review the revised carton and container labels for indocyanine green to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.^{abc}

2 CONCLUSION

The revised carton and container labels for indocyanine green are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Rychlik, I. Label and Labeling Review for Spy Agent Green (Indocyanine green) (NDA 211580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 14. RCM No.: 2018-185.

^b Rychlik, I. Label and Labeling Review for Spy Agent Green (Indocyanine green) (NDA 211580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEPT 14. RCM No.: 2018-185-01.

^c Rychlik, I. Label and Labeling Review for Spy Agent Green (Indocyanine green) (NDA 211580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEPT 27. RCM No.: 2018-185-02.

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/s/

IDALIA E RYCHLIK
11/26/2018

HINA S MEHTA
11/26/2018



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs—ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Lily (Yeruk) Mulugeta, PharmD, Clinical Reviewer
Division of Pediatric and Maternal Health (DPMH)


Through: Hari Cheryl Sachs, MD, Team Leader
John Alexander, MD, MPH, Deputy Director, DPMH

To: Division of Medical Imaging Products (DMIP)

Product: SPY AGENT GREEN (indocyanine green for injection), drug-device combination

NDA: 211580

Proposed indication for fluorescence imaging of:

- Blood flow and tissue perfusion before, during and after: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures.
- Biliary ducts, (b) (4)

- Lymph nodes and delineation of lymphatic vessels in the cervix and uterus during lymphatic mapping in patients with solid tumors

Dosage form and route of administration: Lyophilized powder for injection, for intravenous and interstitial injection.

Sponsor: Novadaq Technologies ULC

Consult Request: DMIP requested DPMH assistance with the pediatric relevant sections of the labeling for this new NDA.

Background

Indocyanine green (ICG) is a water soluble, tricarbocyanine dye used as an intravascular imaging agent. ICG was originally approved by the United States (US) Food and Drug Administration (FDA) in the determination of cardiac output, hepatic function, liver blood flow, and in ophthalmic angiography (NDA 011525; original approval 1959).

Indocyanine green is also approved as a combination product with SPY Intra-operative Imaging System, which consists of device components (light source, camera, etc.) for assessing blood flow and tissue perfusion, as well as related structural biliary anatomy under the following 510(k)s:

- SPY Elite (K042961, K060867, K063345, K071037, K071619, K072222, K073130, K073088, K100371)
- PINPOINT (K091515, K150956, K161792)

Collectively, these systems are referred to as the SPY fluorescence imaging systems and are intended for intraoperative use.

This 505(b)(2) New Drug Application (NDA) proposes a new ICG drug product, SPY AGENT Green (Indocyanine Green for Injection, USP), also known as IC2000, for use with SPY Elite and PINPOINT in the visualization of:

- Blood flow and tissue perfusion before, during and after: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures “(blood flow and tissue perfusion”).
- Biliary ducts, (b) (4)

The sponsor has submitted data from a new clinical trial in adults to support the new indication. Thus, this NDA provides for a new indication, fluorescence imaging of lymph nodes and lymphatic vessels in the cervix and uterus during lymphatic mapping procedures as well as a new interstitial route of administration. The new indication and route triggers PREA.

The sponsor submitted a request for full waiver for pediatric studies for each of the proposed indications with the NDA.

Reviewer comment: An agreed iPSP was not in place when the application was filed, and the pediatric plan has been developed during the application review based on extrapolation of efficacy.

To support the pediatric plan, upon request from the Agency, the sponsor submitted results from a literature search of published articles reporting the use of ICG in the pediatric population to evaluate whether sufficient safety and dosing data using ICG and Novadaq devices are available in pediatric patients.

Discussion:

Planned Waivers:

- **Visualization of Vessels, Blood Flow and Tissue Perfusion:**

A partial waiver in patients less than 1 month of age is reasonable because studies are “not feasible.” The sponsor has provided data to support that ICG is not used in a significant number of patients under 1 month of age.

- **Visualization of Extrahepatic Biliary Ducts**

No data has been provided to support any planned waivers. DPMH defers to the division to determine in what age group contrast-enhanced biliary imaging is used, noting cholangiopancreatography is performed in patients down to 4 days of age¹. The sponsor should be asked to provide use data on comparable procedures.

- **Visualization of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping for Cervical and Uterine Tumors**

A full waiver is appropriate for this adult only indication.

Pediatric Literature Review

The clinical literature search examined the US National Library of Medicine’s MEDLINE database for papers published between January 1, 1959 and June 8, 2018. Search criteria were selected to capture publications containing data related to the use of ICG in the pediatric population either as a single drug or in combination with a medical device.

Per the sponsor, a total of forty-nine pediatric patients 1 month to 21 years received intravenous injections of ICG and fluorescence imaging with SPY in the angiographic indications of cardiovascular/vascular and plastic-micro and reconstructive applications. Analysis of doses administered to a number of pediatric subpopulations, shows that doses used in pediatric patients (1.25-10 mg) are similar to those used in adult patients in similar applications. Overall, the data suggest that ICG was well tolerated and no drug related adverse events were reported.

Extrapolation of Efficacy for the Proposed indications

Extrapolation of efficacy is based on the assumption that successful visualization of vessels, blood flow and tissue perfusion as well as extrahepatic biliary ducts is not expected to be different between adults and pediatric patients. As mentioned above, the safety and dosing and administration recommendations are based on clinical experience.

¹ Nievelstein, Rutger AJ, Simon GF Robben, and Johan G. Blickman. "Hepatobiliary and pancreatic imaging in children—techniques and an overview of non-neoplastic disease entities." *Pediatric radiology* 41.1 (2011): 55-75.

Reviewer's comments:

- *The efficacy of ICG for visualization of blood flow and tissue perfusion before, during and after vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures in pediatric patients 1 month and older can be extrapolated from data in adults provided that dosing is similar. The safety of the product is established based on literature data submitted by the sponsor (see above). The safety database seems adequate. DPMH defers to the clinical pharmacology reviewer regarding the adequacy of the data to support dosing in pediatric patients.*
- *The efficacy of ICG for visualization of extrahepatic biliary ducts in pediatric patients [insert age] and older can also be extrapolated from data in adults. Safety of ICG in this population may be supported by the safety data of ICG in other populations (e.g. microvascular) discussed above. We defer to the clinical pharmacology reviewer regarding the adequacy of the data to support dosing in pediatric patients. The age for the biliary imaging indication should be inserted once the appropriate age for waiver has been agreed upon by the Division and the Pediatric Review Committee (October 17, 2018).*

Discussion:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c) (9) (iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. Since the product will be indicated for visualization of blood flow and tissue perfusion in pediatric patients, the information should be distributed throughout labeling as appropriate and summarized in 8.4 Pediatric Use.

DPMH Recommendations: Sponsor proposed labeling of section 8.4 with DPMH recommended edits (~~strikethroughs~~ represent deletions and underlining represents additions):

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

- Visualization of vessels, blood flow and tissue perfusion before, during, and after surgery, including general minimally invasive surgical procedures in adult and pediatric patients one month of age and older: (1.1).
- Visualization of extrahepatic biliary ducts in adult and pediatric patients [insert age] years of age and older. (1.2)

- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in women with cervical and uterine tumors. (1.3)

Reviewer's comment: As mentioned above, the sponsor has submitted data to support expansion of use to pediatric patients for two indications based on extrapolation of efficacy from adults. The age for the biliary imaging indication should be inserted once the appropriate age for waiver has been agreed upon by the Division and the Pediatric Review Committee (October 17, 2018).

DOSAGE AND ADMINISTRATION

Visualization of Vessels, Blood Flow and Tissue Perfusion (2.5 mg/ml solution):

- The recommended single intravenous dose in adults and pediatric patients 1 month and older for a surgical procedure is 1.25 mg to 5 mg
- The recommended single intravenous dose in adults for visualization of perfusion in extremities through the skin for plastic, micro, and reconstructive surgeries is 3.75 mg to 10 mg.

Additional doses may be administered to obtain additional imaging sequences during the procedure, however, do not exceed a total dose of 2 mg/kg. (2.1)

Visualization of Extrahepatic Biliary Ducts (2.5 mg/ml solution):

- The recommended single intravenous dose in adults and pediatric patients [insert age] years of age and older (b) (4) is 2.5 mg TRADENAME.
- Additional doses may be administered (b) (4) to obtain additional imaging sequences during the procedure, however, do not exceed a total dose of 2 mg/kg. (2.2)

Reviewer's comment: DPMH defers to the clinical pharmacology reviewer regarding dose selection for pediatric patients.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

1.1 Visualization of Vessels, Blood Flow and Tissue Perfusion

TRADENAME is indicated in adults and pediatric patients one month of age and older for:

- fluorescence imaging of micro- and macro-vasculature, blood flow and tissue perfusion before, during and after (b) (4), including minimally invasive procedures (b) (4)

1.2 Visualization of Extrahepatic Biliary Ducts

TRADENAME is indicated in adults and pediatric patients [insert age] years of age and older for:

- fluorescence imaging of extrahepatic biliary ducts (b) (4)

1.3 Visualization of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping for Cervical and Uterine Tumors

TRADENAME is indicated in women for:

- fluorescence imaging of lymph nodes and delineation of lymphatic vessels in the cervix and uterus during lymphatic mapping in solid tumors for which this procedure is a component of intraoperative management (b) (4)

Reviewer's comment: As mentioned above, the sponsor has submitted data to support expansion of use to pediatric patients for two indications based on extrapolation of efficacy from adults. The age for the biliary imaging indication should be inserted once the appropriate age for waiver has been agreed upon by the Division and the Pediatric Review Committee (October 17, 2018).

DOSAGE AND ADMINISTRATION

2.1 Recommended Dose for Visualization of Vessels, Blood Flow and Tissue Perfusion

Patient Population	Dose	Additional Administration Instructions
Adult <u>and</u> pediatric patients <u>one month of age and older:</u>	The recommended dose of TRADENAME is 1.25 mg to 5 mg administered (b) (4)	<ul style="list-style-type: none"> (b) (4) (b) (4) immediately flush with a 10 mL bolus of 0.9% Sodium Chloride, USP. Adjust the amount and type of flush (b) (4)
Adult Patients	The recommended single dose is 3.75 mg to 10 mg administered (b) (4)	<ul style="list-style-type: none"> (b) (4) to avoid volume and/or sodium overload Additional doses may be administered during the procedure Do not exceed a maximum total dose of 2 mg/kg

		<ul style="list-style-type: none">Fluorescence response is visible in blood vessels within 5 to 15 seconds after injection
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2.2 Recommended Dose for Visualization of Extrahepatic Biliary Ducts

The recommended single dose of TRADENAME for adults and pediatric patients [insert age] years of age and older is 2.5 mg administered intravenously as a single dose 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.

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

Reviewer's comment: The age for the biliary imaging indication should be inserted once the appropriate age for waiver has been agreed upon by the Division and the Pediatric Review Committee (October 17, 2018).

2.3 Recommended Dose for Visualization of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping for Cervical and Uterine Tumors

The recommended single dose of TRADENAME is 1.25 mg (b) (4) four (b) (4) interstitially (b) (4) into the cervix, at the three o'clock and the nine o'clock positions:

- (b) (4) superficial (b) (4) 1 mm to 3 mm, and
- (b) (4) deep (b) (4) 1 cm to (b) (4) cm

Fluorescent Lymphatic vessels and lymph nodes (b) (4) visible within 1 minute after injection.

Reviewer's comment: We defer to the clinical pharmacology reviewer regarding dose selection for pediatric patients.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Visualization of Vessels, Blood Flow and Tissue Perfusion

The safety and effectiveness of indocyanine green for visualization of vessels, blood flow and tissue perfusion has been established in pediatric patients one 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 procedures, and by clinical trials in adults.

Adverse reactions in pediatric patients were similar to those reported in adults. The dose range was also similar to the effective dose range in adults [See Dosage and Administration (2.1)]. The safety and effectiveness of indocyanine green for visualization of vessels, blood flow and tissue perfusion has not been established in pediatric patients less than one month of age.

Visualization of Extrahepatic Biliary Ducts

The safety and effectiveness of indocyanine green for visualization of extrahepatic biliary ducts has been established in pediatric patients [insert age] years of age and older. Pediatric use is supported by clinical trials in adults in addition to clinical use in pediatric patients. The safety and effectiveness of indocyanine green for visualization of extrahepatic biliary ducts has not been established in pediatric patients less than [insert age] years of age

Visualization of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping for Cervical and Uterine Tumors

The safety and effectiveness of indocyanine green for visualization of lymph nodes and lymphatic vessels during lymphatic mapping for cervical and uterine tumors have not been established in pediatric patients.

Reviewer's comment: DPMH concurs with the very brief summary of the data used to support safety and dosing for visualization of vessels, blood flow and tissue perfusion as well as extrahepatic biliary duct under 8.4 cross-referencing to the relevant sections of the label.

Conclusions:

DPMH forwarded the above draft comments to DMIP on 08/30/2018 and participated in a labeling meeting on 09/06/2018 and 10/02/2018. The reader is directed to final negotiated labeling which may reflect changes not discussed in this review.

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/s/

YERUK A MULUGETA
10/12/2018

HARI C SACHS
10/12/2018
I agree with these labeling recommendations.

JOHN J ALEXANDER
10/16/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 16, 2018

To: Phillip Davis
Division of Medical Imaging Products (DMIP)

Alberta Davis-Warren, Regulatory Project Manager, DMIP

Michele Fedowitz, Associate Director for Labeling, DMIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (indocyanine green) for injection, for intravenous or interstitial use.

NDA: 211580

In response to DMIP's consult request dated February 21, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for TRADENAME.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMIP on October 10, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DMIP on October 15, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
10/16/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 27, 2018
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 211580
Product Name and Strength:	Indocyanine green for Injection 25 mg/ vial
Applicant/Sponsor Name:	Novadaq Technologies ULC. (now part of Stryker)
FDA Received Date:	September 24, 2018
OSE RCM #:	2018-185-02
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMORANDUM

Division of Medical Imaging Products (DMIP) requested that we review the revised carton and container labels for indocyanine green (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^{a b} The Applicant did not delete the kit identification (i.e. Spy Elite Pack) from the labels as the drug is the device component. We agree that the kit identification within the heading of the product label is an important differentiation between product kits. Furthermore, we note that the carton labels for the SPY Elite and Pinpoint imaging systems have been on the market since 2005 and removing kit identification from the label heading may introduce confusion between the two systems at this time.

2 CONCLUSION

The revised carton and container labels for indocyanine green are unacceptable from a medication error perspective. The expression of total quantity on carton labels does not align

^a Rychlik, I. Label and Labeling Review for Spy Agent Green (Indocyanine green) (NDA 211580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 14. RCM No.: 2018-185.

^b Rychlik, I. Label and Labeling Review for Spy Agent Green (Indocyanine green) (NDA 211580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEPT 14. RCM No.: 2018-185-01.

with their corresponding representation in the Prescribing Information. Furthermore, the proprietary name is represented by a placeholder, we will need to review the updated carton and container labels inclusive of a proprietary name when available.

3 RECOMMENDATIONS FOR NOVADAQ TECHNOLOGIES ULC. (NOW PART OF STRYKER)

We recommend the following be implemented prior to approval of this NDA 211580:

- A. The total quantity of kit components on the carton labeling consists of both the number spelled out and in actual number format. We recommend only including the number spelled out (i.e. Twelve 3 mL syringe, sterile).
- B. As currently presented, the proprietary name is represented by a placeholder, submit the updated carton and container labels inclusive of a proposed proprietary name when available.

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/s/

IDALIA E RYCHLIK
09/27/2018

HINA S MEHTA
09/27/2018



Public Health Service
DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Memorandum

ICCR ICCR2018-03418
Engineering Review

Date: September 24, 2018

To: Michele Fedowitz, CDER/OND/ODEIV/DMIP

From: Mehmet Kosoglu, CDRH/ODE/DSD/GSDB1

CC: Neil Ogden, ODE/DSD/GSDB1, Branch Chief

Subject: NDA 211580 3-12 label

Device: SPY Elite and PINPOINT Fluorescence Imaging Systems and ICG

**Proposed
Indications**

For Use: fluorescence imaging of lymph nodes and lymphatic vessels in the cervix and uterus during lymphatic mapping procedures

Sponsor: Novadaq Technologies ULC/Stryker

Recommendation: Please see my responses to the CDER reviewer's questions.

I. Product Description:

The product in questions is a combination of Indocyanine Green (ICG) imaging agent and Novadaq PINPOINT® Fluorescence Imaging System

Indocyanine green is currently approved for assessing blood flow and tissue perfusion, as well as related structural biliary anatomy under the following 510(k)s when used as part of a combination product (co-package) with the SPY Elite and PINPOINT Systems:

- SPY Elite (K042961, K060867, K063345, K071037, K071619, K072222, K073130, K073088, K100371)
- PINPOINT (K091515, K150956, K161792)

This NDA provides a new indication: Fluorescence imaging of lymph nodes and lymphatic vessels in the cervix and uterus during lymphatic mapping procedures, and a new interstitial route of administration, that has not been previously approved by the CDER.

II. Questions to CDRH and our Responses:

The CDER lead reviewer forwarded me two specific questions. The questions and my responses are listed below.

1. We require assistance in drug labeling, specifically help with describing the device in the labeling.

Consult Reviewer's Comment: *I have reviewed the proposed labeling. The only addition to the labeling should be the specific excitation and emission (also called imaging) wavelengths for the drug so the user can choose an appropriate fluorescence imaging device to be used with ICG.*

2. For the new indication, we request an update on the status of the 510(k) clearance of the new device indication.

Consult Reviewer's Comment: *The sponsor mentioned to the lead reviewer that they submitted a 510(k) notification for the new indication. The lead reviewer requested the project manager Ms. Alberta Davis-Warren to contact the sponsor ask for the specific 510(k) number. The sponsor clarified that the submission for lymphatic mapping indication has not been submitted yet.*

Reviewer Electronic Signature
Mehmet A. Kosoglu -S 2018.09.24 20:12:14 -04'00'

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/s/

ALBERTA E DAVIS WARREN
11/09/2018
Archiving CDRH's review in DARRTS

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 14, 2018
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 211580
Product Name and Strength:	Indocyanine green for Injection 25 mg/ vial
Applicant/Sponsor Name:	Novadaq Technologies ULC. (now part of Stryker)
FDA Received Date:	September 4, 2018
OSE RCM #:	2018-185-01
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 PURPOSE OF MEMORANDUM

Division of Medical Imaging Products (DMIP) requested that we review the revised carton and container labels for indocyanine green (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton and container labels are unacceptable from a medication error perspective. The bold type font and placement of the manufacturer name, Stryker, increases its prominence as compared to other important drug information on the label; as such, it should be relocated, and the bold font removed to increase readability and prominence of important drug production information. Further recommendations for the Sponsor's carton and container labels may be found below in Section 3.

^a Rychlik, I. Label and Labeling Review for Spy Agent Green (Indocyanine green) (NDA 211580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 14. RCM No.: 2018-185.

3 RECOMMENDATIONS FOR NOVADAQ TECHNOLOGIES ULC. (NOW PART OF STRYKER)

We recommend the following be implemented prior to approval of this NDA 211580:

A. General Comments (Carton Labeling)

- a. As currently presented the kit identification (i.e. Spy Elite Kit) is the heading of the product label and more prominent than the drug name. We recommend deleting the kit identification (i.e. *SPY Elite Pack* (b) (4)) heading.
- b. Increase prominence of product strength information on the kit and pack labels.
- c. Increase the prominence of the kit designations (i.e. Kit for use with SPY ELITE System), located within their respective boxes.

B. Container Labels for indocyanine green

- a. The bold type font and placement of the manufacturer name, Stryker, increases its prominence as compared to other important drug information on the label; as such, it should be relocated, and the bold font removed to increase readability and prominence of important drug production information
- b. To increase prominence of product strength information, relocate the drug strength information to the line directly below drug name presentation.

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/s/

IDALIA E RYCHLIK
09/14/2018

HINA S MEHTA
09/14/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 14, 2018
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 211580
Product Name and Strength:	Spy AGENT Green (Indocyanine green) for Injection 25 mg/ vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novadaq Technologies ULC. (now part of Stryker)
FDA Received Date:	January 23, 2018, March 12, 2018, March 16, 2018, May 9, 2018, and May 17, 2018
OSE RCM #:	2018-185
DMEPA Safety Evaluator:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

1 REASON FOR REVIEW

On January 23, 2018, Novadaq Technologies ULC submitted a 505(b)(2) New Drug Application (NDA 211580) for the drug product Spy Agent Green (indocyanine green for injection) for Agency review. The Division of Medical Imaging Products (DMIP) requested DMEPA evaluate the proposed Prescribing Information (PI), carton and container labels for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION

Indocyanine green has been marketed in the United States for almost 60 years for use in determining cardiac output, hepatic function, liver blood flow, and in ophthalmic angiography. Currently, it is available from two manufacturers, Akorn Inc. (NDA 011525) and Diagnostic Green GmbH (ANDA 040811).

Indocyanine green is currently approved for assessing blood flow and tissue perfusion, as well as related structural biliary anatomy under the following 510(k)s when used as part of a combination product with the SPY Elite and PINPOINT Systems:

- SPY Elite (K042961, K060867, K063345, K071037, K071619, K072222, K073130, K073088, K100371)
- PINPOINT (K091515, K150956, K161792)

Novadaq Technologies intends for their marketed product, Spy Agent Green to be used in combination with the Novadaq 510(k) cleared devices, the PINPOINT Endoscopic Fluorescence Imaging System (PINPOINT) and the SPY Fluorescence Imaging System (SPY Elite).

The proposed fluorescence angiographic indications for indocyanine green, presented in this NDA, have been 510(k) cleared with Novadaq SPY Elite and PINPOINT systems, but have not been previously approved by the Center for Drug Evaluation and Research (CDER).

This NDA also provides for a new indication, fluorescence imaging of lymph nodes and lymphatic vessels in the cervix and uterus during lymphatic mapping procedures, and a new interstitial route of administration, that has not been previously approved by the CDER.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), carton and container labels for NDA 211580 to determine if they are acceptable from a medication error perspective. A risk assessment was completed to identify deficiencies that may lead to medication errors. We also searched the Institute for Safe Medication Practices (ISMP) newsletters and DMEPA previous reviews; no previous reviews nor newsletters were relevant for this review.

We identified areas in the labeling that can be improved to increase readability and prominence of important information and further mitigate the risk of medication error. Specifically, we note that the PI contains the omission of specified units-of-measure after each numerical designation, symbols, and utilizes trailing zeros throughout. These factors may lead to reader confusion of intended meaning, inadvertently leading to medication errors such as overdose and/or under-dose for patients. The Dosage and Administration information in the Highlights and Section 2 can be revised for readability. Moreover, the varied preparation instructions dependent on indication would be better highlighted in tabular format. Also, product administration terms such as “tight bolus” may be unclear for healthcare providers and should be defined.

The presentation of the drug product established name on the container label must be reformatted to increase readability and prominence. The established name should be made more prominent on the principal display panel (PDP) and the “Rx Only” and “Sterile” statement although retained, needs to be decreased. The usual dosage statement, reconstitution information and product expiration post-reconstitution is omitted from the PDP- inclusion of this information on carton and container labels, as space permits, would help mitigated product use errors. Further recommendations for the Sponsor’s carton and container labels may be found below in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, labels and labeling can be improved to promote the safe use of the product. We provide recommendations to the Division in Section 4.1 and to Novodaq Technologies in Section 4.2 below.

We advise for the recommendations to be implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. General Comments

- a. To avoid a ten-fold misinterpretation of strength or dose, as referenced in ISMP's List of Error-Prone Abbreviations, Symbols and Dose Designations, remove all trailing zeros throughout the PI
- b. Consider replacing the symbol “-” with the intended meaning to prevent misinterpretation and confusion.
- c. We recommend the unit of measure be included after each value (e.g. 1.5 mL to 4.0 mL) throughout the PI to prevent confusion.

2. Highlights Section: Dosage and Administration

- a. Due to the varied dosing regimens and product reconstitution direction for different indications, consider revising information into tabular format to enhance accessibility of information. In addition, consider deleting (b) (4) information is in the full prescribing information (e.g. See Full Prescribing Information for instructions on reconstitution of lyophilized power, and preparation and administration of injection).

3. Highlights Section: Dosage Forms and Strengths

- a. Revise the dosage form and strength to read as follows:
 - i. For Injection: 25 mg as a sterile, lyophilized, green powder (b) (4) in a single-dose vial for reconstitution.

4. Section 2: Dosage and Administration

- a. In order to increase readability and highlight important dosage and administration information consider revising Section 2 into tabular format as outline below.
 - i. Moreover, due to the varied reconstitution directions based on indication unifying all product preparation into its own subsection and providing reconstitution volumes based on indication in tabular format may help decrease confusion.

2.1 Recommended Dosage and Administration Information

Indication	Dose of SPY AGENT Green	Administration Information
Assessment of Blood Flow and Tissue Perfusion: Single Imaging Sequence	1.25 mg to 5 mg	<ul style="list-style-type: none"> • (b) (4) additional doses may be administered (b) (4) to obtain additional imaging sequences during the procedure. • The total dose should be kept below 2 mg/kg. • Flush with a 10 mL bolus (b) (4) • A fluorescence response should be visible in blood vessels within (b) (4) 5 to 15 seconds after injection.
Assessment of Blood Flow and Tissue Perfusion: Perfusion in extremities through the skin	3.75 mg to 10 mg	
Imaging Extrahepatic Biliary Anatomy	2.5 mg	<ul style="list-style-type: none"> • Inject intravenously 45 minutes prior to surgery to allow indocyanine green to collect in the biliary anatomy • (b) (4) additional doses may be administered (b) (4) to obtain additional imaging sequences during the procedure. • (b) (4) total dose (b) (4) 2 mg/kg.
Imaging Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping	1.25 mg	<ul style="list-style-type: none"> • (b) (4) 5 mg into the cervix, (b) (4) at the three and nine o'clock positions: <ul style="list-style-type: none"> ○ (b) (4) superficial (b) (4) 1 mm to 3 mm ○ (b) (4) deep injection: 1 cm to (b) (4) cm • Fluorescent lymphatic vessels and lymph nodes should begin to be visible within (b) (4) 1 minute after injection.

		<ul style="list-style-type: none"> <div style="background-color: #cccccc; width: 100%; height: 100%;"></div> <div style="text-align: right;">(b) (4)</div>
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2.2 Reconstitution Instructions

Indication	Volume of Sterile Water For Infusion (SWFI) to be added to each 25 mg vial of Spy Agent Green	Final Concentration
Blood Flow and Tissue Perfusion	10 mL	2.5 mg/ mL
Imaging Extrahepatic Biliary Anatomy	10 mL	2.5 mg/ mL
Imaging Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping	20 mL	1.25 mg/mL

(b) (4)

Discard any unused (b) (4) product (b) (4)

(b) (4)

(b) (4) via a central or peripheral venous line using a three-way stopcock attached to an injection port on the infusion line. (b) (4)

(b) (4)

- b. Product administration terminology, such as “tight bolus”, is vague and should be accurately and clearly defined for healthcare providers.

5. Section 3: Dosage Forms and Strengths

- a. Revise the dosage form and strength to read as follows:
 - i. For Injection: 25 mg sterile, lyophilized, green powder (b) (4) in a single-dose vial for reconstitution.
- 6. Section 16: How Supplied/Storage and Handling
 - a. We note that the National Drug Code (NDC) numbers are omitted for the imaging system kits and currently denoted by a placeholder for the drug vial, please submit the proposed NDC numbers for Agency review.
 - b. As currently presented the temperature statement "20 - 25°C (68 - 77°F)" is not consistent in terms of degree symbol and unit between Celsius and Fahrenheit. We recommend consistency in terms of displaying this information in the labeling. [i.e. 20°C - 25°C (68°F - 77°F)]

4.2 RECOMMENDATIONS FOR NOVODAQ TECHNOLOGIES ULC

We recommend the following be implemented prior to approval of this NDA 211580:

A. General Comments (Carton Labeling)

1. As currently presented, it appears as though the product proprietary name is "PINPOINT" and "SPY Elite"; it is not clear that indocyanine green is the drug component. Therefore, revise the carton labeling to ensure clear and prominent placement of the proprietary and established drug names. For example:
Tradename (indocyanine green, USP) for injection
25 mg per vial
Kit for use with SPY Elite
2. Drug products must have a barcode that contains, at a minimum, the National Drug Code (NDC) number in a linear barcode (21 CFR 201.25). We note that the NDC numbers and barcodes are omitted from the product kits; therefore, please submit the proposed NDC numbers for the Agency review.
 - a. Please note, the individual kit labels of one unit and the outer carton label of multiple kits should have different NDC numbers. Ensure the NDC numbers are different for these two package configurations.
3. Add "Reconstitute with Accompanying Sterile Water Diluent Before Use " to the primary display panel (PDP) to help avoid errors associated with using the wrong solution for reconstitution.
4. Include information on post-reconstitution storage on the PDP. These instructions will inform healthcare providers responsible for preparing the product and minimize the risk of administering expired products. Add the following statement, "Use within 6 hours of reconstitution" on all kit labels.
5. As currently presented the temperature statement "20 - 25°C (68 - 77°F)" is not consistent in terms of degree symbol and unit between Celsius and Fahrenheit. We recommend consistency in terms of displaying this information in the labeling, bold and revise to "Store at 20°C - 25°C (68°F - 77°F). [See USP Controlled Room Temperature.]".

B. Container Label for Spy Agent Green

1. As currently presented, the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name considering all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Place adequate space between the numerical dose and unit of measure (e.g. 25 mg instead of 25mg) because the “m” is sometimes mistaken as a zero or two zeros, risking a 10- to 100-fold overdose.
3. Decrease the prominence of the statement “Rx Only” by removing the bolding as this information appears more prominent than the established name on the principal display panel.
4. Decrease the prominence of the statement “Sterile” as this information appears more prominent than the established name on the principal display panel and revise statement to read, “Sterile, single dose vial, discard unused portion”.
5. If space permits, per 21 CFR 201.55, include the “Usual dosage: See prescribing information” statement on the label.
6. To increase readability and prominence of expiration, revise the statement “(b) (4)” to “Use within 6 hours of reconstitution”.
7. Decrease the prominence of manufacturer information as it clutters the principal display panel and takes readers’ attention away from important information such as proprietary and proper names, strength and expiry information.
8. We note that the container’s National Drug Code (NDC) number is currently denoted by a placeholder, submit the proposed NDC number for Agency review.
9. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either
 - DDMMYYYY (e.g., 31JAN2013)
 - MMMYYYY (e.g., JAN2013)
 - YYYY-MMM-DD (e.g., 2013-JAN-31)
 - YYYY-MM-DD (e.g., 2013-01-31)

C. Pinpoint Kit Syringe Labels for PINPOIT Kit and PINPOINT Lymphatics Kit

1. Allow space for healthcare providers to write post-reconstitution expiration date on the label. We recommend, “Discard after __/__/__ at __:__” since “Discard after” is an affirmative statement, and has been shown to result in the desired action. Additionally, the “__/__/__ at __:__” statement will alert the healthcare provider to write a complete date (month, day, year and time) on the syringe label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Spy AGENT Green (Indocyanine green) received on May 9, 2018 from Novodaq Technologies ULC. (now part of Stryker).

Table 2. Relevant Product Information for Spy AGENT Green (Indocyanine green)	
Initial Approval Date	N/A
Active Ingredient	Indocyanine green
Indication	<ul style="list-style-type: none"> fluorescence imaging of blood flow and tissue perfusion during: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgeries, including general minimally invasive surgical procedures (b) (4) fluorescence imaging of lymph nodes and delineation of lymphatic vessels in the cervix and uterus during lymphatic mapping in patients with solid tumors for which this procedure is a component of intraoperative management. (b) (4)
Route of Administration	Intravenous, Interstitial
Dosage Form	Powder for reconstitution
Strength	25 mg/ vial
Dose and Frequency	<p><u>Assessment of Blood Flow and Tissue Perfusion:</u> The recommended dose for a single image sequence is 1.25 mg – 5 mg Spy AGENT Green (b) (4) For visualization of perfusion in extremities through the skin, the recommended dose is 3.75 - 10 mg (b) (4) Additional doses (b) (4) may be administered in order to obtain additional imaging sequences during the procedure.</p>

	<p><u>Imaging Extrahepatic Biliary Ducts:</u> The recommended dose for a single (b) (4) 2.5 mg (b) (4) Additional doses (b) (4) may be administered.</p> <p><u>Imaging of Lymph Nodes and Lymphatic Vessels During Lymphatic Mapping:</u> The recommended dose is four 1.25 mg injections for a total dose of 5 mg.</p>
How Supplied	<p>Spy AGENT™ Green (Indocyanine Green) is supplied (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>Spy Elite Kit containing one 25 mg Spy AGENT Green (Indocyanine Green) vial, one 10 mL Sterile Water for Injection, USP plastic vial, one sterile drape, (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>PINPOINT® Kit containing one 25 mg Spy AGENT Green (Indocyanine Green) vial, one 10 mL Sterile Water for Injection, USP plastic vial, two x 3 ml syringes (sterile), 2 x 10 ml syringes (sterile), one 3-way stopcock (sterile), two 18G, 1 inch needles ((b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>PINPOINT Lymphatics (b) (4) Kit containing one 25 mg Spy AGENT Green (Indocyanine Green for Injection, USP) vial, two 10 mL Sterile Water for Injection, USP plastic vials, (b) (4) x 10 ml syringes (sterile), (b) (4) luer-lock 10 ml syringes with controlled handle (sterile), (b) (4) spinal needles 22G, 3.5 inch (sterile), (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>
Storage	20°C to 25°C (68°F to 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 7, 2018, we searched DMEPA's previous reviews using the terms, Spy Agent Green and Indocyanine. Our search identified 0 previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On May 7, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, Canada Safety Bulletin, Long-Term Care, Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: Indocyanine green

D.2 Results

Our search identified 0 articles relevant for this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with post-market medication error data, we reviewed the following Spy AGENT Green (Indocyanine green) labels and labeling submitted by Novodaq Technologies ULC. (now part of Stryker).

- Container label received on March 16, 2018
- Carton Kit labeling received on March 16, 2018
- Sterile Water for Injection label (provided in kits) received on March 16, 2018
- Prescribing Information (Image not shown) received on March 12, 2018

G.2 Label and Labeling Images

Prescribing Information:

(b) (4)



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IDALIA E RYCHLIK
08/14/2018

HINA S MEHTA
08/15/2018



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Memorandum

Date: August 11, 2018 **Date Consulted:** March 20, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Alberta Davis-Warren, Regulatory Project Manager (RPM)
Division of Medical Imaging Products (DMIP)

Drug: Indocyanine Green Injection, USP

NDA: 211580

Indications: 1. Fluorescence imaging of blood flow and tissue perfusion during: vascular gastrointestinal, organ transplant, plastic, micro, and reconstructive surgeries.

2. Fluorescence imaging of lymph nodes and delineation of lymphatic vessels in the cervix and uterus during lymphatic mapping in patients with solid tumors for which this procedure is a component of intraoperative management.

Applicant: Novadaq Technologies ULC

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 211580 submitted on January 28, 2018.
- Applicant's revised labeling and literature review submitted May 9, 2018

Consult Question: DMIP requests DPMH assistance with the PLLR labeling review for this new NDA.

INTRODUCTION

On January 28, 2018, the applicant, Novadaq, submitted a new NDA 211580 via the 505 (b)(2) regulatory pathway for Indocyanine Green Injection, USP. On March, 20, 2018, DMIP consulted DPMH to provide input on the appropriate format and content of the *Pregnancy* and *Lactation* subsections of Indocyanine Green Injection labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

REGULATORY HISTORY

- The applicant is relying on the FDA-approved drug Indocyanine Green Injection (ICG) NDA 011525 by Akorn, Inc., as the reference listed drug (RLD).
- ICG was FDA approved in 1959 for intravenous injection to determine cardiac output, hepatic function, and liver blood flow; approval granted for ophthalmic angiography in 1975.
- In 2005, ICG was FDA-cleared under multiple 510(k)s as part of a combination product with a fluorescence imaging system for intraoperatively assessing blood flow, tissue perfusion, and biliary anatomy (i.e., SPY Elite, PINPOINT Endoscopic).
- In 2007, an Abbreviated New Drug Application (ANDA 040811) was approved for ICG.
- In the current submission, the applicant proposes a new indication for ICG as follows: fluorescence imaging of lymphatic vessels and lymph nodes during lymphatic mapping procedures in patients with uterine and cervical cancer.
- On April 10, 2018, the Agency sent the Applicant a Filing Communication that requested the prescribing information be resubmitted in PLLR format and to provide a review and summary of published literature regarding the effects of indocyanine green use on pregnancy, lactation, and fertility.
- On May 9, 2018, the Applicant submitted revised labeling and the requested supporting information which was found to be adequate for this PLLR review.

Reviewer's Comment

The applicant is relying on the Agency's previous findings of safety for the ICG RLD and the available published literature for safety and efficacy of ICG for the fluorescence angiography and biliary anatomy indications. The applicant did not submit any new nonclinical studies.

To support the safety and efficacy of the proposed lymphatic mapping indication for ICG, the applicant conducted one meta-analysis and performed one randomized, open-label, single arm clinical trial called the FILM study (lymph node identification in uterine and cervical cancer patients during lymphatic mapping).

BACKGROUND

Drug Characteristics¹

- *Drug Class:* water-soluble, tricarbo-cyanine dye (used as an intravascular imaging agent)
- *Mechanism of action:* absorbs light and emits fluorescence
- *Description:* sterile, lyophilized powder for injection (25 mg/vial)
- *Half-life:* biphasic (initial elimination phase 3-4 minutes; second elimination phase 1 hour)
- *Molecular weight:* 774 Daltons

¹Drugs@FDA. Indocyanine Green Injection (NDA 011525). Approved labeling from 10/5/2015.

- *Plasma protein binding*: 98%;
- *Pharmacokinetics*: following IV injection, ICG is confined to the intravascular compartment with minimal leakage into the interstitium; following interstitial injection, ICG is taken up by lymph fluid and moved to the lymph nodes
- *Excipient*: Sodium Iodide (NaI) at levels not more than 5%

Reviewer's Comment

The applicant noted ICG has been marketed in the U.S. for almost 60 years and over 260,000 procedures have been performed worldwide with the SPY fluorescence imaging systems.

Current State of the Labeling¹

- Indocyanine Green Injection (NDA 011525), the RLD for this submission, currently approved labeling is in Physician Labeling Rule (PLR) format but is not in PLLR format.
 - *Warnings and Precautions*: Death due to anaphylaxis reported during cardiac catheterization.
 - *8.1 Pregnancy*: Category C. Animal reproduction studies have not been conducted. It is also not known if indocyanine green can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
 - *8.3 Nursing Mothers*: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, use caution.

REVIEW

PREGNANCY

Nonclinical Experience

No animal reproduction studies have been performed with indocyanine green.

Review of Published Literature

-Applicant's Review: a systematic review was performed in PubMed for published literature between January 1, 1959 and April 26, 2018, related to the use of ICG in the pregnant population (as a single agent or in combination with a medical device). The following search terms were used: (indocyanine green or verdye or diagnogreen or IC-green) AND (pregnancy or pregnant or maternal or fetal or fetus).

- 5 articles were identified as summarized below (see Appendix A, Table 1 for details):
 - *Drug Exposure and Pregnancy Outcome*
 - Pregnancy (total n=60; single ICG dose given IV ranging 7 mg to 350 mg)
 - ✓ 3rd trimester prior to elective C-section² (n=36, outcome: no data)
 - ✓ Each trimester and postpartum³ (n=12, outcome: all term live births)
 - ✓ 3rd trimester during labor⁴ (n=9, outcome: all term live births)

² Ueyama H, et al. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective Cesarean section. *Anesthesiology*. 1999 Dec; 91(6):1571-6.

³ Robson et al. Apparent liver blood flow during pregnancy: a serial study using ICG clearance. *BR J Obstet Gyn*. 1990 Aug(8): 720-4.

⁴ Probst et al (1970). Studies on clearance and placental transfer of indocyanine green during labor. *Clin Chim Acta* 29 (1): 157-160.

- ✓ 2nd trimester prior to cervical cancer surgery (n=2, outcome: 1 preterm live birth at 35 weeks, 1 term live birth)⁵
- ✓ 1st trimester prior to cerclage surgery (n=1, outcome: 1 preterm live birth at 36 weeks)⁶
- *Pharmacokinetic data:*
 - Study 1³: No significant differences were noted in the ICG peak concentration or clearance after administration of 35 mg IV to pregnant women (n=12) during each trimester and postnatally. Author's conclusion: ICG is safe to use in pregnancy for maternal liver function evaluation.
 - Study 2: No ICG was detected in fetal blood during scalp sampling (n=9) or umbilical vein cord blood at birth (n=4) following injection of high dose ICG (5 mg/kg) in pregnant women at full-term during labor. Author's conclusion: these data suggest no placental transfer of ICG.
- *Adverse events:*
 - Overall, no cases of anaphylaxis or other adverse events related to ICG use during pregnancy were retrieved in the published literature.

Reviewer's Comment

The limited available published data do not suggest an increased risk of adverse pregnancy outcomes related to ICG exposure. However, the majority of ICG pregnancy exposures occurred during the 3rd trimester rather than the 1st trimester (i.e., period of organogenesis).

-DPMH's Review: PubMed, Embase, Micromedex⁷, TERIS⁸, Reprotox⁹, and Briggs¹⁰ were searched using "indocyanine green" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." Additional relevant literature not cited by the applicant was identified as described below:

- **Reprotox** states: "There have been anecdotal reports of the safe use of indocyanine green during pregnancy, but we have not been able to determine how thoroughly infants were evaluated. ICG did not cross the term human placenta."
- **Micromedex** pregnancy rating: "Infant risk cannot be ruled out." Available data is inconclusive or inadequate to assess the fetal risk. Due to the lack of human safety data, weigh the potential benefits versus potential risks of drug treatment.

⁵ Papadia A, et al. Laparoscopic Indocyanine Green Sentinel Lymph Node Mapping in Pregnant Cervical Cancer Patients. J Minim Invasive Gynecol. 2016 Feb; 23(2):270-3.

⁶ Zeybek B, et al. Overcoming the obstacles of visualization in robotically assisted abdominal cerclage using indocyanine green. J Robot Surg. 2016 Dec; 10(4):361-364.

⁷ Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 7/25/18.

⁸ TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/25/18.

⁹ Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 7/25/18.

¹⁰ Briggs, GG, Freeman, RK, & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

Pharmacovigilance Database

The applicant stated no pregnancies were reported during the FILM study. Females of reproductive potential were required to have a negative pregnancy test prior to enrollment. In addition, the applicant reported no postmarketing surveillance cases have been received related to the use of ICG with Novadaq's SPY Imaging System in pregnancy.

Applicant's Overall Conclusions (Pregnancy)

Overall, the applicant concluded available data are insufficient to determine safe dosing and administration recommendations for use of ICG in pregnant women. However, no adverse events have been reported in the published literature or to the pharmacovigilance database for Novadaq's SPY Imaging System after administration of ICG to pregnant women.

For PLLR labeling in subsection 8.1 of TRADENAME, the applicant proposed to include a (b) (4) which describes the pharmacokinetic study⁴ that suggests ICG does not cross the placenta. In addition, the applicant proposed (b) (4).

Reviewer's Comment

This reviewer agrees with the applicant's conclusions that available published data specific to ICG use during pregnancy are limited in quality and quantity. However, ICG has been approved and marketed for almost 60 years without any adverse maternal or fetal outcomes reported in the published literature. In addition, no adverse outcomes in pregnant women, fetuses, or neonates have been reported to the applicant's safety database for SPY Imaging System. Nonetheless, this Reviewer acknowledges the inability to accurately quantify the number of pregnant women who have been exposed to ICG.

DPMH discussed the applicant's proposal to include (b) (4) in 8.1 describing available placental transfer data with the Clinical Pharmacology Team. The Clinical Pharmacology Team noted the data is from a study published 1970 and limited in quality due to the insensitivity of the spectrophotometric method used for analysis. Therefore, DPMH and the Clinical Pharmacology Team recommend describing this data with limitations briefly under the Risk Summary heading in the Pregnancy subsection of labeling (b) (4)

LACTATION

Nonclinical Experience

No animal lactation studies have been performed with indocyanine green.

Review of Published Literature

-Applicant's Review: a systematic review was performed in PubMed for published literature between January 1, 1959 and April 26, 2018, related to the use of ICG in the lactating population (as a single agent or in combination with a medical device). The following search terms were used: (indocyanine green or verdye or diagnogreen or IC-green) AND (lactation or lactating or neonatal or neonate or infant or breastfeeding or breast-feeding or nursing).

- A total of 7 articles were identified as summarized below:

- One pharmacokinetic study³ (described in the pregnancy section above) did not report any adverse events in the breastfed infants of lactating women exposed to ICG postpartum (n=6).
- Multiple published case reports that describe ICG administration (dose range 7 mg to 50 mg) in postpartum women. However, the lactation status (i.e., breastfeeding versus bottlefeeding) of these postpartum women is not specified (n=15).^{11,12,13,14,15,16}

Reviewer's Comment

The applicant calculated the total number of lactation exposures to ICG as 21; however, this reviewer only noted 6. This discrepancy is likely related to the applicant including all reported cases of ICG use in postpartum women, rather than only including the postpartum women with confirmed lactation status (i.e., breastfeeding).

-DPMH's Review: PubMed, Embase, Micromedex¹⁷, TERIS¹⁸, Reprotox¹⁹, and Briggs²⁰, *Medications and Mother's Milk*²¹, and LactMed²² were searched using "indocyanine green" AND "breastfeeding," or "lactation." Additional relevant articles not cited by the applicant include:

- *Medications in Mother's Milk* lactation rating: "No Data-Probably Compatible." Recommendations are based on the large molecular weight (774 Daltons) which limits drug entry in breastmilk and the short plasma half-life (3-4 minutes) which reduces the likelihood of breastfed infant exposure. No pediatric concerns have been reported in the breastfed infants of lactating women exposed to ICG.

¹¹ Rychlik A, et al. Utility of Laparoscopic Indocyanine Green-guided Sentinel Node Biopsy in Open Cervical Cancer Surgery. *Int J Gynecol Cancer*. 2016 Sep; 26(7):1288-9.

¹² Sayman Muslubas, I et al. Spontaneous regression of serous retinal detachment associated with circumscribed choroidal hemangioma after childbirth. *Retin Cases Brief Rep*. 2017 Winter; 11(1):7-11.

¹³ DeWilde E, et al. Hypertensive choroidopathy in pre-eclampsia: two consecutive cases. *Ophthalmic Surg Lasers Imagin Retina*. 2014 Jul-Aug; 45(4):343-6.

¹⁴ Shen J, et al. Choroidal tuberculoma in pregnancy. *Retina*. 2007 Jan; 27(1):106-9.

¹⁵ Spaide RF, et al. Atypical choroidal neovascularization in radiation retinopathy. *Am J Ophthalmol*. 2002 May; 133(5):709-11.

¹⁶ Valluri S, et al. Diagnostic indocyanine green angiography in pre-eclampsia. *Am J Ophthalmol*. 1996 Nov; 122(5):672-7.

¹⁷ Truven Health Analytics information, <http://www.micromedexsolutions.com/> Accessed 7/25/18.

¹⁸ TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/25/18.

¹⁹ Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 7/25/18.

²⁰ Briggs, GG, Freeman, RK, & Yaffe, SJ. (2017). *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

²¹ Hale, Thomas (2017) *Medications and Mothers' Milk*. Amarillo, Texas. Hale Publishing.

²² <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 7/25/18.

- **Micromedex** lactating rating: “Infant risk cannot be ruled out.” It is not known if ICG is present in human milk. Weigh the potential benefits versus the potential risks of drug treatment.

Pharmacovigilance Database

The applicant stated there were no cases of ICG exposure in lactation during the FILM study. The applicant noted that no postmarketing lactation cases have been reported with the use of ICG in Novadaq’s SPY Imaging System.

Applicant’s Overall Conclusion (Lactation)

The applicant concluded the limited available data for ICG use during lactation are insufficient to determine safe dosing and administration in lactating women. However, no adverse events have been reported in the breastfed infants of lactating women after ICG administration.

For PLLR labeling in subsection 8.2 of TRADENAME, the applicant proposed to include a statement that there are no data regarding the presence of ICG in human milk, (b) (4) or the effects on milk production. The applicant also proposed to include the risk/benefit statement for lactation.

Reviewer’s Comment

This Reviewer agrees with the applicant’s conclusions. The available published data for ICG use during lactation are limited in quality and quantity. However, as stated above in the pregnancy section, ICG has been approved and marketed for almost 60 years. In addition, no adverse events in lactating women or breastfed infants have been reported to the applicant’s safety database for the SPY Imaging System. Nonetheless, this Reviewer acknowledges the inability to accurately quantify the number of lactating women who have been exposed to ICG.

Therefore, DPMH agrees with the applicant’s proposal to include the risk/benefit statement in subsection 8.2 of labeling. In addition, DPMH agrees with including a statement that there are no data regarding the presence of ICG in human milk or the effects on milk production. However, DPMH disagrees with the applicant’s proposal to (b) (4). DPMH recommends lactation labeling state no adverse effects on breastfed infants have been identified after administration of ICG in a small number of lactating women.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No animal studies have been performed with ICG to evaluate fertility.

Review of Published Literature

-Applicant’s Review: The applicant did not perform a search for ICG use and fertility effects.

-DPMH’s Review: PubMed, Embase, Reprotox⁹ were searched using, “indocyanine green” AND “fertility,” “infertility,” “contraception,” and “oral contraceptives.”

- No relevant articles were retrieved.

Applicant's Overall Conclusions (Females and Males of Reproductive Potential)

Because there are no available data regarding the effects of ICG use on human or animal fertility, the applicant proposed to omit subsection 8.3 for PLLR labeling of TRADENAME.

Reviewer's Comment

DPMH agrees with the applicant's conclusions and proposal to omit subsection 8.3 since there are no available data to suggest an adverse effect on fertility. In addition, pregnancy testing and contraception recommendations are not indicated because the available data do not suggest an increased risk of embryofetal toxicity.

DISCUSSION AND CONCLUSIONS

Pregnancy

DPMH recommends subsection 8.1 of labeling for TRADENAME describe the limited available human data from published literature on the use of ICG in pregnant women and the several decades of postmarketing experience with ICG. Despite the inability to accurately quantify the number of postmarketing pregnancy exposures to ICG, no published literature or postmarketing reports to the SPY imaging system safety database have identified any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Moreover, limited available human data suggest ICG does not cross the placenta. Nonetheless, animal reproduction studies have not been performed with ICG.

Lactation

DPMH recommends subsection 8.2 of labeling for TRADENAME contain the risk/benefit statement for lactation. There are no data on the presence of ICG in human milk or the effects on milk production. However, limited available published literature describes ICG administration in a small number lactating women with no adverse events observed in the breastfed infant. In addition, the short half-life, large molecular weight, and high protein binding of ICG suggest minimal potential for drug exposure in the breastfed infant.

Females and Males of Reproductive Potential

DPMH recommends subsection 8.3 of labeling for TRADENAME be omitted because there are no available human or animal data suggesting ICG effects fertility adversely. In addition, pregnancy testing and contraception recommendations are not recommended in labeling for ICG because the available data do not suggest an increased risk of embryo-fetal toxicity.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. The labeling recommendations below reflect input from the Clinical Pharmacology and Nonclinical Review Teams. DPMH discussed our labeling recommendations with DMIP on August 7, 2018. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Indocyanine Green for Injection, USP Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a small number of published studies and postmarketing experience with indocyanine green use in pregnant women over several decades have not identified 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. 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 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

A small number of cases of indocyanine green use in lactating women have been reported in the published literature with no adverse events observed in the breastfed infant. However, there are no data on 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 TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

APPENDIX A

Table 1: Literature of ICG exposure in Pregnancy and Lactation cited by the Applicant*

Reference	Study Type +Objective	Drug, Dose, Duration	Exposure Timing	Pregnancy Outcome	Reviewer's Comments
Zeybek et al, 2016	Case report (n=1) Vascular anatomy visualization with ICG during a robotic-assisted abdominal cerclage surgery in a pregnant woman	7 mg IV x 1	1 st trimester (13 wk)	Preterm birth 36 wk via C-section Healthy infant	<i>The patient's underlying medical history of cervical insufficiency and 2nd trimester loss are established risk factors for recurrent preterm birth.</i>
Papadia et al, 2015	Case reports (n=2) Sentinel lymph node mapping in pregnant women with a cervical cancer	40 mg x1 injected interstitially at the cervix	2 nd trimester (14 wk)	Preterm birth 35 wk C-section, 2650 g Healthy infant Patient disease free and child well at 24 month follow-up.	<i>Concomitant meds included chemotherapy in pregnancy.</i>
		40 mg x1 injected interstitially at the cervix	2 nd trimester (21 weeks)	Term birth 39 wk NSVD	
Ueyama et al, 1999	Pharmacodynamic (n=36) Evaluate changes in blood volume and cardiac output with crystalloid vs. colloid injection in pregnant women undergoing spinal anesthesia for C/S	10 mg x 1	3 rd trimester (immediately prior to delivery)	Not reported	<i>This study was not designed to assess the safety of ICG administration in pregnancy</i>
Robson et al, 1990	Pharmacokinetic (n=12) Evaluate liver blood flow using ICG clearance during pregnancy and postpartum	35 mg IV x1	Each trimester (12-14 wk, 24-26 wk, 36-38 wk) + postnatally (10-12 wk)	Uncomplicated 12 term live births Healthy infants	<i>No adverse events were reported in the 6 breastfed infants of lactating women exposed to ICG postpartum.</i>
Probst et al, 1970	Pharmacokinetic (n=9) Evaluate drug clearance and placental transfer during labor	350 mg IV	3 rd trimester in labor	9 term live births 1 maternal pre-E	<i>Limitations of these data include: 1. variation in delivery timing after ICG injection in labor (9 min to 6 hrs) 2. small sample size (only 4 umbilical cord blood samples collected; fetal scalp sampling collected in all 9 pts)</i>

*Source: Reviewer's Table

Acronyms defined: n=total number, mg=milligram, wk=weeks, NSVD=normal spontaneous vaginal delivery, ICG=indocyanine green, IV=intravenous, pre-E=pre-eclampsia, min=minutes, hrs=hour

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KRISTIE W BAISDEN
08/11/2018

TAMARA N JOHNSON
08/13/2018