**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Pharmacovigilance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance Review

| | |
|---|---|
| **Date:** | November 17, 2023 |
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| **Product Name:** | Spy Agent Green (indocyanine green) |
| **Pediatric Labeling Approval Date:** | November 21, 2018 |
| **Application Type/Number:** | NDA 211580 |
| **Applicant:** | Novadaq Technologies |
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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Spy Agent Green (indocyanine green) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with indocyanine green in pediatric patients.

Spy Agent Green Kit (indocyanine green) is an optical imaging agent initially approved in the U.S. on November 21, 2018. Spy Agent Green is currently indicated for use with a fluorescence imaging device for:

- Visualization 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
- Visualization of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older
- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in adults with cervical and uterine cancer
- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in adults with breast cancer

This pediatric postmarketing safety review was prompted by the pediatric labeling at initial FDA approval on November 21, 2018, that included the pediatric indications listed above. A pediatric postmarketing pharmacovigilance review for indocyanine green has not been previously presented before the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with indocyanine green in pediatric patients less than 18 years of age through October 16, 2023, and identified eight reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with indocyanine green in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for indocyanine green at this time and will continue routine pharmacovigilance monitoring for indocyanine green.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Spy Agent Green (indocyanine green) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with indocyanine green in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Spy Agent Green Kit (indocyanine green) is an optical imaging agent initially approved in the U.S. on November 21, 2018. Spy Agent Green is currently indicated for use with a fluorescence imaging device for:

- Visualization 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
- Visualization of extrahepatic biliary ducts in adults and pediatric patients aged 12 years and older
- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in adults with cervical and uterine cancer
- Visualization of lymph nodes and lymphatic vessels during lymphatic mapping in adults with breast cancer

This pediatric postmarketing safety review was prompted by the pediatric labeling at initial FDA approval on November 21, 2018, that included the pediatric indications listed above. A pediatric postmarketing pharmacovigilance review for indocyanine green has not been previously presented before the Pediatric Advisory Committee.

## 1.2 RELEVANT LABELED SAFETY INFORMATION

The Spy Agent Green labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Spy Agent Green labeling information, please refer to the full prescribing information.[1]

> ----------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)

----------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)

**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.

## 2 METHODS AND MATERIALS

### 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

| **Table 1. FAERS Search Strategy*** | |
|---|---|
| Date of search | October 17, 2023 |
| Time period of search | All dates through October 16, 2023 |
| Search type | RxLogix Quick Query |
| Product terms | Product active ingredient: indocyanine green |
| MedDRA search terms (Version 26.0) | All Preferred Terms |
| * See Appendix A for a description of the FAERS database.<br>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities | |

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

**Table 2** presents the number of adult and pediatric FAERS reports through October 16, 2023, with indocyanine green.

**Table 2. Total Adult and Pediatric FAERS Reports[*] Received by FDA Through October 16, 2023, With Indocyanine Green**

| | All Reports (U.S.) | Serious[†] (U.S.) | Death (U.S.) |
|---|---|---|---|
| Adults (≥ 18 years) | 105 (70) | 98 (64) | 7 (7) |
| Pediatrics (0 - < 18 years) | 8[‡] (3) | 8[‡] (3) | 2[‡] (1) |

* May include duplicates and transplacental exposures, and have not been assessed for causality

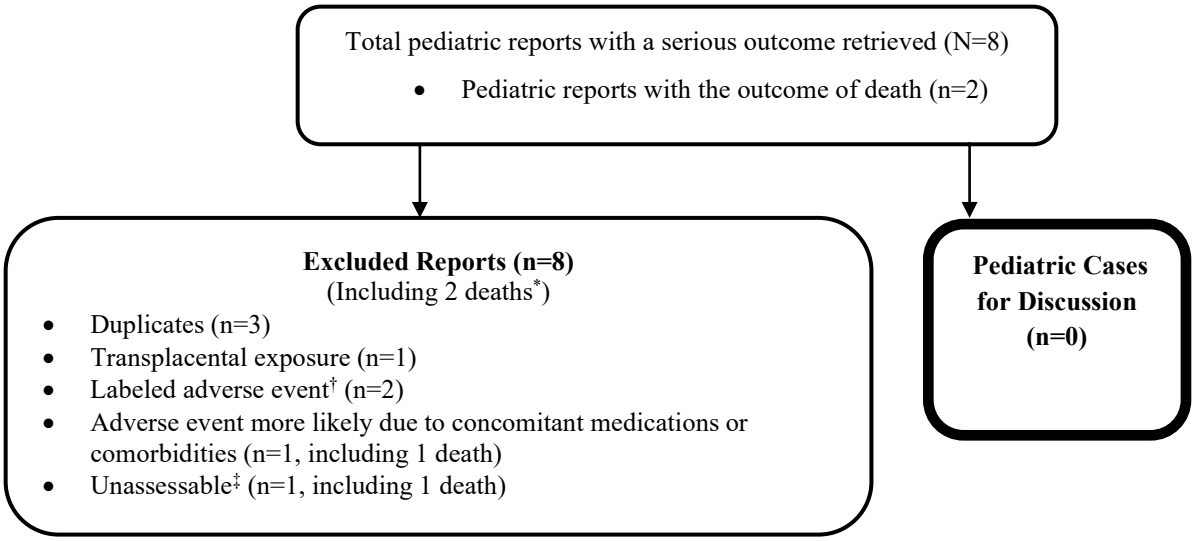
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

‡ See Figure 1. One additional report describing a pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.

### *3.1.2 Selection of Serious Pediatric Cases in FAERS*

Our FAERS search retrieved eight serious pediatric reports through October 16, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all eight reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

**Figure 1. Selection of Serious Pediatric Cases With Indocyanine Green**




* Two excluded FAERS cases described fatal outcomes. Neither of the deaths were determined to be attributed to indocyanine green. One report described an infant who died from complications of chylothorax following Norwood operation for hypoplastic left heart syndrome. The second report described a neonate who died while undergoing an unspecified procedure. This case had no additional clinical information to allow for a causality assessment.

† Labeled adverse event does not represent increased severity or frequency.

‡ Un-assessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

### *3.1.3 Summary of Fatal Pediatric Cases (N=0)*

There are no fatal pediatric adverse event cases for discussion.

### *3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)*

There are no non-fatal pediatric adverse event cases for discussion.

## 4 DISCUSSION

DPV reviewed all serious FAERS reports with indocyanine green in pediatric patients less than 18 years of age through October 16, 2023, and identified eight reports. However, DPV excluded all reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with indocyanine green in pediatric patients less than 18 years of age.

## 5 CONCLUSION

DPV did not identify any new pediatric safety concerns for indocyanine green at this time and will continue routine pharmacovigilance monitoring for indocyanine green.

## 6 REFERENCES

1. Spy Agent Green (indocyanine green for injection) for intravenous, interstitial, or intradermal use. [Prescribing information]. Burnaby, BC, Canada; Novadaq Technologies ULC: June, 2023.

## 7 APPENDICES

### 7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's post marketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonization. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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