CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216264Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: June 22, 2022

To: Joseph G. Rajendran, Clinical Reviewer
Division of Imaging and Radiation Medicine (DIRM)

Alberta E. Davis Warren, Regulatory Project Manager, DIRM

Younsook Kim, Associate Director for Labeling, DIRM

From: Nazia Fatima, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for BLUDIGO™ (indigotindisulfonate sodium injection) for intravenous use

NDA: 216264

In response to DIRM's consult request dated October 10, 2021, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for BLUDIGO™ (indigotindisulfonate sodium injection) for intravenous use (Bludigo).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DIRM on June 1, 2022, and have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 15, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NAZIA FATIMA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	June 16, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216264
Product Name and Strength:	Bludigo (indigotindisulfonate sodium) Injection, 40 mg/5 mL (8 mg/mL)
Applicant/Sponsor Name:	Provepharm Inc. (Provepharm)
OSE RCM #:	2021-1916-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Provepharm Inc. (Provepharm) submitted revised vial container labels and carton labeling on June 15, 2022 for Bludigo (indigotindisulfonate sodium) injection. We reviewed the revised vial container labels and carton labeling for Budigo (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Kane, D. Label and Labeling Review for Bludigo (NDA 216264). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 26. RCM No.: 2021-1916.

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/s/

DEVIN R KANE
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HINA S MEHTA
06/17/2022 11:52:58 AM

Clinical Inspection Summary

Date	June 7, 2022
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE)
To	Alberta Davis-Warren, Regulatory Project Manager Joseph Rajendran, M.D., Medical Officer Venkata Mattay, M.D., Clinical Team Leader Libero Marzella, M.D., Ph.D., Division Director Division of Imaging and Radiation Medicine (DIRM)
Application	NDA 216264
Applicant	Provepharm, SAS
Drug	Indigo Carmine (Indigotindisulfonate Sodium, Bludigo®)
Original NDA	Yes (New Chemical Entity)
Review Timeframe	Standard
Proposed Indication	(b) (4)
Consultation Date	January 12, 2022
CIS Goal Date	June 8, 2022
Action Goal Date	July 8, 2022
PDUFA Due Date	July 9, 2022

I. OVERALL ASSESSMENT OF FINDINGS

Study PVP-19IC01 was audited at good clinical practice (**GCP**) inspections of three study sites: two clinical investigators (**CIs,** Drs. S.W. Robinson and L.R. Wiegand) selected as the major representative sites to audit general study conduct and the adverse event (AE) data, and an imaging contract research organization (**CRO**, (b) (4) to verify the primary efficacy (imaging) endpoint data. No significant GCP violations were identified at the three study sites. Study PVP-19IC01 appears to have been conducted in adequate compliance with GCP regulations and standards. The clinical data generated at the three inspected study sites appear to be acceptable in support of the sponsor's proposed product indication for use.

II. BACKGROUND

Indigo carmine (**IC**) is a blue dye that has been used in diagnostic medicine for over a century. Its clinical use is well described in the literature including its current common intraoperative use. IC is currently not approved in the United States (**US**) although (permitted to be) marketed. This NDA from Provepharm, Inc. is in support of the formal US approval of IC as a visualization aid in (b) (4) the ureters (b) (4) surgical or endoscopic procedures. This 505(b)(2) NDA makes no reference to a previously approved drug (Reference Listed Drug, **RLD**) and relies primarily on the results of a single pivotal study. The following description of the study outlines its major features that served as a guide in verifying GCP-compliant study conduct at three inspections (two CIs and one imaging CRO).

Study PVP-19IC01: *An Open-Label, Randomized, Multicenter Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Physician Satisfaction of Two Different Doses of 3,3'-Dioxo-2,2'-bisindolylidene-5,5'-disulfonate disodium 0.8% Solution when used as an Aid in the Determination of Ureteral Patency*

This Phase 3 randomized study was conducted over 16 months (February 2020 to June 2021) in 121 subjects enrolled at 7 US CI sites. The primary study objective was to determine if the use of IC provides a diagnostic advantage relative to saline in visual evaluation of ureteral patency. The sponsor claims that the study results support the efficacy of IC (relative to saline, at either high or low dose level) in visualizing urine flow, with no significant clinical safety or tolerability concerns.

The study consisted of three periods: (1) screening, (2) randomization and IC dosing, and (3) post-operative safety monitoring. Subjects were randomized in equal ratio to either low dose (2.5 mL) or high dose (5.0 mL) of IC. At surgery, the subject was given intravenously 5.0 mL of normal saline, followed by either low or high dose of IC as randomized. The ureteral urine flow was evaluated intraoperatively by the surgeon for 10 minutes following IC administration. Video recordings of the 10-minute evaluation were sent to (b) (4) (b) (4) for central blinded interpretation (primary endpoint). The subjects and the central readers were blinded; the study personnel was not blinded (surgeon blinded to IC dose).

- Inclusion: adult subjects (18 to 85 years old) scheduled for urological or gynecological surgery or endoscopic procedure requiring ureteral patency assessment
- Exclusion: stage 4 or 5 chronic kidney disease (glomerular filtration rate ≤ 30 mL/min/1.73 m^2), current or anticipated dialysis, having only one kidney; known severe hypersensitivity to IC or other contrast dyes
- Primary efficacy endpoint (b) (4): conspicuity score (**CS**) as determined by the blinded central readers at (b) (4), where 1 = no jet (ureteral urine flow), 2 = weak jet with no significant color contrast, 3 = significant jet or color contrast, 4 = strong jet with good color contrast, and 5 = strong jet with striking color contrast
- Major secondary endpoints: (1) proportion of physicians (CIs) who agreed that IC improved visualization of ureteral patency; (2) minutes to visualization of blue color in the ureter following IC administration; and (3) proportion of responders with ≥ 1-point improvement in CS and CS ≥ 3 for IC

III. INSPECTION RESULTS

1. Steven W. Robison, M.D.

Rosemark Women's Care Specialists
3450 Potomac Way
Idaho Falls, Idaho 83404

Inspection dates: March 28-31, 2022
Study PVP-19IC01, Site 106

Thirty-nine subjects were enrolled and 37 completed the study. One subject was withdrawn (surgical complication, bladder perforation) and one subject was lost to follow up. Subject case records were reviewed in detail for all subjects.

The inspectional findings were noteworthy for scattered instances of incomplete or inaccurate information on progress notes (missing or inconsistent signatures or dates), which appeared to be isolated recordkeeping errors. The correct information was typically captured on the electronic case report forms (**eCRFs**) and accurately reported in the NDA. One isolated unreported adverse event (**AE**) was noted (telephone report of sore throat, subject lost to follow up).

The deficiency observations appear unlikely to be significant. GCP deficiencies were otherwise not observed. No evidence of GCP non-compliant study conduct was observed as potentially contributing to the CS non-concordance noted at preliminary NDA review (CS values obtained by unblinded surgeons at this CI site notably different from those obtained by blinded central readers at (b) (4)

Study files and subject case records were well maintained and readily available for review. No unreported protocol deviations were discovered. All audited major efficacy endpoint data (applicable to CI site) were verifiable against the data reported in the NDA, including all CS data.

2. Lucas R. Wiegand, M.D.

Tampa General Hospital
One Tampa General Circle
Tampa, Florida 33606

Inspection dates: April 13-18, 2022
Study PVP-19IC01, Site 202

Twenty-one subjects were enrolled and 18 completed the study. Two subjects were withdrawn (CI discretion, surgery cancellation) and one subject was lost to follow up. Subject case records were reviewed in detail for all subjects.

No evidence of GCP non-compliant study conduct or recordkeeping was observed as potentially contributing to the CS non-concordance noted at preliminary NDA review (CS values obtained by unblinded surgeons at this CI site notably different from those obtained by blinded central readers at (b) (4)

No significant GCP deficiencies were observed, including no unreported AEs or protocol deviations. Study files and subject case records were adequately maintained. All audited efficacy endpoint data (applicable to CI site) were verifiable against the data reported in the NDA, including all CS data.

3. (b) (4) (b) (4)

Inspection dates: April 14-26, 2022
Study PVP-19IC01, CRO site for videography (imaging)

(b) (4) performed the following major study tasks: (1) feasibility assessment of CI sites, including training and on-going guidance; (2) central reviewer training and videography review oversight; (3) video receipt, quality control, and videography review; and (4) imaging data generation and data transfer (to sponsor).

Records of all major study tasks were audited, to include reviews of: (a) study protocol; (b) contractual agreement (and on-going communication) with sponsor; (c) validation of (b) (4) imaging software; (d) center manuals for general staff training and standard operating procedures (**SOPs**); and (e) videography reference manual (**VRM**).

A total of 121 subjects were enrolled in the study. Subject records and videos were reviewed for 96 subjects across all CI sites, including all subjects at Site 106 (Robison) and at Site 202 (Wiegand). The following observations appear relevant to the preliminary NDA review concerns noted in *Request for GCP Inspections*.

- The three blinded central reviewers interpreted the videos remotely and recorded the review results (imaging source records) using (b) (4) software developed by (b) (4) in-house in 2005, with on-going (audit trail) updates.
- As specified in VRM, an average of the two CS values (Readers 1 and 2) were reported to the first decimal in order to capture (and reflect) a score difference of 1 between the two original CS scores.
- Paired CS values (Readers 1 and 2) with score differences greater than 1 were independently reviewed (Adjudicator) to select one CS value over the other (adjudication rate = 1/3 of all paired original scores). Occasional missing central CS values appeared to be (typically) due to poor quality videography, not necessarily missing in pairs since the two primary readers could disagree about video quality (adequacy for interpretation).

No significant GCP deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations were discovered. The audited primary efficacy (videography) endpoint data were verifiable against the data reported in the NDA, including all CS data.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
Team Leader
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Kassa Ayalew, M.D., M.P.H.
Division Director and Acting Branch Chief
Good Clinical Practice Assessment Branch
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CC:

Central Document Room / NDA 216264

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DIRM / Team Leader / Venkata Mattay
DIRM / Medical Officer / Joseph Rajendran
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OSI / Database Project Manager / Dana Walters

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/s/

JONG HOON LEE
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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

Pharmacovigilance Review

Date:	May 11, 2022
Reviewer:	Samantha Cotter, PharmD, BCPS, FISMP Division of Pharmacovigilance II (DPV II)
Team Leader:	Mallika Mundkur, MD, MPH DPV II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS DPV II
Product Name*:	(b) (4) (Indigotindisulfonate Sodium Injection) *Marketed unapproved product as Indigo Carmine
Subject:	505(b)(2) NDA, All Adverse Events
Application Type/Number:	NDA 216264
Sponsor:	ProvePharm SAS
OSE RCM #:	2021-2346

Acknowledgements: Thank you to Dr. Danielle Molnar for her expertise and assistance in searching the VigiBase data for this review.

****This document contains information obtained by FDA using VigiLyze, a tool for searching VigiBase, the World Health Organization-Uppsala Monitoring Centre's global database of individual case safety reports (ICSRs). The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information included does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organization. Use of VigiBase data in any document or publication, in whole or in part, must be accompanied by this statement.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In this review, the Division of Pharmacovigilance (DPV) assessed the FDA Adverse Event Reporting System (FAERS) database, published medical literature, VigiBase and sponsor materials ("Clinical Safety Data") for adverse events (AEs) and safety data reported with indigotindisulfonate sodium injection. On December 7, 2021, the Division of Imaging and Radiation Medicine (DIRM) consulted DPV requesting an assessment of postmarket safety data to inform the evaluation of a New Drug Application (NDA 216264: Indigotindisulfonate sodium [currently marketed as an unapproved product, "Indigo carmine," application submitted via 505(b)(2) pathway]).

DPV identified 57 cases reporting at least one adverse event with indigotindisulfonate sodium injection in FAERS and the medical literature providing evidence that may warrant labeling updates. We did not identify additional cases from VigiBase or the Sponsor's "Clinical Safety Data" report. DPV identified the following unlabeled AEs: *cardiac arrest*, *atrioventricular block second degree*, *anaphylactic reaction*, and *injection site discolouration* that may warrant inclusion in labeling. We also identified cases describing labeled AEs (*hypotension* and *hypertension*) that could be characterized further in existing labeling. Structural similarities between indigotindisulfonate and serotonin as well as adrenergic receptor activation, have been hypothesized to explain the clinical observations of drug-induced hypertension and bradycardia. Drug-induced hypotension may occur due to nitric oxide-mediated vasodilation.

Our analysis has several limitations. Spontaneous reporting databases are subject to underreporting, leading to incomplete capture of relevant cases. Submitted reports often lack relevant detail, such as information on route, drug formulation, and patient data including concomitant medications and disease states. Although FDA requires the reporting of AEs for unapproved marketed drugs, other factors can influence whether or not an event will be reported, such as the amount of time a product has been marketed and public awareness about an AE.

Based upon findings from this review, DPV recommends the following:

1. Add two new Warnings to the WARNINGS AND PRECAUTIONS section regarding each of the following AEs: *hypersensitivity reactions* (including *anaphylactic reactions*) and *atrioventricular block second degree*

2. Update the current WARNINGS AND PRECAUTIONS section 5.1 (b) (4) for *hypotension* and *hypertension* and include severity of events characterized by *cardiac arrest* and *arrythmia*.

3. Expand the ADVERSE REACTIONS section 6.2 Post Marketing Experience to include *injection site discoloration*.

1 INTRODUCTION

In this review, the Division of Pharmacovigilance (DPV) assessed the FDA Adverse Event Reporting System (FAERS) database, published medical literature, VigiBase and sponsor materials ("Clinical Safety Data") for adverse events (AEs) and safety data reported with indigotindisulfonate sodium injection. On December 7, 2021, the Division of Imaging and Radiation Medicine (DIRM) consulted DPV requesting an assessment of postmarket safety data to inform the evaluation of a New Drug Application (NDA 216264: Indigotindisulfonate sodium [currently marketed as an unapproved product, "Indigo carmine," application submitted via 505(b)(2) pathway]).

1.1 BACKGROUND

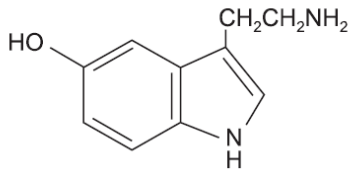
Indigotindisulfonate sodium injection is currently a marketed unapproved drug[a] available for use in the United States and is available under the marketed unapproved brand name Indigo Carmine. Indigotindisulfonate sodium is a (b) (4) (b) (4) by its deep blue color (ProvePharm SAS 2021). When administered intravenously, indigotindisulfonate sodium causes dark blue discoloration of urine within (b) (4) minutes of injection. (b) (4) Use of indigotindisulfonate sodium was first documented in 1903 as a diagnostic agent to visualize the urine stream emerging from the ureter (Voelcker 1903). In modern medicine, it is widely employed as a diagnostic aid in urology and is utilized during surgery to identify vessels, tissues, and fistulae, and to visualize ureteral urine ejection jets after urogynecological surgery (Luketic 2016). It also has been used in intraoperative cystoscopy following pelvic or abdominal surgeries due to risk of injury to the urinary tract (Luketic 2016).

Indigotindisulfonate sodium goes by many other names including indigo carmine, idigotine, 3,3'-Dioxo-2,2'-bisindolylidene-5,5'-disulfonate disodium, and FD&C Blue No. 2.[b] Herein for this review, we refer to the product as indigotindisulfonate sodium. As indigotindisulfonate sodium has been available as an unapproved drug for many years, the Sponsor has estimated that "(b) (4) patients have been exposed to indigotindisulfonate sodium via intravenous (IV) or intramuscular routes (IM)" (ProvePharm SAS 2021).

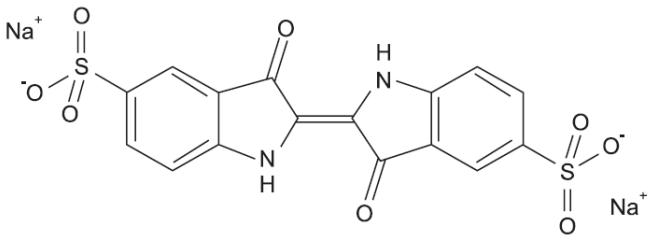
The chemical structure of indigotindisulfonate sodium shares similarities to serotonin (5-hydroxytryptamine). Serotonin is a neurotransmitter that has direct vasoconstrictive and positive inotropic properties (Nguyen 1998). The molecular structure of indigotindisulfonate sodium resembles two adjoining molecules of serotonin (Lee 2012). See Figure 1.

[a] https://www fda.gov/drugs/enforcement-activities-fda/unapproved-drugs
[b] Reference to CFR 74 PART 74 - LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION (74.102)

Figure 1. Comparison of the Molecular Structures of Serotonin and Indigotindisulfonate Sodium



The structural formula of serotonin.



The structural formula of indigotindisulfonate sodium.

(Lee 2012)

Some have proposed that this structural similarity to serotonin, via adrenergic receptor activation, might underlie known drug-induced clinical manifestations of *hypertension* and *bradycardia* (Nguyen 1998; Jo 2013). In animal models, indigotindisulfonate sodium significantly inhibited receptor- and non-receptor-mediated endothelium-dependent vasorelaxation and selectively inhibited nitric oxide-mediated responses, suggesting that the drug may elevate blood pressure by interfering with these nitric oxide-mediated vasodilatory mechanisms (Chang 1996).

Indigotindisulfonate sodium is also known to cause *hypotension* and has been hypothesized to do so by inducing a temporary decrease in cardiac output secondary to nitric oxide inhibition and/or serotonin-mediated ventricular inotropy (Sutton 2016).

1.2 REGULATORY HISTORY

From 2015 – 2018, indigotindisulfonate sodium was on the national drug shortage list. As of 2018, the drug shortage has been resolved (ASHP 2018).

- December 20, 2017 – ProvePharm SAS began re-Investigational New Drug (IND) talks with FDA
- January 22, 2018 – ProvePharm SAS submitted (b) (4) which was denied by FDA
- January 23, 2019 – ProvePharm SAS had a Type C[c] meeting with FDA
- October 10, 2019 – ProvePharm SAS submitted a Pediatric Study Plan (iPSP) that FDA later accepted
- September 9, 2022 - ProvePharm submitted NDA 216264 505(b)(2) Indigo Carmine (indigotindisulfonate sodium injection) with a proprietary name request for (b) (4)

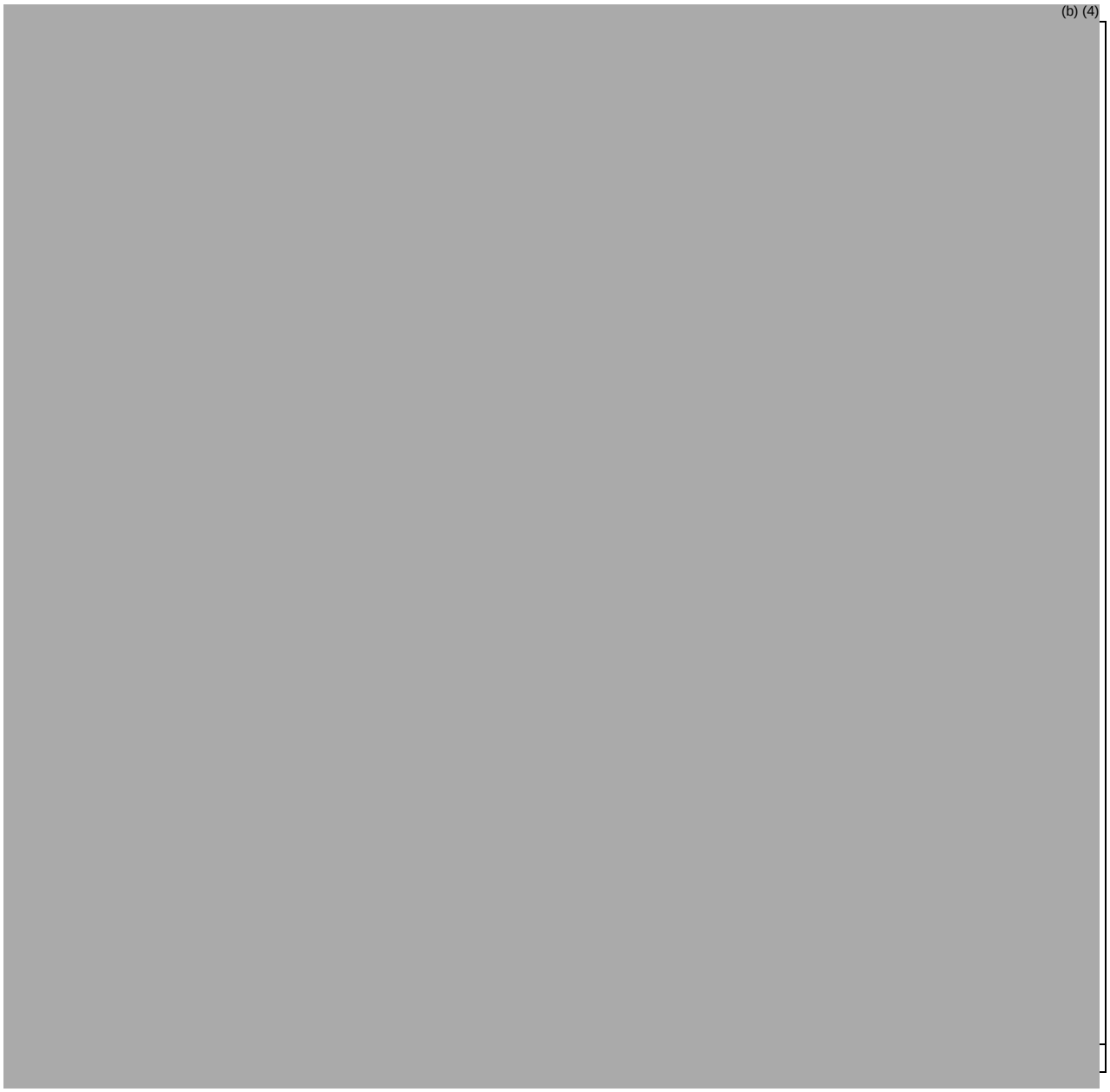
[c] Phase 3 efficacy and safety study

1.3 RELEVANT PRODUCT LABELING

Relevant Contraindications, Warnings and Precautions, and Adverse Reactions in the proposed draft labeling for indigotindisulfonate sodium are in Table 1. The comparative labeling information from the unapproved indigo carmine injection drug label (American Regent 2017) is provided in Appendix A.

Table 1. Proposed Draft Label for Indigotindisulfonate Sodium 0.8% Solution for Injection 40 milligram (mg)/5 milliliter (mL)

(b) (4)



2 METHODS AND MATERIALS

In this review, DPV reviewed FAERS reports, the published medical literature, VigiBase and the Sponsor's "Clinical Safety" report submitted with the NDA for all AEs following use of indigotindisulfonate sodium. Details of this methodology are described below.

2.1 CASE SELECTION

We applied the following selection criteria to identify eligible cases for further analysis. For cases meeting selection criteria, we reviewed all preferred terms (PTs) for new potential safety signals.

Inclusion Criterion:

- Reports that describe indigotindisulfonate sodium or indigo carmine administered as an injection, infusion, or administered in a manner to stain tissue (e.g., lymph node visualization).

Exclusion Criterion:

- Reports that describe indigotindisulfonate sodium being used as a dye/excipient in oral drugs or food substances.

2.2 CAUSALITY CRITERIA

We evaluated all reports meeting selection criteria for a causal relationship between indigotindisulfonate sodium exposure and the occurrence of an adverse event. We used the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment instrument (See Appendix B) (WHO-UMC 2013).

We excluded reports from the case series where we deemed causality as unassessable or unlikely.

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*

Date of search	March 4, 2022
Time period of search	All Dates through - March 3, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Indigotindisulfonate Sodium, Indigotindisulfonic Acid (Product Active Ingredient)
MedDRA search terms (Version 24.1)	All Preferred Terms
Case Narrative Contains	Indigo carmine

* See Appendix C for a description of the FAERS database.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PV = pharmacovigilance

2.4 LITERATURE SEARCH STRATEGY

DPV searched the published medical literature with the strategy described in Tables 3 and 4.

Table 3. Literature Search Strategy	
Date of search	March 4, 2022
Database	Embase
Search terms*	'indigo carmine'/exp/dd_ae OR (('indigo carmine'/exp OR 'indigo carmine') AND ('case report'/exp OR 'case report') AND 'indigo carmine':ti)
Years included in search	All years
Other Criteria	Human, English
* Embase and PubMed recommend use of the term "indigo carmine" as a broader search for indigotindisulfonate sodium	

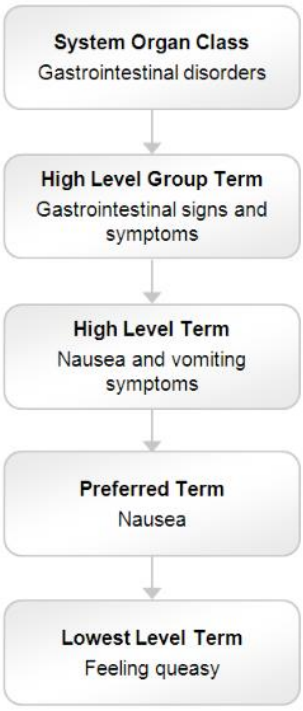
Table 4. Literature Search Strategy	
Date of search	March 4, 2022
Database	PubMed
Search terms*	(("indigo carmine"[MeSH Terms] OR ("INDIGO"[All Fields] AND "CARMINE"[All Fields]) OR "indigo carmine"[All Fields]) AND (("adverse"[All Fields] OR "adversely"[All Fields] OR "adverses"[All Fields]) AND ("event"[All Fields] OR "event s"[All Fields] OR "events"[All Fields]))) OR ("indigo carmine"[Title] AND ("case reports"[Publication Type] OR "case report"[All Fields]))
Years included in search	All years
Other Criteria	Human, English
* Embase and PubMed recommend use of the term "indigo carmine" as a broader search for indigotindisulfonate sodium	

2.5 MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES (MEDDRA) TERMINOLOGY – CODING OF SYSTEM ORGAN CLASS (SOC) AND PTS

At DIRM's request, DPV assessed and analyzed cases of adverse events using the MedDRA coding system (i.e., PTs and SOCs).

Cases retrieved from FAERS (e.g., reported from health care professionals, patients or manufacturers) are pre-coded with MedDRA terms (i.e.., lower level term [LLT], PT, high level term [HLT], high level group term [HLGT], SOC) (Brajovic 2010). Such coding is often conducted by manufacturers and/or contractors and undergoes quality-control assessments by specially trained FDA coding staff. See Figure 2 for a schematic depicting the MedDRA hierarchy (MedDRA 2022).

Figure 2. MedDRA Hierarchy Structure



Accessed April 26, 2022, at https://www.meddra.org/how-to-use/basics/hierarchy

For cases retrieved from the literature only (i.e., not submitted to FAERS), DPV followed MedDRA terminology guidance and assigned the MedDRA LLT to each adverse event documented in the case that most accurately reflected the reported verbatim information (MedDRA 2022). Once these LLTs were categorized, they were mapped to the correlating PT and this information was recorded. These terms were then further mapped to the system organ classes (SOCs) that the PT is found in. Some PTs are only found under a single SOC; however, many PTs are located under multiple SOCs. This is referred to as "multiaxiality," and allows a PT to be represented in more than one SOC and to be grouped by different classifications.

2.6 VIGIBASE

DPV searched the VigiBase database (See Appendix D) with the strategy described in Table 5. VigiBase is a global database of more than 20,000,000 individual case safety reports (ICSRs) maintained by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC 2013). VigiBase reports were classified as unassessable due to the lack of narrative information and were not included in the case series. Despite this limitation of VigiBase data, we provided the PTs identified in VigiBase for descriptive purposes (See Section 3.3).

Table 5. VigiBase Search Strategy*	
Date of search	February 10, 2022
Time period of search	All dates through December 31, 2021†
Search type	VigiLyze: Overview and Line Listing
Product terms	Indigo Carmine (Active ingredient)
MedDRA search terms (Version 24.1)	All adverse events
* See Appendix D for a description of the VigiBase database † Based on VigiBase Initial Date Abbreviations: MedDRA=Medical Dictionary for Regulatory	

2.7 SPONSOR'S SUMMARY OF CLINICAL SAFETY

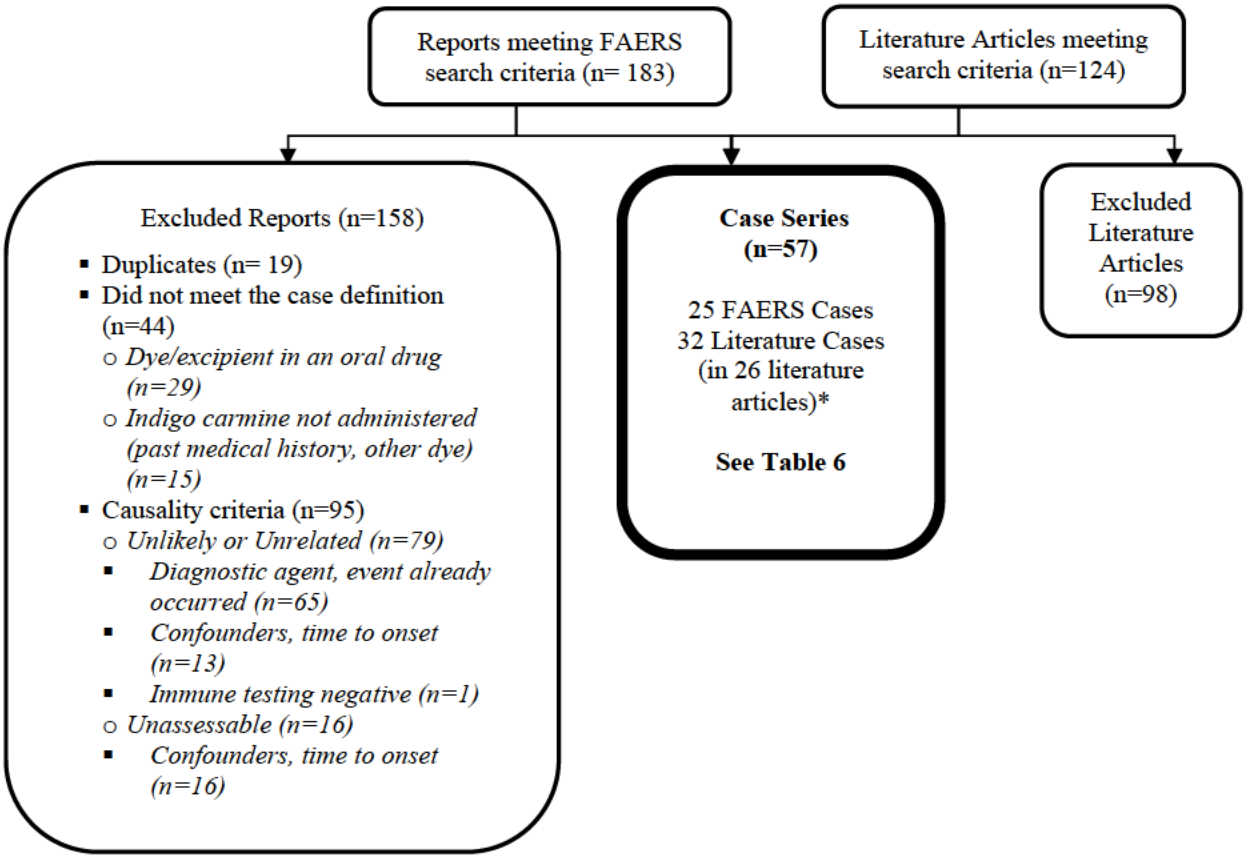
DPV also reviewed Section 2.7.4. "Summary of Clinical Safety - PostMarketing Data" for NDA 216264 (dated August 19, 2021) for any additional relevant postmarket safety data not identified in other aspects of the review.

3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION

We identified a total of 57 cases (FAERS cases n=25, literature cases n=32 [in 26 literature articles]) for inclusion in the case series (see Figure 3).

Figure 3. FAERS and Literature Case Selection



* 26 literature articles provided a total of 32 cases due to multiple cases identified in three literature articles (Jeon 2012 [n=3], Kazbek 2019 [n=2], Fairly 1993 [n=4])

Table 6 summarizes key characteristics of the case series (See Appendix E for a line listing).

Table 6. Descriptive Characteristics of All Adverse Events with Indigotindisulfonate Sodium in This FAERS and Literature Case Series, Received by FDA or Published for all Dates through March 3, 2022 (N=57)	
Case source†	
FAERS	25
Literature	32
Age (years)	
Mean	59
Median	61.5
Range	27 – 85
NR	1
Sex	
Female	35
Male	21
NR	1
Report type	
Expedited	10
Direct	15
Literature	32
Country derived	
Domestic	38
Foreign	19
Initial year received or published	
1977	1
1987	1
1990 - 1999	11
2000 – 2009	16
2010 -2019	26
2020 – 2022	2
Reason for use	
Visualize ureters*	44
Visualize nodes (biopsy/define tumor border/ mapping)	5
Surgery NOS	2
Diagnostic aid NOS	3
Stained tissue -endoscopic discectomy	2
Fallopian tube contrast – radiography	1
Time to Onset	
Immediately– 2 minutes	22
3 – 5 minutes	11
6 – 10 minutes	4
15 – 20 minutes	2
35 – 50 minutes	2
During procedure	8
17 days	1

NR	7
Serious outcome(s) in FAERS cases[†‡]	
DE[§]	1
LT	6
HO	5
OT	13
Not Serious	1
NR (Literature)	32
Clinical Outcome	
Death[§]	1
Recovered/Resolved	46
Recovering/Resolving	1
Not Reported	9
Causality assessment	
Probable	45
Possible	12

* Reason for use visualize ureters was documented in prostate surgery (17), gynecological surgery (14), bladder tumor (5), urologic surgery (4), and visualize ureters NOS (4)
† 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. A case can have more than one serious outcome.
‡ Literature cases do not have serious regulatory outcomes
§ (FAERS Case # 5792376) The patient with a documented myocardial infarction also experienced sinus arrhythmia and ventricular tachycardia and represented the one death in our case series. Events occurred during the procedure after indigotindisulfonate was utilized to visualize the ureters during urologic surgery (see Section 3.2.2.1 and 3.2.3.1 below).
DE = death, LT = life threatening, HO = hospitalization; OT = other serious, RI = required intervention, NR = not reported, NOS = not otherwise specified

Of the 57 cases in our case series, we deemed the causal association between indigotindisulfonate sodium exposure and the events as "probable" in 45 cases, and "possible" in the remaining 12 cases, based on the WHO-UMC causality criteria (WHO-UMC 2013). Fifty-six of the cases reported an age with a mean of 59 years (range 27 – 85 years [median = 61.5 years]). The majority of cases were domestic (n=38). The FDA initial received date and publication dates spanned from 1977 to 2022. Among the 49 cases reporting a time-to-onset, 33 reported events occurring within 5 minutes of administration.

Among the FAERS cases (n=25), 24 were associated with serious regulatory outcomes[d] including death (n=1), life threatening (n=6), hospitalization (n=5), and "other" serious (n=13).

[d] A case can have more than one serious outcome.

3.2 FAERS AND LITERATURE, ANALYSIS OF MEDDRA TERMS

DPV divided the 57 cases into the system organ classes (SOCs) represented by the adverse events and further identified the preferred terms (PTs) from the case series. See Section 3.2.1.

3.2.1 All Adverse Events: SOCs and PTs

Table 7 summarizes the adverse events reported in our cases, organized by SOC. The cases in this series reported a total of 15 SOCs. The most frequently identified SOCs included vascular disorders (n=32), cardiac disorders (n=24), and investigations (n=18). Because of the "multiaxiality" of the MedDRA hierarchy, some PTs were represented under multiple SOCs.

Table 7. Adverse Events with Indigotindisulfonate Sodium, by SOC, Received by FDA or Published for all Dates through March 3, 2022
N = 57

System Organ Class	Cases Reporting a PT in the SOC (n)	PTs in the SOC (n)
Vascular disorders (VD)	32	42
Cardiac disorders (CD)	24	35
Investigations (Inv)	18	27
Injury, poisoning and procedural complications (IPPC)	15	18
Respiratory, thoracic, and mediastinal disorders (RTMD)	11	17
Immune system disorders (ISD)	11	15
Skin and subcutaneous tissue disorders (SSTD)	10	15
General disorders and administration site conditions (GDASC)	9	14
Nervous system disorders (NSD)	8	8
Infections and infestations (II)	2	4
Psychiatric disorders (PD)	2	2
Gastrointestinal disorders (GI)	1	1
Metabolism and nutrition disorders (MND)	1	1
Pregnancy, puerperium, and perinatal conditions (PPPC)	1	1
Renal and urinary disorders (RUD)	1	1

*A preferred term (PT) may exist in more than one System Organ Class (SOC)
Appendix F provides the full list of MedDRA SOC terms (15 SOCs identified in the case series and 12 SOCs not identified in the case series [e.g.: endocrine disorders])

Table 8 provides the list of adverse events, by PT. The cases summarized in the table were limited to those with the indicated PT identified in two or more cases (See Appendix G for all PTs). The most frequently reported PTs included *hypotension* (n=22), *hypertension* (n=8), *bradycardia* (n=7), and *oxygen saturation decreased* (n=7). The SOC for the PTs is also

provided in the table. PTs listed in the proposed label for indigotindisulfonate sodium are also noted and the label location is provided.

Table 8. Preferred Terms (PTs) for All Adverse Events with Case Count 2 or More with Indigotindisulfonate Sodium in the FAERS and Literature Case Series, Received by FDA or Published for all Dates through March 3, 2022
(N=57)

PT	System Organ Class (SOC)	Cases with PT (n)	Proposed Labeling (Label Location)	Reviewers Comments
Hypotension	VD	22	Yes (W/P) 5.1	See Section 3.2.2.1
Hypertension	VD	8	Yes (W/P) 5.1	See Section 3.2.2.2
Bradycardia	CD	7	Yes (W/P) 5.1, 5.2	See Section 3.2.3
(b) (4)	Inv	7	(b) (4)	See Section 3.2.3.1 and 3.2.4
Anaphylactic reaction	ISD; VD	5	No ((b) (4) ‡	See Section 3.2.4
Cardiac arrest	CD	4	No	See Section 3.2.3.1
(b) (4)	IPPC	4	(b) (4)	See Section 8.8.2
Atrioventricular block second degree†	CD	3	No†	See Section 3.2.3.2
(b) (4)	CD; NSD; VD	3	No	See Section 8.8.5
(b) (4)	(b) (4)	3	Yes (W/P) 5.1	See Section 8.8.1
(b) (4)	(b) (4)	3	No	See Section 3.2.2.1, 8.8.1.1, and 8.8.3
(b) (4) ‡‡	(b) (4)	2	Yes – (AR-PME) 6.2	See Section 3.2.3.1 and 3.2.4
(b) (4)	(b) (4)	2	Yes (W/P) 5.1	See Section 3.2.2.1 and 8.8.1
Bronchospasm	ISD; RTMD	2	Yes (W/P) 5.1	See Section 3.2.4 and 8.8.3
(b) (4)	(b) (4)	2	Yes (W/P) 5.1	See Section

				3.2.3 and 8.8.3
Erythema	SSTD	2	Yes (W/P) 5.1	See 3.2.4
Injection site discolouration	GDASC; IPPC; SSTD	2	Yes (AR-PME) 6.2 'Skin discoloration'	See Section 3.2.5, 8.8.2 and 8.8.4
(b) (4)	(b) (4)	2	No	See Section 3.2.5 and 8.8.2
(b) (4)	(b) (4)	2	No – Alt Ex	See Section 3.2.3 and 3.2.5
(b) (4)	(b) (4)	2	No	See Section 3.2.3 and 8.8.3
(b) (4)	(b) (4)	2	Yes (W/P) 5.1	See Section 8.8.4
(b) (4)	(b) (4)	2	Yes (W/P) 5.1	See Section 8.8.4
Urticaria	ISD; SSTD	2	No	See Section 3.2.4 and 8.8.4
(b) (4)	(b) (4)	2	No	See Section 3.2.2.2 and 3.2.3
(b) (4)	(b) (4)	2	No	See Section 3.2.4 and 8.8.3

* For these literature cases, the reviewer followed MedDRA terminology guidance and assigned the MedDRA lowest level term(s) (LLT) to each adverse event documented in the case that most accurately reflected the reported verbatim information (MedDRA 2022).
† Although the Sponsors draft prescribing information 6.2 contains atrioventricular block and states (b) (4) (b) (4) atrioventricular block. In addition, draft labeling does not mention atrioventricular block second degree which is a higher degree of atrioventricular (AV) block compared with first-degree AV block and can result in more severe damage to the conduction system (Kashou 2019).
‡ Although *anaphylactoid reaction*s resemble generalized anaphylaxis, they are not caused by IgE-mediated allergic reaction but rather by a nonimmunologic mechanism (Miller-Keane 2003).

System Organ Class (SOC) Abbreviations: Cardiac disorders (CD); Gastrointestinal disorders (GI); General disorders and administration site conditions (GDASC); Immune system disorders (ISD); Infections and infestations (II); Injury, poisoning and procedural complications (IPPC); Investigations (Inv); Metabolism and nutrition disorders (MND) ; Nervous system disorders (NSD); Pregnancy, puerperium and perinatal conditions (PPPC); Psychiatric disorders (PD); Renal and urinary disorders (RUD); Respiratory, thoracic and mediastinal disorders (RTMD); Skin and subcutaneous tissue disorders (SSTD); Vascular disorders (VD)

Other Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, BW = Boxed Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, Alt Ex = Alternative explanation (disease-related, indication-related, or concomitant medication-related), PME= postmarketing experience, PR = Procedure-related, U = Uninformative

3.2.2 Specific AEs: SOC Vascular disorders (n= 32 cases)

We identified 32 cases reporting an adverse event within the SOC "Vascular Disorders." The most frequently reported PTs included within this SOC included *hypotension* (n=22), *hypertension* (n=8), *anaphylactic reaction* (n=5), *dizziness* (n =3) and one each of *anaphylactic shock*, *cerebral ischaemia*, *infusion site discolouration*, and *myocardial infarction*. Each of these frequently reported PTs are discussed below in further detail.

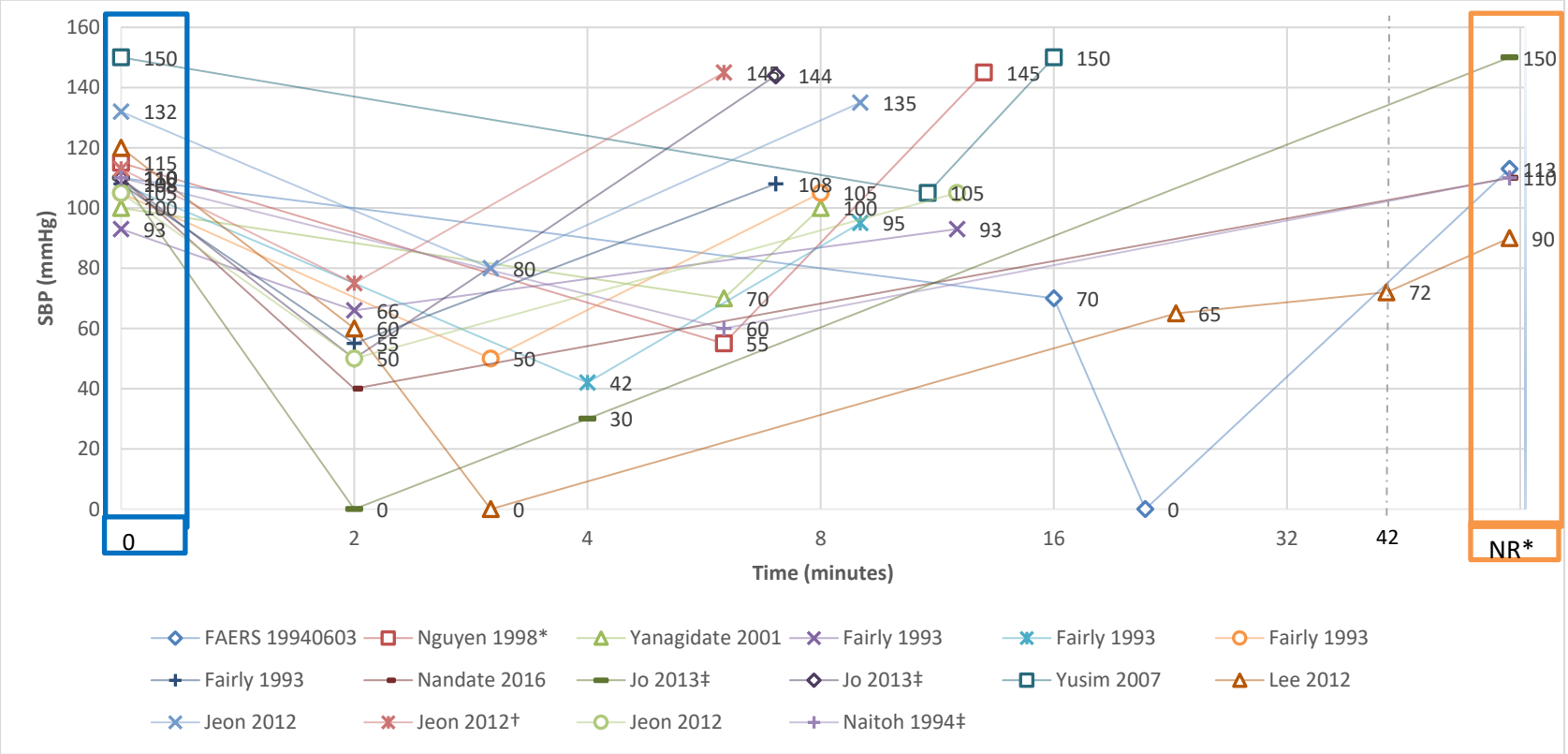
3.2.2.1 Hypotension (n=27 cases)

We identified 22 cases with the PT *hypotension* and an additional five cases that documented a drop in blood pressure for a total of 27 cases in the case series for *hypotension* following the administration of indigotindisulfonate sodium. Clinical outcomes included at the time of the report for these cases included the following: one death (described below), 24 recovered, one recovering, and one not reported.

Twenty of the cases reported the events within 5 minutes of administering indigotindisulfonate sodium. Seven of the 27 cases were in the context of *hypersensitivity reactions* or *anaphylactic reaction*. Of the other 20 cases, four experienced *cardiac arrest* following a rapid decrease in blood pressure (See Section 3.2.3.1). One patient suffered a *myocardial infarction* and died. Twenty-six *hypotension* cases reported one or more treatments including intravenous fluids, vasopressor drugs (e.g., epinephrine, ephedrine, phenylephrine), and cardiopulmonary resuscitation. Three cases, describing *dizziness* and *hypoxia,* occurred in the context of these cases of *hypotension*. One patient experienced a positive rechallenge (Lee 2015) following a second dose of indigotindisulfonate sodium 1 hour after the first dose.

Sixteen of the 27 cases of *hypotension* in our case series included the following case characteristics: baseline systolic blood pressure (SBP), time-to-nadir SBP level, nadir SBP level, time-to-recovery, and the recovery SBP. We plotted these changes in SBP in Figure 4, below.

Figure 4. Cases of Decreased SPB (mmHg) Following Administration of Indigotindisulfonate Sodium Over Time Received by FDA or Published for all Dates through March 3, 2022 (n=16 with detailed temporal information regarding changes in blood pressure)



* Time to recovery was not reported (NR) but SBP was provided
‡ Reported as "baseline stable (not otherwise specified)" (plotted as 110 mmHg)
† Reported as 124/85 – 102/68 mmHg (plotted as the average SBP 113 mmHg)
Each plot line in the figure represents one case. The blue box at the left side of the figure indicates the baseline SBP and time = 0 when indigotindisulfonate sodium was administered. As the plot line for each case travels from left to right (time – logarithmic scale), the SBP experienced by the patient is plotted. All 16 cases had a drop in blood pressure following administration with indigotindisulfonate sodium at different times and at varying drops in blood pressure. An orange box to the far right indicates the four cases that did not specify the exact time to recovery, however, did report a recovered SBP.
Abbreviations: systolic blood pressure (SBP); millimeters of mercury (mmHg)

We highlight the following literature case of *hypotension.*

- **Literature Case (Korea) (Lee 2015)**

A 66-year-old male was scheduled for robotic-assisted laparoscopic radical prostatectomy (RALP). His past medical history included hypertension and wall-motion abnormality of the right coronary artery territory. "RALP proceeded under carbon dioxide (CO_2) pneumoperitoneum[e] in the 45-degree steep Trendelenburg position". Three minutes after an intravenous (IV) injection of indigotindisulfonate sodium, his *blood pressure decreased* to 40/30 millimeters of mercury (mmHg). Treatment of the decrease in blood pressure included phenylephrine and crystalloid fluids. One hour after the first hypotensive episode, the patient received indigotindisulfonate sodium (indication not provided), and again his *blood pressure decreased* to 42/29 mmHg. After administration of additional phenylephrine and crystalloid, he again recovered. According to the case, hypovolemia and embolism were excluded as etiologies for the hypotension (lack of bleeding, no changes in oxygen saturation (Sp02), end-tidal CO_2 and peak airway pressure). The authors attributed the recurrent *hypotension* due to "immunoglobulin E (IgE)-mediated histamine release". However, the patient's IgE levels were reported to be 262 international units (IU)/milliliter (mL) (normal reference range: 150- 300 IU/mL (Laurent 1985)) during the first episode and 311 IU/mL on the first postoperative day.

Reviewer Comments: We categorized this case as probable due to the critically low blood pressures experienced following repeated administration of indigotindisulfonate sodium with a short time-to-onset for both events. His baseline blood pressure was not provided; however, it was noted that he had a history of hypertension. Without treatment involving resuscitation and vasopressor medications, outcomes could have been more serious. The IgE levels reported on the first postoperative day were marginally elevated and potentially consistent with a hypersensitivity reaction (Laurent 1985). However, given the absence of other suggestive signs of a hypersensitivity reaction (e.g. rash, urticaria, bronchospasm) an alternate drug-related mechanism (induced by indigotindisulfonate sodium) could be drug-induced vasodilation.

WHO Causality: Probable

3.2.2.2 Hypertension (n=10 cases)

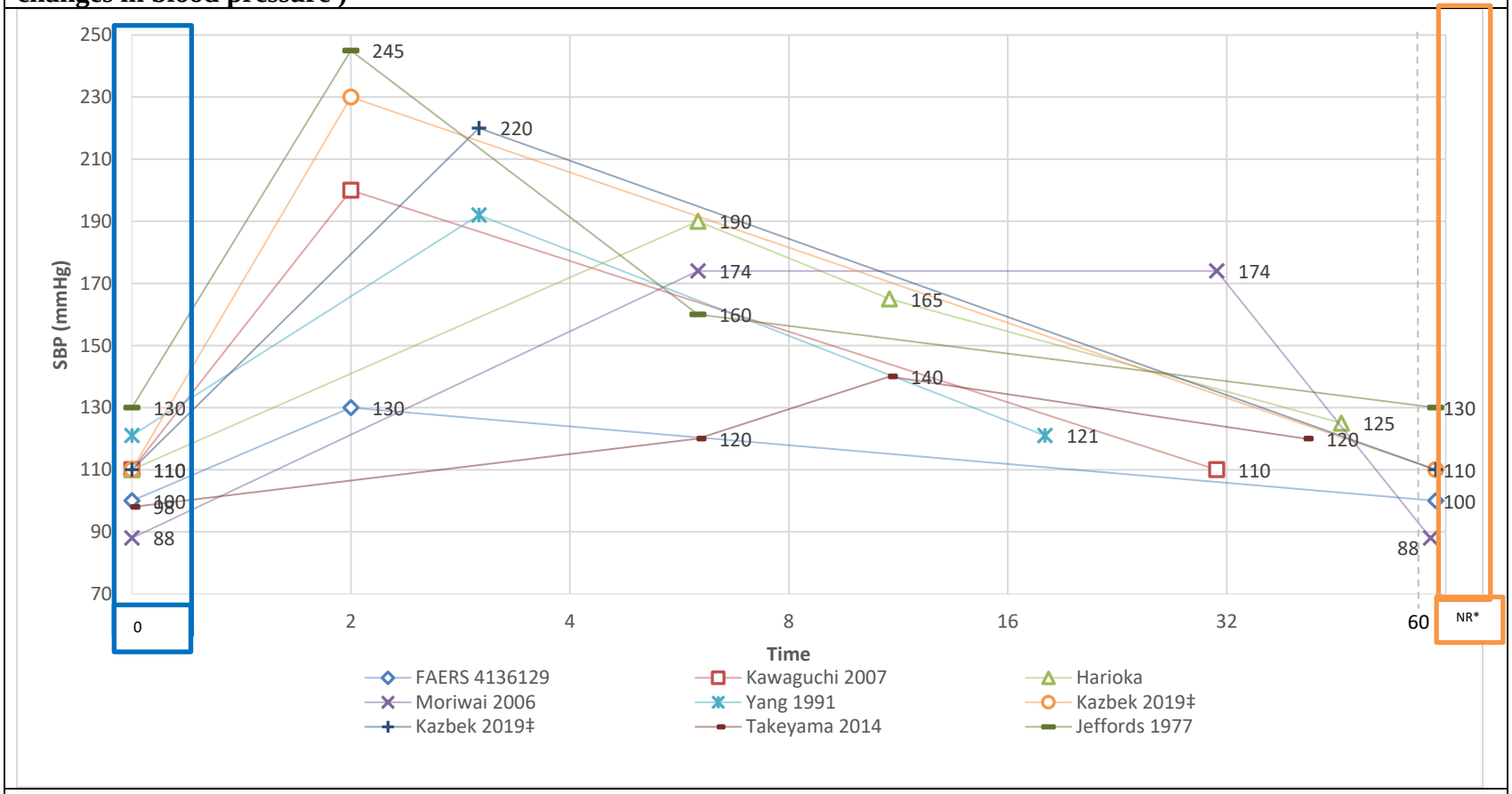
We identified a total of eight cases with the PT *hypertension* and an additional two cases that documented *blood pressure increased* for a total of 10 cases documenting an increase in blood pressure or *hypertension* following the administration of indigotindisulfonate sodium. Eight of the cases reported the events within two minutes of administering indigotindisulfonate sodium. Of these cases, events also included *ventricular tachycardia* (n=1), *cardiac index increased*

[e] Laparoscopic surgery is accomplished by creating a pneumoperitoneum with a gas (usually carbon dioxide [CO_2]) and involves insufflation of a CO_2 into the peritoneal cavity. This allows the laparoscopic surgery to be completed. CO_2 pneumoperitoneum may cause an increase in intra-abdominal pressure (IAP) which may lead to an alteration adverse effects within the cardiovascular and respiratory systems (Atkinson 2017).

(n=1), increased ventricular afterload with *acute left ventricular failure* (n=1), *ventricular extrasystoles* and *bradyarrhythmia* (n=1), *sinus tachycardia* (n=1), and *atrioventricular block* (n=1). Five of the *hypertension* cases reported treatments including lidocaine, propofol, hydralazine, atropine, and nitroglycerin. One patient experienced a positive rechallenge (Jeffords 1977) following a second dose of indigotindisulfonate sodium at a later date. Clinical outcomes included nine recovered and one not reported.

Nine of the ten cases of *hypertension* in our case series included the following case characteristics: baseline SBP, time to peak SBP level, peak SBP level, time to recovery, and the recovery SBP. We plotted these fluctuations in SBP in Figure 5, below.

Figure 5. Cases of Increased SPB (mmHg) Following Administration of Indigotindisulfonate Sodium Over Time, Received by FDA or Published for all Dates through March 3, 2022 (n=9 with detailed temporal information regarding changes in blood pressure)



* Time to recovery was not reported (NR) but SBP was provided
‡ Reported as "baseline stable (not otherwise specified)" (plotted as 110 mmHg)
Each plot line in the figure represents one case. The blue box at the left side of the figure indicates the baseline SBP for each case and time = 0 for when indigotindisulfonate sodium was administered. As the plot line for each case travels from left to right (time logarithmic scale), the SBP experienced by the patient is plotted. All nine cases had an increase in blood pressure following administration with indigotindisulfonate sodium at different times and at varying increases compared to their base line. An orange box to the far right indicates the three cases that did not specify the exact time to recovery, however, did report a recovered SBP.
Abbreviations: systolic blood pressure (SBP); millimeters of mercury (mmHg)

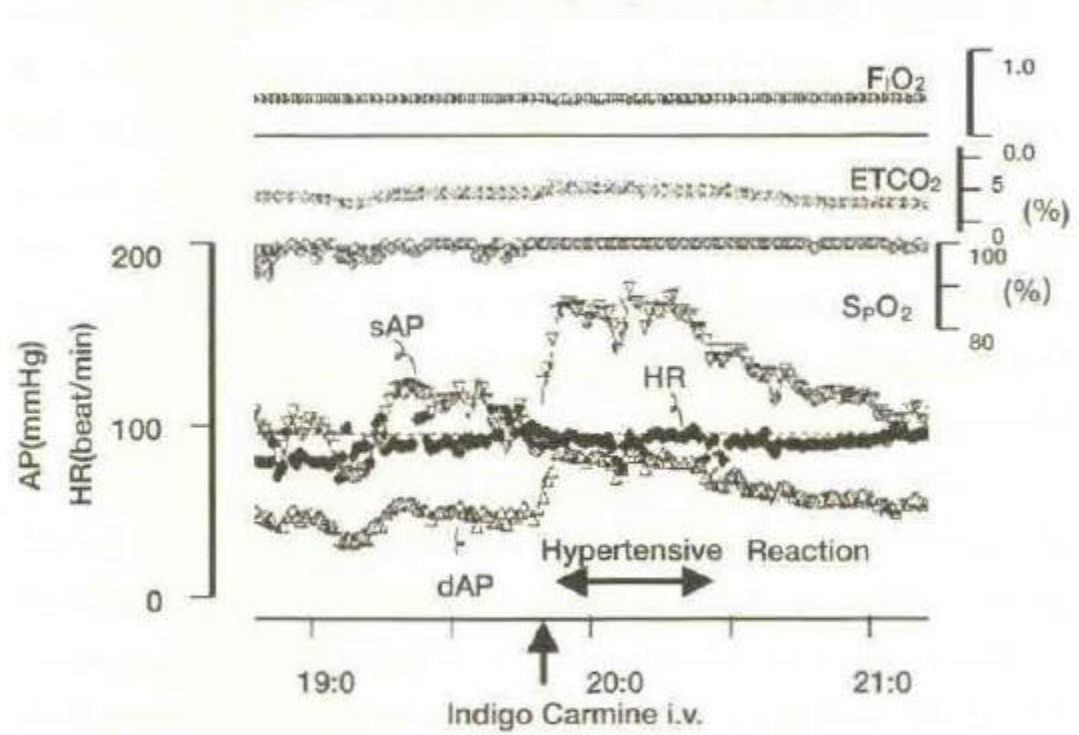
We highlight the following literature case of *hypertension* in a patient exposed to indigotindisulfonate sodium.

- **Literature Case (Japan) (Moriwaki 2006)**

A 73-year-old female with a past medical history of low anterior resection of rectal cancer underwent resection of recurrent pelvic cancer. The patient had mild anemia with a hemoglobin concentration of 10.4 gram(g)/ deciliter (dL) (reference range: 12 – 16 g/dL)[f] but no other preoperative complications. Anesthesia was induced with fentanyl and propofol supplemented with vecuronium and was maintained with combined epidural and general anesthesia. Five mL of 1.5% mepivacaine was administered into the epidural space every 45-60 minutes and basal continuous infusion of 0.2% ropivacaine supplemented with 2.5 microgram (µg)/mL of fentanyl was also administered to the epidural space at the rate of 4 mL/hour(hr) after stabilization of anesthesia. Propofol was infused continuously at 1 µg/mL and supplemented with 0.4 % to 1% of sevoflurane. The radial arterial pressure, electrocardiogram (ECG), SpO_2, and end-tidal carbon dioxide ($ETCO_2$) were monitored continuously and recorded in an electronic anesthesia chart system. Depth of anesthesia was monitored continuously using bispectral index (BIS)[g]. The patient was ventilated at a constant minute-volume with a mechanical ventilator. The duration of surgery and anesthesia, respectively, were 8 hours and 19 min, and 9 hours and 42 min. Six-and-a-half hours after the start of surgery, 10 mg indigotindisulfonate sodium was given intravenously over 30 seconds to identify the ureter. After administration of indigotindisulfonate sodium, the systolic arterial pressure increased over 5 minutes from 88 mmHg to 174 mmHg and remained at the peak pressure for 30 min (See Figure 6). Blood pressure gradually decreased to the previous pressure over another 30 min. Both heart rate and BIS stayed within 95-98 (units not otherwise specified [NOS]) and 40 to 45 (units NOS), respectively, during the hypertensive period. Until administration of indigotindisulfonate sodium, blood pressure "was maintained within acceptable levels but relatively low" with fluid resuscitation and four units of concentrated red blood cells (total surgical blood loss was 2000 mL).

[f] The normal Hb level for males is 14 to 18 g/dl; that for females is 12 to 16 g/dl. (Billett 1990)
[g] Bispectral Index (BSI) monitoring technology is utilized in anesthesia to access electroencephalogram (EEG) information as a measure of the effect of anesthetics (Medtronic 2022).

Figure 6. Hypertension Following Administration of Indigotindisulfonate Sodium



Hypertensive reaction induced by indigo carmine recorded with an Electronic Anesthesia Recording System (VOCAAR II, sAP = systolic arterial pressure; dAP = diastolic arterial pressure; HR= heart rate; SpO_2= oxygen saturation measured by a pulse oximeter).
(Moriwaki 2006)

Reviewer Comments: This patient had been in surgery for 6 ½ hours and had maintained an acceptable blood pressure. It was not until administration of indigotindisulfonate sodium that she experienced a severe increase in systolic blood pressure (88 mmHg to 174 mmHg) with a short time-to-onset (5 minutes). We also note that blood pressure increased despite blood loss occurring during the procedure. Although the patient lost a significant amount of blood during surgery (2000 mL), it is not uncharacteristic for patients undergoing abdominal sacral resection for rectal cancer to have significant blood loss (Bebenek 2014). Although the patient recovered, sudden increases in blood pressure can result in hypertensive urgency/emergency with end-organ damage (e.g., neurologic, renal, or cardiac).

WHO Causality: Probable

3.2.3 Specific AEs: SOC Cardiac disorders (n=24 cases)

We identified 24 cases reporting the SOC "Cardiac disorders." These cases reported PTs[h] including *bradycardia* (n=7), *cardiac arrest* (n=4), *atrioventricular block second degree* (n=3), *dizziness* (n=3), *dyspnoea* (n=2), *peripheral swelling* (n=2), *pulmonary oedema* (n=2), *ventricular tachycardia* (n=2), and one each of *acute left ventricular failure*, *bradyarrhythmia*, *chest pain*, *myocardial infarction*, *pulseless electrical activity*, *sinus arrhythmia*, *sinus bradycardia*, *sinus tachycardia*, *tachycardia*, and *ventricular extrasystoles*. Cases with these reported PTs are summarized below.

3.2.3.1 Cardiac Arrest (n=4 cases)

We identified four cases in the case series that documented an event of *cardiac arrest* following the administration of indigotindisulfonate sodium (FAERS Case # 5792376, 19940603, Lee 2012, Gousse 2000). Time to onset of events included 1 minute, 2 minutes, 15 minutes, and during the procedure. Of these cases, events also included *hypotension* in every case, with three documenting asystole, and one case documenting *myocardial infarction*. Two of the cases also documented *anaphylactoid reaction*. Treatments for all cases include cardiopulmonary resuscitation, vasopressor medication (epinephrine), and intravenous fluids. The patient with a documented *myocardial infarction* also experienced *sinus arrhythmia* and *ventricular tachycardia* and represented the one death in our case series. Two of the other three cases (both with concomitant *anaphylactoid reaction*) recovered from the events, and one case with concomitant cerebral ischemia was recovering from the events at the time of reporting.

We highlight the following case of *cardiac arrest* in a patient exposed to indigotindisulfonate sodium.

- **Literature Case (Korea) (Lee 2012)**

A 43-year-old female patient diagnosed with uterine myoma was scheduled to undergo total laparoscopic hysterectomy. The case indicated that the patient had "no unusual medical history." Before surgery, the mean corpuscular hemoglobin concentration was 7.5 g/dL. Premedication was not used, and upon arrival in the operating room, an electrocardiogram, pulse oximeter, and non-invasive blood pressure monitor were attached. Before anesthesia, the patient's blood pressure was 150/90 mmHg; heart rate was 90 beat/min, and peripheral oxygen saturation was 100%. Glycopyrrolate (0.1 mg) and propofol (120 mg) were IV injected, and while conducting mask ventilation with O_2, rocuronium (5 liter (L)/ minute (min), 50 mg) was IV injected. The patient was intubated, and anesthesia was maintained with sevoflurane (1-2 vol%), O_2 (2 L/min), and NO_2 (2 L/min). Breathing was controlled to a tidal volume of 600 mL, and the breathing rate was 10 breaths/min. Hysterectomy was completed. Two units of concentrated red blood cells were transfused and there were no abnormalities with blood pressure at 120/80 mmHg, heart rate at 100 beats/min, and 99% peripheral oxygen saturation. Two hours after inducing anesthesia, 5 mL of indigo carmine was slowly injected IV to identify the ureter. One minute later, the $ETCO_2$

[h] more than one PT is possible per case

fell from 33 mmHg to 12 mmHg; blood pressure became 60/40 mmHg; peripheral oxygen saturation fell to 89%, and patient displayed *bradycardia* and then asystole on the ECG. Inhalation anesthesia was immediately stopped and normal saline with 100% O_2 was administered.

One milligram of epinephrine was administered IV; chest compressions were given, the right radial artery was punctured, and a catheter inserted to continually monitor the arterial pressure. The pulse was recovered, but the patient's state did not improve (NOS), so 1 mg of epinephrine was administered three more times over a total duration 20 minutes. A pH of 7.095 was measured by the arterial blood gas analysis and 60 mL of 8.4% sodium bicarbonate was administered IV.

Twenty minutes after *cardiac arrest*, blood pressure was 65/50 mmHg, peripheral oxygen saturation was 72%, $ETCO_2$ was 18 mmHg and dopamine was infused at 20 μg/kg/min to maintain blood pressure. Atropine (0.5 mg), epinephrine (1 mg) was injected, and 20 mL of 8.4% sodium bicarbonate was injected due to a pH of 7.204, as measured by the arterial blood gas analysis. Forty minutes after *cardiac arrest*, the patient's status improved with a blood pressure of 70/40 mmHg, SpO_2 of 100%, and $ETCO_2$ of 38 mmHg, and spontaneous breathing commenced. The patient's vital signs normalized so the surgery was completed; muscle relaxation was reversed with intravenous injection of glycopyrrolate (0.4 mg) and pyridostigmine (10 mg), and the patient was transferred to the intensive care unit (ICU) with intubation.

In the ICU, the blood pressure was 90/50 mmHg, heart rate was 100 beats/min and O_2 (5 L/min) was administered through the endotracheal tube. Mental status had not returned to baseline. There were no abnormalities in the brain computed tomography (CT), but in the brain magnetic resonance imaging (MRI) taken on the second postoperative day, the reporter noted bilateral infarctions in the subcortical white matter in the parieto-occipital lobe. On the seventh postoperative day, mechanical ventilation was stopped. Twenty days after surgery, the patient was extubated, and on the twenty-fifth postoperative day, the patient's mental status recovered, but there was persistent motor weakness in the left arm and visual disturbance with difficulty in the lateral gaze. Three months after surgery, the patient had fully recovered from motor weakness and visual disturbance. At the time of the case, the patient was still hospitalized for rehabilitation.

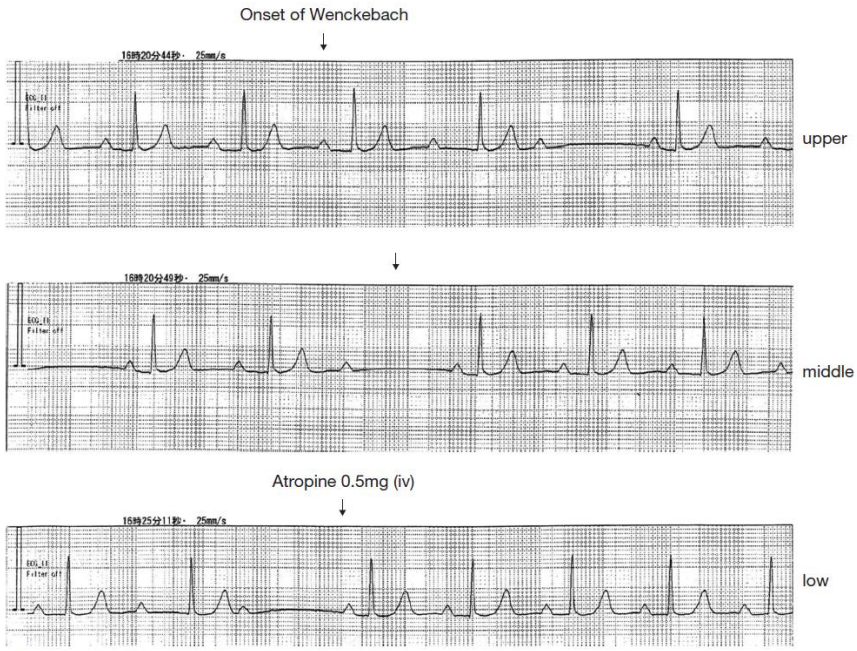
Reviewer Comments: This relatively young patient with no other "unusual medical history" had been stable in surgery for more than 2 hours. The close temporal relationship (1 minute) is highly suggestive that the administration of indigotindisulfonate sodium caused the events of bradycardia and cardiac arrest. The seriousness of the events requiring aggressive cardiopulmonary resuscitation, mechanical ventilation following the completion of surgery, cerebral infarction and stroke with long-term disability necessitating rehabilitation highlights the serious potential outcomes of a cardiac arrest, despite successful resuscitation.

WHO Causality: Probable

3.2.3.2 Atrioventricular Block, Second Degree (n=3 cases)

We identified three cases of *atrioventricular block second degree*[i], all occurring within 10 minutes following administration of indigotindisulfonate sodium (FAERS Case # 7541338, 7541339, and Takeyama 2014). The two female patients (41 and 49 years) received indigotindisulfonate sodium during gynecologic surgery, and one male patient (64 years) received indigotindisulfonate sodium during prostate surgery. Two of the patients had a documented medical history of first-degree atrioventricular block. Takeyama 2014 documented electrocardiogram changes with the PQ interval lengthening and an abnormal QRS complex on the ECG monitor shortly after the administration of indigotindisulfonate sodium (See Figure 7). Treatment included glycopyrrolate and ephedrine for the 49-year-old female, atropine for the 41-year-old female, and no treatment for the 64-year-old male. Although atrioventricular block is labeled in section 6.2 of the proposed prescribing information, *atrioventricular block second degree* is not.

Figure 7. Case of Atrioventricular Block Second Degree following Administration of Indigotindisulfonate Sodium



Upper: The electrocardiogram (ECG) shows onset of second-degree A-V block (the PQ interval began to lengthen gradually and the QRS wave form dropped out)
Middle: The arrow (↓) shows QRS wave form dropped out on the ECG
Low: The ECG shows Wenckebach type A-V block recovered to first-degree A-V block after administration of atropine.

[i] Second-degree atrioventricular (AV) block, also referred to as second-degree heart block, is a disease of the cardiac conduction system in which the conduction of atrial impulse through the AV node and/or His bundle is delayed or blocked. Patients with second-degree AV block may be asymptomatic or they may experience a variety of symptoms such as lightheadedness and syncope. Mobitz type II AV block may progress to complete heart block, with an associated increased risk of mortality (Sovari 2017). Cardiac medications may bring on AV block. These include medications like digoxin, beta-blockers, calcium channel blockers, and certain antiarrhythmic drugs (Sovari 2017).

We highlight the following case of *atrioventricular block second degree* in a patient exposed to indigotindisulfonate sodium.

- **FAERS Case # 7541339 (USA) (Hobai 2008)**

A 49-year-old woman underwent cystoscopy and anterior colporrhaphy[j] with sling under spinal anesthesia. The case described no significant past medical history and no known drug allergies. The preoperative ECG showed normal sinus rhythm at 64 beats/minute with a PR-interval of 148 milliseconds (msec). Bupivacaine was administered, 72 minutes later, before closing of the anterior vaginal wall, indigotindisulfonate sodium 40 mg intravenous was administered to assess for ureteral injury. "Quickly thereafter," the patient developed *sinus bradycardia* [heart rate (HR) decreased quickly from the 72 beats/minute to 32 beats/minute], an increase in the PR interval (from a baseline of 148 msec to 240–280 msec), and frequent non-conducted P waves (i.e., second degree atrioventricular block type II). Blood pressure was maintained in the "100s/60s mmHg". She complained of acute *anxiety* and shortness of breath, and her spinal sensory level was thoracic 6 (T6)[k]. Treatment included glycopyrrolate 0.6 mg IV (in 0.2 mg doses) and ephedrine 25 mg IV. Heart rate (HR) gradually increased "(peaking in the 120s beats/minute)" with a PR interval of 160 msec and 1:1 conduction. However, blood pressure increased to 180/110 mmHg, and she developed diffuse ST segment depressions and T wave inversions. Treatment for these events included esmolol 80 mg IV (in divided doses), midazolam 1 mg IV, and propofol 20 mg IV. Her HR decreased to the 90s, and the ST depression diminished. In the recovery room, she was stable and asymptomatic; with no recollection of the event, and the ECG returned to the normal preoperative pattern. The cardiologist concluded that the *atrioventricular block second degree* represented an idiosyncratic reaction to indigotindisulfonate sodium.

Reviewer Comments: This relatively young patient with no significant medical history and a preoperative ECG depicting normal sinus rhythm had been stable in surgery for more than an hour prior to the events. It appears that the surgery was successful up until the administration of indigotindisulfonate sodium. The time-to-onset of "quickly thereafter" suggests indigotindisulfonate sodium was responsible for second-degree atrioventricular block type II. Treatment of the event was complicated by additional adverse events of increase in heart rate, blood pressure, and ST segment changes, which might also be drug-related. Although this patient recovered from these events, more serious potential complications of second-degree atrioventricular block include arrhythmia, cardiac arrest, and sudden cardiac death (NIH 2022).

WHO Causality: Probable

3.2.4 SOC Immune system disorders (n = 11 cases)

[j] Colporrhaphy, also known as vaginal wall repair, is a surgical procedure performed to correct defects in the vaginal wall, or pelvic-organ prolapse, including cystoceles and rectoceles (CWC 2022).
[k] The spinal sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation (Kirshblum 2011).

We identified 11 cases with a total of 15 PTs[l] from the immune system disorders SOC. These terms included *anaphylactic reaction* (n=5), *anaphylactoid reaction* (n=2), *bronchospasm* (n=2), *urticaria* (n=2), and one each of *acute respiratory distress syndrome*, *anaphylactic shock*, *immune-mediated adverse reaction*, and *angioedema***.** Of the 11 cases in the immune system disorders SOC, seven of the cases clearly documented *hypersensitivity* reactions that could be further categorized as anaphylaxis. Five of the cases reported the events within 5 minutes of administering indigotindisulfonate sodium. Many of the cases experienced multiple signs of a *hypersensitivity reaction* including *urticaria*, *bronchospasm*, *erythema*, *rash*, and *wheezing*. The two unlabeled cases of *wheezing* occurred in the context of *anaphylactic reaction*. Ten of the eleven cases reported one or more treatments including epinephrine (n=6), injectable corticosteroids (n=4), cardiopulmonary resuscitation (n=3), and other vasopressor drugs (ephedrine, phenylephrine, dopamine.) One case, reporting the events of *anaphylactic reaction* had a positive intradermal skin test at a 1:10 dilution of indigotindisulfonate sodium (Newton 2012).

We highlight the following case of anaphylaxis in a patient exposed to indigotindisulfonate sodium.

- **Literature Case (USA) (Nandate 2016)**

A 66-year-old man presented with prostate cancer. There was no other pertinent medical history including cardiovascular or respiratory diseases, history of surgical procedure, or prior exposure to indigotindisulfonate sodium. He was reported to have a history of allergy to bee venom. For the prostate cancer, the patient was scheduled to undergo elective radical retropubic prostatectomy with pelvic lymph node dissection under general anesthesia. Induction of general anesthesia was achieved with midazolam, fentanyl, and propofol. Muscle relaxation was achieved with rocuronium, and the patient was successfully intubated. No unusual events were noted during general anesthesia induction and preparation for surgery. A 5 mL dose of 0.8% sodium indigotindisulfonate sodium was administered IV to ensure that the ureters were not injured during prostatectomy. At this time, estimated surgical blood loss was 1500 mL, and the patient had been given 2 units of red blood cells, 3500 mL of crystalloid solution, and low doses of vasopressors (phenylephrine 0.1 microgram/kg/min) to stabilize vital signs. Within 1 minute of indigotindisulfonate sodium administration, vital signs deteriorated. Systolic blood pressure dropped from 110 to 40 mmHg, heart rate remained at 60 beats/min, and *oxygen saturation decreased* from 99% to 75% (on 40% inspired oxygen) with bilateral diffuse *wheezing*. In addition, marked cutaneous *erythema* was observed at the upper extremities. Surgery was suspended temporarily. Treatment included 100% oxygen, epinephrine (total, 1.5 mg), hydrocortisone (100 mg), diphenhydramine (50 mg), albuterol nebulizer (0.083%), and continuous infusion of epinephrine (0.15 μg/ kilogram (kg)/min), with normalization of vital signs (NOS). Emergency transesophageal echocardiography was performed and did not identify evidence of myocardial infarction or pulmonary embolism. The reporters arrived at a diagnosis of *anaphylactic reaction* due to indigotindisulfonate sodium on the basis of sudden decrease in blood pressure, respiratory difficulty, and cutaneous lesions immediately after the administration

[l] more than one PT is possible per case

of indigotindisulfonate sodium. The patient was released from the critical care unit to the ward after 48 hours and discharged from the hospital on postoperative day 7 without any further complications.

Reviewers Comments: Cases of immune system disorders
Events described in this case would meet the Sampson Criteria for a diagnosis of anaphylaxis as the patient experienced multiple organ systems affected (hypotension, oxygen saturation decrease, wheezing, subcutaneous lesions and marked cutaneous erythema) (Sampson 2006). Events resolved after treatment with epinephrine, hydrocortisone, diphenhydramine, albuterol, and oxygen, which brings us to conclude that this was a case of indigotindisulfonate sodium induced anaphylaxis. This patient had a relatively uneventful surgery until he experienced an anaphylactic reaction with a compelling time-to-onset following the administration of indigotindisulfonate sodium.

WHO Causality: Probable

3.2.5 SOC General disorders and administration site conditions (n = 9 cases)

We identified a total of 14 PTs from the general disorders and administration site conditions SOC identified in nine cases. These terms included injection site discoloration (n=2), *injection site extravasation* (n=2), *peripheral swelling* (n=2), and one each of *chest pain, infusion site discolouration, infusion site haematoma, infusion site necrosis, infusion site reaction, infusion site swelling, oedema, tissue infiltration***.** We were able to obtain images of three cases with administration site conditions (Lindo 2013; Choi 2012; O'Hara 1996). See Figure 8 below. Each of the three cases experienced the events following surgery and all events resolved without treatment within 48 hours.

Figure 8. Images of Administration Site Conditions

(Lindo 2013)

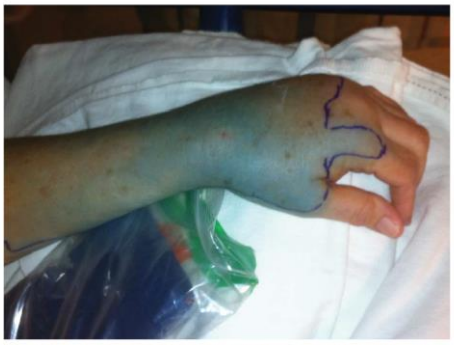


Fig. 1. Left arm with tracing of edema and blue discoloration from indigo carmine extravasation immediately after surgery.

Lindo. Indigo Carmine Extravasation. Obstet Gynecol 2013.

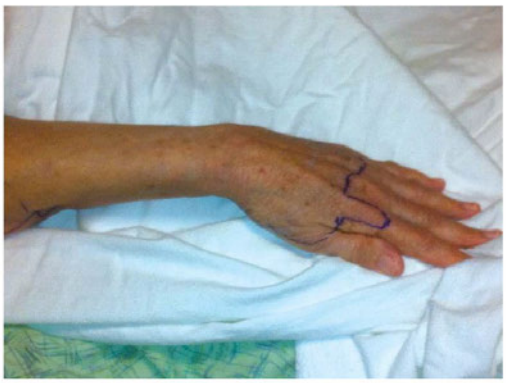
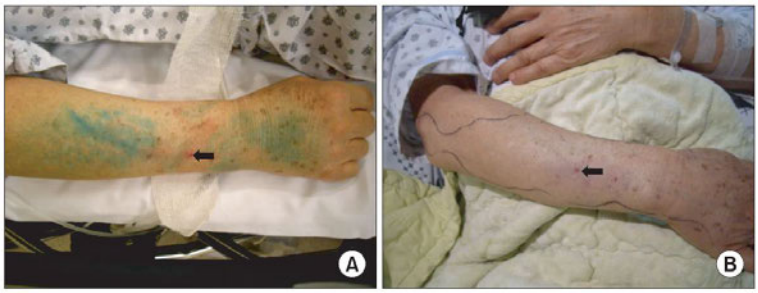
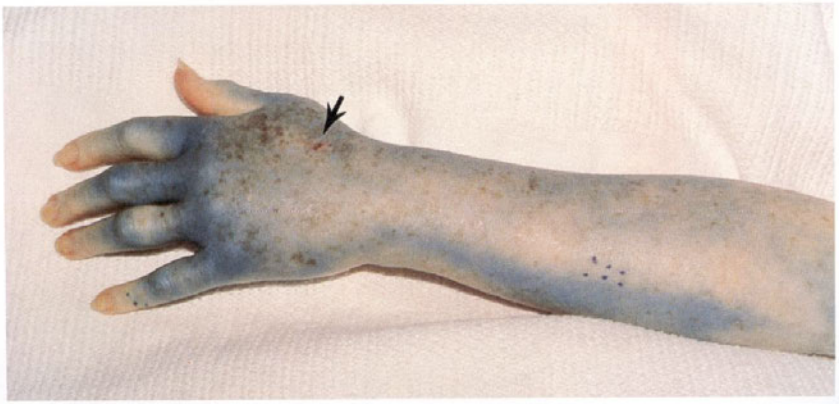


Fig. 2. Left arm with tracing 24 hours postoperatively, with resolved edema and no signs of blue discoloration.

Lindo. Indigo Carmine Extravasation. Obstet Gynecol 2013.

(Choi 2012)	 **Fig. 1.** Right forearm showing discoloration with indigo carmine. Arrow identifies the site of where the 16-gauge catheter was inserted (A). The black lines are the demarcation lines of the borders (B).
(O'Hara 1996)	 **Figure 1.** Left forearm showing discoloration with indigo carmine after intravenous catheter infiltration. Arrow identifies the site of where the infiltrated catheter was inserted.

Reviewers Comments: Administration site condition
The time-to-onset of events following the end of surgery and the compelling pictures provided of blue-tinted extremities where indigotindisulfonate sodium was injected provide supportive evidence suggesting that injection site discoloration can occur following administration of indigotindisulfonate. There were no long-term clinical consequences described in these three events. However, the physical appearance of this drug-related AE might be confused with limb ischemia and may be a source of concern for patients or health care providers.

WHO Causality: Probable for all three cases

3.2.6 Additional SOC PTs Identified in the Case Series

Within the case series, there were a number of unlabeled PTs that did not appear to be causally associated with indigotindisulfonate sodium or the PTs were supportive of a pathophysiologic event described above (Sections 3.2.1 – 3.2.6) and would better characterize the reaction in those sections (e.g.: PT *abdominal pain lower* in a case of *anaphylactic shock*) (FDA 2006). For more information on additional SOCs and PTs identified in the case series and not addressed in Sections 3.2.1 – 3.2.5, see Appendix H.

3.3 VIGIBASE

The VigiBase search retrieved 104 reports. Due to a lack of narrative case level details, unclear time to onset for reports in the VigiBase database (limited to 24-hour intervals), and lack of

causality assessment by reporters in the data output, all cases obtained from VigiBase were categorized as unassessable, based on the WHO-UMC causality criteria (WHO-UMC 2013). These reports could not be deduplicated from the FAERS and literature case series and we could not determine if the event is associated with indigotindisulfonate sodium. However, a consolidated list of the top 10 reported PTs from the VigiBase reports is available in Table 9. The top reported PTs included *hypotension*, *anaphylactic shock*, *urticaria*, *oxygen saturation decreased*, and *tachycardia*. The PTs are consistent with the terms identified in the FAERS and literature search.

Table 9. Top 10 Reported Preferred Terms Reported with Indigotindisulfonate Sodium in VigiBase

Top Reported PTs (MedDRA)	Count	Percentage
Hypotension	25	24.0%
Anaphylactic shock	10	9.6%
Urticaria	8	7.7%
Oxygen saturation decreased	7	6.7%
Tachycardia	7	6.7%
Bradycardia	5	4.8%
Hypersensitivity	4	3.8%
Rash	4	3.8%
Procedural complication	4	3.8%
Anaphylactoid reaction	3	2.9%

3.4 SPONSOR'S SUMMARY OF CLINICAL SAFETY

As discussed previously, DPV reviewed the Sponsor's submission. The Sponsor searched the Eudravigilance database[m] from 01 January 1980 to 31 October 2020 for AEs reported for indigotindisulfonate sodium. The search retrieved 22 cases with a total of 57 AEs (See Table 10).

Table 10. Adverse Events Reported in Eudravigilance Database for Indigotindisulfonate Sodium from 01 January 1980 to 31 October 2020 by SOC and PT

SOC	No. of events under the SOC
PT	No. of events matching the PT
Cardiac disorders	**2**
Atrioventricular block second degree	1
Tachycardia	1
Congenital, familial and genetic disorders	**3**

[m] EudraVigilance is the system for managing and analyzing information on suspected adverse reactions to medicines which have been authorized or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network. (EMA 2022)

Brain malformation	1
Cerebellar hypoplasia	1
Microcephaly	1
Eye disorders	**1**
Eye irritation	1
Gastrointestinal disorders	**4**
Colitis	1
Abdominal pain	1
Vomiting	1
Gastrointestinal necrosis	1
General disorders and administration site conditions	**5**
Pyrexia	2
Inflammation	1
Oedema	1
Tenderness	1
Immune system disorders	**12**
Type I hypersensitivity	1
Hypersensitivity	2
Reaction to excipient	2
Anaphylactic reaction	1
Anaphylactic shock	4
Anaphylactoid reaction	1
Anaphylactoid shock	1
Infections and infestations	**1**
Peritonitis	1
Injury, poisoning and *procedural complication*s	**3**
Foetal exposure during pregnancy	1
Occupational exposure to product	1
Labelled drug-drug interaction medication error	1
Investigations	**6**
Electrocardiogram PR prolongation	1
Electrocardiogram QRS complex shortened	1
Blood pressure decreased	2
Oxygen saturation decreased	2
Nervous system disorders	**1**
Nervous system disorder	1
Pregnancy, puerperium and perinatal conditions	**1**
Abortion spontaneous	1
Product issues	**1**
Product quality issue	1
Renal and urinary disorders	**1**
Acute kidney injury	1
Respiratory, thoracic and mediastinal disorders	**2**
Laryngeal oedema	1
Nasal polyps	1
Skin and subcutaneous tissue disorders	**12**
Angioedema	3
Urticaria chronic	1
Skin discolouration	1
Erythema	3
Pruritus	2
Rash	1
Rash erythematous	1
Vascular disorders	**2**

Hypotension	2
Total Events	**57**
Abbreviation: SOC = System organ Class; PT = Preferred Term Modified Table 7-1 2.7.4 Summary of Clinical Safety page 34 (ProvePharm SAS 2021)	

Reviewer Comments: The Sponsor's search retrieved 22 reports (57 PTs). Many of the PTs in Table 10 are consistent with the terms we identified in the FAERS and literature search. Due to a lack of narrative case level details, all cases obtained from the Sponsor were categorized as unassessable, based on the WHO-UMC causality criteria (WHO-UMC 2013). DPV sent an information request[n] on February 4, 2022, to the Sponsor in an attempt to obtain additional information about the reports (Davis-Warren 2022). However, in the Sponsor's response on February 11, 2022, the Sponsor reported that they did not have narrative data available for the 22 reports (ProvePharm SAS 2022). These reports could not be deduplicated from the FAERS and literature case series due to a lack of case information (patient age, time to onset, country of origin, event dates, etc.) and we could not determine if the event was actually related to indigotindisulfonate sodium.

4 DISCUSSION

We identified several serious AEs including *cardiac arrest*, *atrioventricular block second degree*, *anaphylactic reaction*, *hypotension*, *hypertension* and *injection site discolouration* with the use of unapproved indigotindisulfonate sodium from the FAERS and literature case series. Overall, DPV identified 57 cases for all adverse events in the case series.[o] Draft labeling is currently under review by DIRM for this 505(b)2 application and information from this review has been requested to help inform the approved label.

All of the FAERS cases except one were categorized as serious and the majority of adverse reactions (n=33) had a short time-to-onset (less than 5 minutes) following administration of indigotindisulfonate sodium, supporting a causal association. In addition, many of the patients had been stable in a surgical procedure for an extended period of time prior to indigotindisulfonate sodium administration which appeared to be the catalyst of their serious events.

In our case series, we saw rapid changes in blood pressure, both in patients experiencing *hypotension* and patients experiencing *hypertension*. For a subset of these patients, serious outcomes included cardiac rhythm disturbances (*atrioventricular block second degree*, *ventricular tachycardia*, *ventricular extrasystoles* with *bradyarrhythmia*, and *sinus tachycardia*) and four cases of *cardiac arrest* with three documenting asystole and one fatal *myocardial infarction*. The majority of patients with *hypotension* required treatment (intravenous fluids,

[n] *"We request that you provide case-level information for the twenty-two postmarketing adverse event cases that are described in subsection 7.0 "POSTMARKETING DATA" and utilized to create Table 7.1 "Adverse Events Reported in Eudravigilance Database for Indigo Carmine from 01 January 1980 to 31 October 2020 by SOC and Preferred Term."*

[o] No additional cases were identified in VigiBase or the Sponsor's "Clinical Safety Data" report.

vasopressors, cardiopulmonary resuscitation) and some patients with *hypertension* required treatment (atropine, hydralazine, nitroglycerine). Due to the clinical seriousness of many of these cases and the rapid onset following administration of indigotindisulfonate sodium, we recommend updating the current WARNINGS AND PRECAUTIONS section 5.1 (b) (4) in the draft label to communicate the severity and sudden nature of these events specifically for *hypotension*, *hypertension*, *atrioventricular block second degree,* and *cardiac arrest.*

Cases of anaphylaxis presented with the classic presentations involving cutaneous (*urticaria*, *erythema*, *rash*), respiratory (*bronchospasm*, *wheezing*), cardiovascular (*hypotension*, *bradycardia*), and gastrointestinal system (*nausea*) events. Many of the patients required treatment with epinephrine. Ten of the eleven cases reported one or more treatments including epinephrine, injectable corticosteroids, and cardiopulmonary resuscitation. Due to the rapid time-to-onset of the events following administration of indigotindisulfonate sodium, it is prudent to provide information about hypersensitivity reactions including anaphylaxis in the WARNINGS AND PRECAUTIONS.

Although all patients with injection site discoloration recovered, the visualization of unexpected blue dye in the tissue can be alarming and concerning to both patients and healthcare providers. While there were no long-term clinical consequences described in these three cases, we feel it is important to communicate these events in the ADVERSE REACTIONS Section of the label, so that providers and patients are aware.

Strengths of our case series include close temporal relationships between indigotindisulfonate sodium administration and the adverse events, rapid clinical effects and changes in otherwise healthy patients, and quick reversal and recovery with appropriate treatment. Although our case series included many PTs that are not in the current label, FDA Guidance recommends that "adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction." We feel the pathophysiologic adverse events that should be added to the label include *cardiac arrest*, *atrioventricular block second degree*, *anaphylactic reaction*, and *injection site discolouration*. In addition, labeled adverse reactions of *hypotension* and *hypertension* should be better described to include the severity and the rate at which blood pressure changes occur.

Our analysis has several limitations. Spontaneous reporting databases are subject to underreporting, leading to incomplete capture of relevant cases. Submitted reports often lack relevant detail, such as information on route, drug formulation, and patient data including concomitant medications and disease states. Although FDA requires the reporting of AEs for unapproved marketed drugs (21CFR310.305), other factors can influence whether or not an event will be reported, such as the amount of time a product has been marketed and public awareness about an AE.

5 CONCLUSION

Based on our analysis of FAERS, the published medical literature, VigiBase, and the Sponsor's Clinical Safety Data, we find an association between indigotindisulfonate sodium and the

following events: *hypotension* with *cardiac arrest*, *hypertension* with complications due to sudden *blood pressure increase*, *atrioventricular block second degree*, *hypersensitivity* with *anaphylactic reaction*, and *injection site discoloration.*

6 RECOMMENDATIONS

Based upon findings from this review, DPV recommends the following:

1. Add two new Warnings to the WARNINGS AND PRECAUTIONS section regarding each of the following AEs: *hypersensitivity reactions* (including *anaphylactic reactions*) and *atrioventricular block second degree*

2. Update the current WARNINGS AND PRECAUTIONS section 5.1 (b) (4) for *hypotension* and *hypertension* and include severity of events characterized by *cardiac arrest* and *arrythmia*.

3. Expand the ADVERSE REACTIONS section 6.2 Post Marketing Experience to include *injection site discoloration*.

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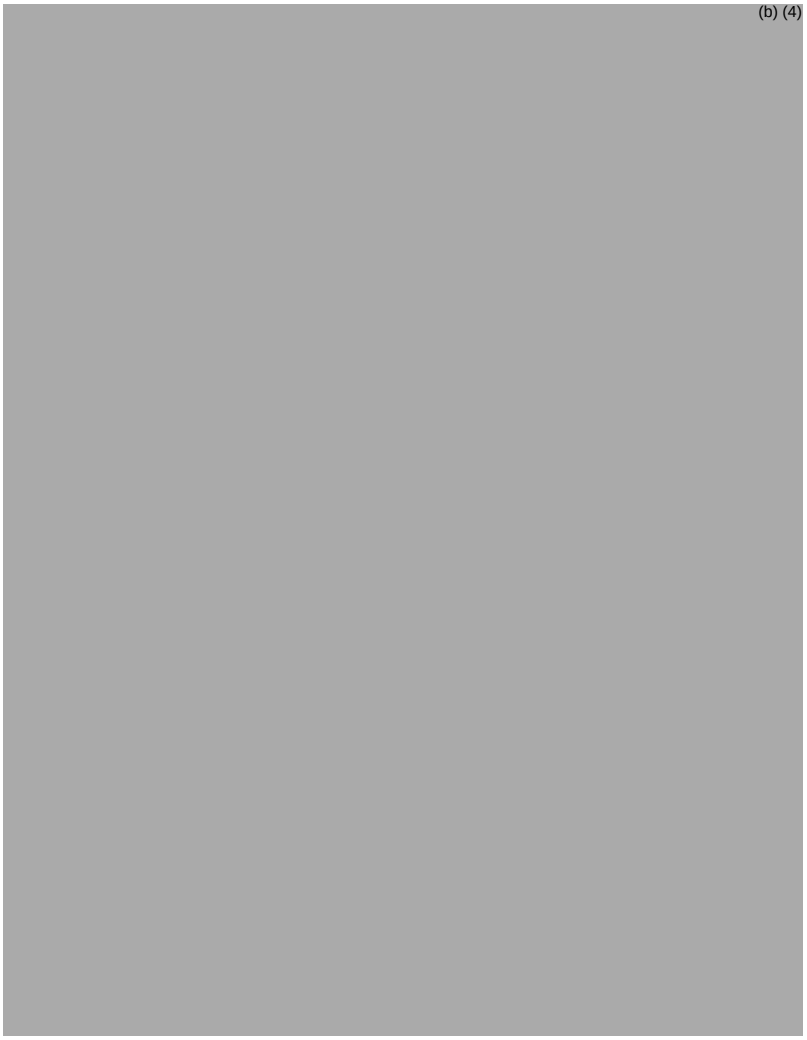
8 APPENDICES

8.1 APPENDIX A. UNAPPROVED DRUG LABEL INDIGO CARMINE INJECTION (INDIGOTINDISULFONATE SODIUM INJECTION, USP) (AMERICAN REGENT 2017)

(b) (4)



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

8.2 APPENDIX B. WORLD HEALTH ORGANIZATION-UPPSALA MONITORING CENTRE (WHO-UMC) CAUSALITY ASSESSMENT CATEGORIES

World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment Categories	
Causality term	**Assessment criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 postmarketing 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 Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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.

8.4 APPENDIX D. VIGIBASE DATABASE

VigiBase is a global database of individual case safety reports (ICSRs) received by the Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. VigiLyze is a tool used to search and analyze VigiBase. VigiBase includes ICSRs submitted by over 130 countries, including the U.S., for allopathic medicines, traditional medicines (herbals), and biological medicines, including vaccines. The FDA does not have access to case narratives in VigiBase but may request them from the regulatory authorities that submitted the ICSRs. Some cases in VigiBase may also be in the FDA Adverse Event Reporting System (FAERS). The limitations and qualifications that apply to VigiBase information and its use include:

Tentative and variable nature of the data
Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication
Variability of source: Reports submitted to national centers come from both regulated and voluntary sources. Practice varies: some national centers accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.
Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.
No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.
Time to VigiBase: Some national centers make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national center until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centers.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

8.5 APPENDIX E. FAERS LINE LISTING OF ALL ADVERSE EVENTS WITH INDIGOTINDISULFONATE SODIUM CASE SERIES

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
1	FAERS 3041302 1997	v1 15-DAY 2719/11856	27 F JPN	Fallopian tube contrast - radiography	6-10 min	*anaphylactic shock; bradycardia; restlessness; heart rate decreased; blood pressure decreased; abdominal pain lower; rash erythematous*	LT, OT	Recovered/ resolved	Possible
2	FAERS 4136116 1997	v1 DIRECT 63882	39 F USA	Diagnostic aid NOS	NR	*pulmonary oedema*	HO	Recovered/ resolved	Possible
3	FAERS 4136129 1998	v1 DIRECT 83024	68 M USA	Prostate surgery - visualize ureters	2 min or less	*heart rate decreased; ventricular tachycardia; blood pressure increased*	LT	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
4	FAERS 4136134 2001	v1 DIRECT	68.8 M USA	Prostate surgery - visualize ureters	during procedure	*anaphylactic reaction*	LT	Recovered/ resolved	Probable
5	FAERS 4141629 2001	v1 DIRECT	38 F USA	Gynecological surgery - visualize ureters	during procedure	*traumatic lung injury; lung infiltration; acute respiratory distress syndrome; haemoglobin decreased*	HO	NR	Possible
6	FAERS 4141630 2003	v1 DIRECT 189653	76 F USA	Bladder tumor - visualize ureters	2 min or less	*anaphylactic reaction*	LT	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
7	FAERS 5792376 2005	v1 15-DAY 1781-150	65 M USA	Urologic surgery - visualize the ureters	NR	*myocardial infarction; hypotension; sinus arrhythmia; cardiac arrest; ventricular tachycardia; procedural complication;*	DE	Death	Possible
8	FAERS 7534628 2010	v1 15-DAY 20100328	61 M USA	Prostate surgery - visualize ureters	3-5 min	*oxygen saturation decreased; procedural complication;*	OT	Recovered/ resolved	Probable
9	FAERS 7534630 2010	v1 15-DAY 20100329	66 M USA	Prostate surgery - visualize ureters	6-10 min	*cerebral disorder; oxygen saturation decreased;*	OT	Recovered/ resolved	Probable
10	FAERS 7541311 2010	v1 15-DAY 20100327	59 M USA	Prostate surgery - visualize ureters	3-5 min	*oxygen saturation decreased; procedural complication;*	OT	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
11	FAERS 7541314 2010	v1 15-DAY 20100325	58 M USA	Prostate surgery - visualize ureters	6-10 min	*oxygen saturation decreased; procedural complication;*	OT	Recovered/ resolved	Probable
12	FAERS 7541318 2004	v1 15-DAY 400150805	57 F USA	Visualize the ureters	3-5 min	*seizure;*	OT	Recovered/ resolved	Possible
13	FAERS 7541337 2004	v1 DIRECT 227667	80 M USA	Bladder tumor - visualize ureters	NR	*injection site extravasation; infusion site haematoma; infusion site swelling;*	OT	NR	Probable
14	FAERS 7541338 Hobai 2008	v1 DIRECT 363554	64 M USA	Prostate surgery - visualize ureters	6-10 min	*atrioventricular block second degree*	OT	Recovered/ resolved	Probable
15	FAERS 7541339 Hobai 2008	v1 DIRECT 363566	49 F USA	Gynecological surgery - visualize ureters	during procedure	*sinus bradycardia; atrioventricular block second degree; anxiety; dyspnoea;*	OT	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
16	FAERS 7541340 2009	v1 DIRECT 383186	56 F USA	Urologic surgery - visualize the ureters	NR	*oxygen saturation decreased; blood pressure decreased; bronchospasm; urticaria;*	HO	NR	Possible
17	FAERS 7841387 2011	v1 DIRECT 444499	46 F USA	Diagnostic aid NOS	during procedure	*infusion site discolouration;*	Not serious	NR	Probable
18	FAERS 8179104 2011	v1 15-DAY 20110659	34 F USA	Gynecological surgery - visualize ureters	2 min or less	*hypertension; vascular resistance systemic increased; cardiac index increased; maternal exposure during pregnancy;*	OT	NR	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
19	FAERS 8277878 2011	v1 DIRECT US-FDA-7961819	64 F USA	Visualize nodes for biopsy/define tumor boarder/ mapping	2 min or less	*pulmonary oedema; pneumothorax; myocardial necrosis marker increased;*	HO	NR	Possible
20	FAERS 10356438 2015	v1 DIRECT 559019	45.791 F USA	Diagnostic aid NOS	3-5 min	*hypotension; hypoxia; tachycardia;*	LT	Recovered/ resolved	Probable
21	FAERS 11423039 2015	v1 DIRECT 611988	73 F USA	Surgery NOS	NR	*blood pressure systolic decreased;*	OT	Recovered/ resolved	Possible
22	FAERS 11434625 2015	v1 DIRECT 612383	50 F USA	Visualize the ureters	3-5 min	*hypotension;*	OT	Recovered/ resolved	Probable
23	FAERS 15412613 2018	v2 15-DAY JP-LPDUSPRD-20181742	52 F JPN	Visualize nodes for biopsy/define tumor boarder/ mapping	17 days	*infusion site necrosis; postoperative wound infection;*	HO	Recovered/ resolved	Possible

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
24	FAERS 17604643 2020	v1 DIRECT FDA-CDER-CTU-2020-35463	49.5 F USA	Visualize the ureters	NR	*chromaturia;*	OT	NR	Probable
25	FAERS 19940603 2021 (Smith 2016)	v1 15-DAY US-AMERICAN REGENT INC-2021002619	42 F USA	Gynecological surgery - visualize ureters	15-20 min	*anaphylactoid reaction; cardiac arrest; product use in unapproved indication;*	LT	Recovered/ resolved	Probable
26	Nandate 2016	‡	66 M USA	Prostate surgery - visualize ureters	2 min or less	*hypotension; hypoxia; wheezing; erythema; anaphylactic reaction*	‡	Recovered/ resolved	Probable
27	Graziano 2005	‡	72 F USA	Gynecological surgery - visualize ureters	3-5 min	*chest pain; dyspnoea; bradycardia; hypotensive;*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
28	Lee 2015	‡	66 M Korea	Prostate surgery - visualize ureters	3-5 min	*hypotension; immune-mediated adverse reaction*	‡	Recovered/ resolved	Probable
29	Jeffords 1977	‡	66 F USA	Gynecological surgery - visualize ureters	2 min or less	*hypertension*	‡	Recovered/ resolved	Probable
30	Kawaguchi 2007	‡	81 M Japan	Bladder tumor - visualize ureters	2 min or less	*hypertension*	‡	Recovered/ resolved	Probable
31	Satoh 2001	‡	62 F Japan	Surgery NOS	2 min or less	*bradycardia (positive rechallenge)*	‡	Recovered/ resolved	Probable
32	O'Hara 1996	‡	75 F USA	Gynecological surgery - visualize ureters	during procedure	*injection site discoloration; peripheral swelling*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
33	Harioka 1987	‡	85 F USA	Bladder tumor - visualize ureters	2 min or less	*hypertension; bradycardia*	‡	Recovered/ resolved	Probable
34	Nguyen 1998	‡	65 F USA	Urologic surgery - visualize the ureters	3-5 min	*hypotension*	‡	Recovered/ resolved	Possible
35	Yanagidate 2001	‡	37 F France	Gynecological surgery - visualize ureters	3-5 min	*hypotension; heart rate increased*	‡	Recovered/ resolved	Probable
36	Moriwaki 2006	‡	73 F Japan	Urologic surgery - visualize the ureters	NR	*hypertension*	‡	Recovered/ resolved	Probable
37	Fairly 1993	‡	59 M USA	Prostate surgery - visualize ureters	2 min or less	*dizziness; hypotension*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
38	Fairly 1993	‡	62 M USA	Prostate surgery - visualize ureters	3-5 min	*dizziness; hypotension; nausea; bradycardia; electrocardiogram ST segment elevation*	‡	Recovered/ resolved	Probable
39	Fairly 1993	‡	69 M USA	Prostate surgery - visualize ureters	2 min or less	*dizziness; hypotension*	‡	Recovered/ resolved	Probable
40	Fairly 1993	‡	61 M USA	Prostate surgery - visualize ureters	2 min or less	*hypotension*	‡	Recovered/ resolved	Probable
41	Newton 2012	‡	39 F USA	Gynecological surgery - visualize ureters	15-20 min	*hypotensive; angioedema; rash papular; rash erythematous; urticaria; immune-mediated adverse reaction; anaphylactic reaction*	‡	NR	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex- Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
42	Chu 2015	‡	46 F Spain	Gynecological surgery - visualize ureters	35-50 min	*infusion site reaction; rash*	‡	Recovered/ resolved	Probable
43	Jo 2013	‡	57 F Korea	Visualize nodes for biopsy/define tumor boarder/ mapping	2 min or less	*hypotension; pulseless electrical activity*	‡	Recovered/ resolved	Probable
44	Jo 2013	‡	46 F Korea	Visualize nodes for biopsy/define tumor boarder/ mapping	2 min or less	*hypotension*	‡	Recovered/ resolved	Probable
45	Yang 1991	‡	68 F USA	Visualize the ureters	2 min or less	*increase ventricular afterload; acute left ventricular failure;]cardiac output decreased; hypertension*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
46	Yusim 2007	‡	NR NR Israel	Visualize nodes for biopsy/define tumor boarder/ mapping	NR	*blood methemoglobin present; hypotension*	‡	NR	Possible
47	Lee 2012	‡	43 F Korea	Gynecological surgery - visualize ureters	2 min or less	*hypotension; oxygen saturation decreased; bradycardia; cardiac arrest; cerebral ischaemia*	‡	Recovering/ resolving	Probable
48	Choi 2012	‡	72 M Korea	Prostate surgery - visualize ureters	during procedure	*injection site discoloration; peripheral swelling*	‡	Recovered/ resolved	Probable
49	Kazbek 2019	‡	59 F turkey	Stained tissue for selective endoscopic discectomy.	2 min or less	*ventricular extrasystoles; hypertension; bradyarrhythmia*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
50	Kazbek 2019	‡	54 F turkey	Stained tissue for selective endoscopic discectomy.	2 min or less	*sinus tachycardia; hypertension*	‡	Recovered/ resolved	Probable
51	Lindo 2013	‡	72 F USA	Gynecological surgery - visualize ureters	35-50 min	*tissue infiltration; injection site extravasation*	‡	Recovered/ resolved	Probable
52	Jeon 2012	‡	65 M Singapore	Prostate surgery - visualize ureters	2 min or less	*hypotension*	‡	Recovered/ resolved	Probable
53	Jeon 2012	‡	62 M Singapore	Prostate surgery - visualize ureters	2 min or less	*hypotension*	‡	Recovered/ resolved	Probable
54	Jeon 2012	‡	67 M Singapore	Prostate surgery - visualize ureters	2 min or less	*hypotension*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
55	Takeyama 2014	‡	41 F Japan	Gynecological surgery - visualize ureters	during procedure	*electrocardiogram pr prolongation; electrocardiogram QRS complex abnormal; atrioventricular block second degree; blood pressure systolic increased; heart rate decreased*	‡	Recovered/ resolved	Possible
56	Gousse 2000	‡	58 F USA	Gynecological surgery - visualize ureters	2 min or less	*hypotensive; bradycardia; hypoxia; cardiac arrest; anaphylactoid reaction; bronchospasm*	‡	Recovered/ resolved	Probable

	Case Initial FDA Receipt (year)	Version Number Report Type Manufacturer Control Number	Age in Years Sex-Gender Country Derived	Reason for Use	Time-to-onset	All PTs	All Regulatory Outcomes	Clinical Outcome	WHO-UMC Causality Assessment
57	Naitoh 1994	‡	72 M USA	Bladder tumor - visualize ureters	3-5 min	*wheezing; oxygen saturation decreased; hypotensive; electrocardiogram ST segment depression; oedema; erythema; rash; anaphylactic reaction*	‡	Recovered/ resolved	Probable

‡ Literature cases do not have a version number, reporting type, manufacturing number, or serious regulatory outcomes
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, F = female, HO=hospitalization, LT= life-threatening, M = male, min = minute, NR = not reported, OT = other medically significant

8.6 APPENDIX F. MEDDRA SYSTEM ORGAN CLASSES (SOC)S

1. Blood and lymphatic system disorders
2. Cardiac disorders
3. Congenital, familial and genetic disorders
4. Ear and labyrinth disorders
5. Endocrine disorders
6. Eye disorders
7. Gastrointestinal disorders
8. General disorders and administration site conditions
9. Hepatobiliary disorders
10. ISD
11. Infections and infestations
12. Injury, poisoning and *procedural complication*s
13. Investigations
14. Metabolism and nutrition disorders
15. Musculoskeletal and connective tissue disorders
16. Neoplasms benign, malignant and unspecified (incl cysts and polyps)
17. Nervous system disorders
18. Pregnancy, puerperium and perinatal conditions
19. Psychiatric disorders
20. Renal and urinary disorders
21. Reproductive system and breast disorders
22. Respiratory, thoracic and mediastinal disorders
23. Skin and subcutaneous tissue disorders
24. Social circumstances
25. Surgical and medical procedures
26. Vascular disorders
27. Product issues

8.7 APPENDIX G. PREFERRED TERMS FOR ALL ADVERSE EVENTS WITH INDIGOTINDISULFONATE SODIUM IN THE FAERS AND LITERATURE CASE SERIES, RECEIVED BY FDA OR PUBLISHED FOR ALL DATES THROUGH MARCH 3, 2022 (N=57)

PT	System Organ Class (SOC)	Number of Cases with PT	Proposed Labeling (Label Location)	Reviewers Comments
Hypotension	VD	22	Yes (W/P) 5.1	See Section 3.2.2.1
Hypertension	VD	8	Yes (W/P) 5.1	See Section 3.2.2.2
Bradycardia	CD	7	Yes (W/P) 5.1, 5.2	See Section 3.2.3
Oxygen saturation decreased	Inv	7	No (b) (4)	See Section 3.2.3.1 and 3.2.4
Anaphylactic reaction	ISD; VD	5	No (b) (4) ‡	See Section 3.2.4
Cardiac arrest	CD	4	No	See Section 3.2.3.1
Procedural complication	IPPC	4	No (b) (4)	See Section 8.8.2
Atrioventricular block second degree†	CD	3	No†	See Section 3.2.3.2
Dizziness	CD; NSD; VD	3	No	See Section 8.8.5
(b) (4)	(b) (4)	(b) (4)	Yes (W/P) 5.1	See Section 8.8.1
Hypoxia	RTMD	3	No	See Section 3.2.2.1, 8.8.1.1, and 8.8.3
(b) (4)			Yes – (b) (4)	See Section 3.2.3.1 and 3.2.4
(b) (4)	(b) (4) (4	(b) (4)	Yes (b) (4)	See Section 3.2.2.1 and 8.8.1
Bronchospasm	ISD; RTMD	2	Yes (W/P) (b) (4)	See Section 3.2.4 and 8.8.3
Dyspnoea	CD; RTMD	2	Yes (W/P) (b) (4)	See Section 3.2.3 and 8.8.3
Erythema	SSTD	2	Yes (W/P) (b) (4)	See 3.2.4
Injection site discolouration	GDASC; IPPC; SSTD	2	Yes (AR-PME) 6.2 (b) (4)	See Section 3.2.5, 8.8.2 and 8.8.4
Injection site extravasation	GDASC; IPPC	2	No	See Section 3.2.5 and 8.8.2

Peripheral swelling	CD; GDASC	2	No – [redacted]	See Section 3.2.3 and 3.2.5
Pulmonary oedema	CD; RTMD	2	No	See Section 3.2.3 and 8.8.3
[redacted]			Yes (W/P) 5.1	See Section 8.8.4
[redacted]			Yes (W/P) 5.1	See Section 8.8.4
Urticaria	ISD; SSTD	2	No	See Section 3.2.4 and 8.8.4
Ventricular tachycardia	CD	2	No	See Section 3.2.2.2 and 3.2.3
Wheezing	RTMD	2	No	See Section 3.2.4 and 8.8.3
Abdominal pain lower	GI	1	No	See Section 8.8.8
Acute Left ventricular failure	CD	1	No	See Section 3.2.2.2 and 3.2.3
Acute respiratory distress syndrome	ISD; RTMD; VD	1	No	See Sections 3.2.4 and 8.8.3
Anaphylactic shock	ISD; VD	1	No (*Anaphylactoid reaction* is)	See Sections 3.2.2. and 3.2.4
Angioedema	ISD; RTMD; SSTD	1	No	See Sections 3.2.4, 8.8.3, and 8.8.4
Anxiety	PD	1	No	See Sections 3.2.3.2 and 8.8.7
Blood methaemoglobin present	Inv	1	No	See Section 8.8.1
Blood pressure increased	Inv	1	Yes (W/P) 5.1	See Section 3.2.2.2 and 8.8.1
[redacted]			Yes (W/P) 5.1	See Section 3.2.2.1 and 8.8.1
			Yes (W/P) 5.1	See Section 3.2.2.2 and 8.8.1
Bradyarrhythmia	CD	1	No	See Section 3.2.2.2 and 3.2.3
Cardiac index increased	Inv	1	No	See Section 3.2.2.2 and 8.8.1
Cardiac output decreased	Inv	1	No	See Section 8.8.1
Cerebral disorder	NSD	1	No	See Section 8.8.5

Cerebral ischaemia	NSD; VD	1	No	See Section 3.2.2 and 3.2.3.1
Chest pain	CD; GDASC; RTMD	1	No	See Section 3.2.3 and 3.2.5
Chromaturia	RUD	1	No	See Section 8.8.11
Electrocardiogram PR prolongation	Inv	1	No	See Section 8.8.1
Electrocardiogram QRS complex abnormal	Inv	1	No	See Section 3.2.3.2 and 8.8.1
Electrocardiogram ST segment depression	Inv	1	No	See Section 3.2.3.2 and 8.8.1
Electrocardiogram ST segment elevation	Inv	1	No	See Section 8.8.1
Haemoglobin decreased	Inv	1	No	See Section 8.8.1
Heart rate increased	Inv	1	Yes - Yes (W/P) 5.1 '*tachycardia*'	See Section 8.8.1
Immune-mediated adverse reaction	ISD	1	Yes (AR-PME) 6.2 'ISD'	See Section 3.2.4
Increase ventricular afterload	Inv	1	No	See Section 8.8.1
Infusion site discolouration	GDASC; IPPC; VD	1	Yes (AR-PME) 6.2 'Skin discoloration'	See Section 3.2.2, 3.2.5, and 8.8.2
Infusion site haematoma	GDASC; IPPC	1	No	See Section 3.2.5 and 8.8.2
Infusion site necrosis	GDASC; IPPC; SSTD	1	No	See Section 3.2.5, 8.8.2, and 8.8.4
Infusion site reaction	GDASC; IPPC; SSTD	1	No	See Section 3.2.5, 8.8.2, and 8.8.4
Infusion site swelling	GDASC; IPPC; SSTD	1	No	See Section 3.2.5, 8.8.2, and 8.8.4
Lung infiltration	RTMD	1	No	See Section 8.8.3
Maternal exposure during pregnancy	IPPC; PPPC	1	No - (b) (4)	See Section 8.8.2 and 8.8.10
Myocardial infarction	CD; VD	1	No	See Section 3.2.2.1, 3.2.3.1, and 3.2.4

Myocardial necrosis marker increased	Inv	1	No	See Section 8.8.1
Nausea	GD	1	No	See Section 8.8.8
Oedema	GDASC; MND	1	No	See Section 3.2.5 and 8.8.9
Pneumothorax	RTMD	1	No	See Section 8.8.3
Postoperative wound infection	II; IPPC	1	No	See Section 8.8.2 and 8.8.6
Product use in unapproved indication	IPPC	1	No - (b) (4)	Section 8.8.2
Pulseless electrical activity	CD	1	No	See Section 3.2.3
(b) (4)		1	Yes (W/P) 5.1	See Section 8.8.4
Restlessness	NSD; PD	1	No	See Section 8.8.5 and 8.8.7
Seizure	NSD	1	No	See Section 8.8.5
(b) (4) *arrhythmia*	CD	1	No	See Section 3.2.3.1
(b) (4)			Yes (W/P) 5.1, 5.2	See Section 3.2.3.2
			Yes (W/P) 5.1, 5.2	See Section 3.2.2.2 and 3.2.3
Tachycardia	CD	1	Yes (W/P) 5.1, (b) (4)	See Section 3.2.2.2 and 3.2.3
Tissue infiltration	GDASC	1	No	See Section 3.2.5
Traumatic lung injury	IPPC; RTMD	1	No	See Section 8.8.2
Vascular resistance systemic increased	Inv	1	No	See Section 8.8.1
Ventricular extrasystoles	CD	1	No	See Section 3.2.2.2 and 3.2.3

* For these literature cases, the reviewer followed MedDRA terminology guidance and assigned the MedDRA lowest level term(s) (LLT) to each adverse event documented in the case that most accurately reflected the reported verbatim information (MedDRA 2022).
† Although the Sponsors draft prescribing information 6.2 contains atrioventricular block and states (b) (4) (b) (4)
‡ Although *anaphylactoid reactions* resemble generalized anaphylaxis, they are not caused by IgE-mediated allergic reaction but rather by a nonimmunologic mechanism (Miller-Keane 2003).
SOC Abbreviations: Cardiac disorders (CD); Gastrointestinal disorders (GI); General disorders and administration site conditions (GDASC); Immune system disorders (ISD); Infections and infestations (II); Injury, poisoning and *procedural complications* (IPPC); Investigations (Inv); Metabolism and nutrition

disorders (MND) ; Nervous system disorders (NSD); Pregnancy, puerperium and perinatal conditions (PPPC); Psychiatric disorders (PD); Renal and urinary disorders (RUD); Respiratory, thoracic and mediastinal disorders (RTMD); Skin and subcutaneous tissue disorders (SSTD); Vascular disorders (VD)
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, BW = Boxed Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, Alt Ex = Alternative explanation (disease-related, indication-related, or concomitant medication-related), PR = Procedure-related, U = Uninformative

8.8 APPENDIX H. SYSTEM ORGAN CLASS PREFERRED TERMS IDENTIFIED IN THE CASE SERIES NOT ADDRESSED IN SECTION 3.2

8.8.1 Specific AEs: SOC Investigations (n=18 cases)

There were a total of 18 cases reporting the SOC "Investigations." PTs within this SOC included *oxygen saturation decreased* (n=7), *heart rate decreased* (n=3), *blood pressure decreased* (n=2), and one each of *blood methaemoglobin present, blood pressure increased, blood pressure systolic decreased, blood pressure systolic increased, cardiac index increased, cardiac output decreased, electrocardiogram PR prolongation, electrocardiogram QRS complex abnormal, electrocardiogram ST segment depression, electrocardiogram ST segment elevation, haemoglobin decreased, heart rate increased, increase ventricular afterload, myocardial necrosis marker increased,* and *vascular resistance systemic increased*. Cases with these commonly reported PTs are summarized below.

8.8.1.1 Oxygen Saturation Decrease (n=7 cases)

A total of seven cases contained the unlabeled PT oxygen saturation decrease. Four of the cases came from the same reporter who hypothesized that the event was artifact, and not truly indicative of *hypoxia* (FAERS Case # 7534628, 7534630, 7541311, 7541314) (McDonagh 2007). The other three cases of *oxygen saturation decrease* occurred in two patients with *hypersensitivity* reactions (FAERS Case # 7541340, Naitoh 1994) and in one patient with *cardiac arrest* (Lee 2012).

Reviewers Comments: PT Oxygen Saturation Decrease
Although oxygen saturation decrease is not a labeled event, the totality of the evidence did not provide adequate support for it as a signal.

8.8.2 SOC Injury, poisoning and procedural complications (n =14 cases)

There were a total of 17 PTs from the Injury, poisoning and *procedural complication*s SOC identified in 15 cases. These terms included *procedural complication* (n=4), *injection site discolouration* (n=2), *injection site extravasation* (n=2), and one each of , *infusion site discolouration, infusion site haematoma, infusion site necrosis, infusion site reaction, infusion site swelling, maternal exposure during pregnancy, postoperative wound infection, product use in unapproved indication,* and *traumatic lung injury***.**

Reviewers Comments: PT Procedural Complications

Four cases in the case series included the PT procedural complications. Three of these cases were reported by a single reporter and are discussed previously in Section 3.3.3 (FAERS Case # 7534628, 7541311, 7541314) (McDonagh 2007). The other case was previously discussed in Section 3.3.2 (FAERS Case # 5792376). Although procedural complications is not a labeled event, the totality of the evidence did not provide adequate support for it as a signal.

8.8.3 SOC Respiratory, thoracic and mediastinal disorders (n = 11 cases)

There were 17 PTs from the Respiratory, thoracic and mediastinal disorders SOC identified in 11 cases. These terms included *hypoxia* (n=3), *bronchospasm* (n=2), *dyspnoea* (n=2), *pulmonary oedema* (n=2), *wheezing* (n=2), and one each of *acute respiratory distress syndrome*, *angioedema*, *chest pain*, *lung infiltration*, *pneumothorax*, and *traumatic lung injury***.**

Reviewers Comments: PT Pulmonary Oedema
Two unlabeled events of pulmonary oedema were documented in the case series. Although it was possible that indigotindisulfonate sodium contributed to the event, both cases were limited in information and the totality of the evidence does not support addition to the prescribing information at this time.

8.8.4 SOC Skin and subcutaneous tissue disorders (n = 10 cases)

We identified a total of 15 PTs from the Skin and subcutaneous tissue disorders SOC identified in 10 cases. These terms included *erythema* (n=2), injection site discoloration (n=2), *rash* (n=2), *rash erythema*tous (n=2), *urticaria* (n=2), and one each of *angioedema*, *infusion site necrosis*, *infusion site reaction*, *infusion site swelling*, *rash papular*.

8.8.5 SOC Nervous system disorders (n = 7 cases)

We identified a total of 7 PTs from the nervous system disorders SOC in 7 cases. These terms included *dizziness* (n=3), and one each of *cerebral disorder*, *cerebral ischaemia*, *restlessness*, and *seizure***.**

Reviewers Comments: SOC Nervous system disorders
These events did not by themselves appear drug related; however, they appear to be part of a greater constellation of events. For example, all dizziness cases occurred in the context of hypotension, the cerebral disorder was mentioned as a possible consequence of oxygen saturation decrease, the cerebral ischaemia was in the context of a cardiac arrest, the restlessness occurred in the context of

anaphylactic shock, and the generalized seizure occurred in a patient who had received indigotindisulfonate sodium to visualize the ureters during surgery, but was limited in additional details.

8.8.6 SOC Infections and infestations (n = 1 case)

We identified one PT (*postoperative wound infection*) from the infections and infestations SOC identified in one case.

Reviewers Comments: *The event of postoperative wound infection did not by itself appear to be drug related, however may have been a complication of technique/administration error.*

8.8.7 SOC Psychiatric disorders (n = 2 cases)

We identified a total of two PTs from the psychiatric disorders SOC identified in two cases. These terms included one each of *anxiety* and *restlessness***.**

Reviewers Comments: *Theses events by themselves did not appear drug related; however, they appear to be part of a greater constellation of events. For example, restlessness occurred in the context of a case of anaphylactic shock (n=1) and anxiety occurred in the context of atrioventricular block second degree (n=1).*

8.8.8 SOC Gastrointestinal disorders (n = 2 cases)

We identified a total of two PTs from the gastrointestinal disorders SOC identified in two cases. These terms included one each of *nausea* and *abdominal pain lower*.

Reviewers Comments: *Theses events by themselves did not appear drug related; however, they appear to be part of a greater constellation of events. For example, both events occurred in the context of hypotension and anaphylactic shock.*

8.8.9 SOC Metabolism and nutrition disorders (n = 1 case)

We identified one PT (*oedema*) from the metabolism and nutrition disorders SOC identified in one case.

Reviewers Comments: *This event by itself did not appear drug related, however appears to be part of a greater constellation of events as the oedema occurred in the context of anaphylactic reaction and rash.*

8.8.10 SOC Pregnancy, puerperium and perinatal conditions (n = 1 case)

We identified one PT (*maternal exposure during pregnancy*) from the pregnancy, puerperium and perinatal conditions SOC identified in one case.

Reviewers Comments: *This event by itself did not appear drug related, however occurred in a patient that experienced hypertension which did appear to be drug related.*

8.8.11 SOC Renal and urinary disorders (n = 1 case)

We identified one PT (*chromaturia*) from the renal and urinary disorders SOC identified in one case.

Reviewers Comments: *The specific verbatim term chromaturia i*s not in the draft label, however the statement "[indigo carmine] (b) (4)

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/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	April 26, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216264
Product Name, Dosage Form, and Strength:	Bludigo (indigotindisulfonate sodium) Injection, 40 mg/5 mL (8 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Provepharm Inc. (Provepharm)
FDA Received Date:	September 9, 2021, September 29, 2021, November 4, 2021, December 8, 2021, and February 15, 2022
OSE RCM #:	2021-1916
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Provepharm Inc. (Provepharm) submitted a 505(b)(2) application for NDA 216264 for Bludigo (indigotindisulfonate sodium) injection on September 9, 2021. Bludigo is a diagnostic dye proposed for use as a visualization aid in the [redacted] (b) (4) of the integrity and [redacted] (b) (4) of the ureters [redacted] (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures. We evaluated the proposed Bludigo prescribing information (PI), vial container label, and carton labeling for areas of vulnerability that may lead to medication errors.

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 – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note this marketing application does not include a referenced drug. According to Provepharm, a referenced drug was not included since "Indigo Carmine is not approved in the US, despite being marketed as an unapproved drug. There are no prescription drug products or discontinued drug products listed in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations that contain the active ingredient".

We performed a risk assessment of the proposed prescribing information (PI), vial container label, and carton labeling for Bludigo to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI, vial container label, and carton labeling for Bludigo identified areas of vulnerability that may lead to medication errors. For the PI we recommend defining the dosage form for the proposed product as a part of the dosage forms and strengths section and removing the use of symbols in

order to avoid confusion. For the vial container label and carton labeling, we recommend providing the proposed format for the expiration date and removing the statement [redacted] as it is not part of the established name. Additionally, for the carton labeling, we recommend revising the storage information to align with the storage information presented in the PI. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Bludigo prescribing information, vial container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for Provepharm Inc. We ask that the Division convey Section 4.2 in its entirety to Provepharm Inc. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. As currently presented, the first line of this section reads [redacted] We recommend revising the first line of this section to read "Recommended [redacted] 5 mL [redacted] intravenously over 1 minute".

2. Dosage Forms and Strengths

a. We recommend including the dosage form at the beginning of the highlights of dosage forms and strengths. Additionally, we recommend including the active ingredient after the strength. Revise to read "Injection: 40 mg/5 mL (8 mg/mL) indigotindisulfonate sodium in a single-dose ampule. (3)".

B. Prescribing Information

1. Section 2: Dosage and Administration

a. As currently presented, the first line of Section 2.1 Recommended Dosage includes [redacted] Bludigo. We note this information is not needed as part of the dosage information. We recommend removing [redacted] from the first line of Section 2.1.

b. We note Section 2.1 includes [redacted] We recommend removing this information from Section 2.1 as it is not needed here and should be in Section 14.

c. As currently presented, (b) (4)
(b) (4)

d. We note the proposed Section 2 Dosage and Administration does not currently include a subsection for information regarding imaging with Bludigo. We recommend adding a Section as part of Section 2 for imaging guidelines.

2. Section 3: Dosage Forms and Strengths

a. We note the dosage form is not presented at the beginning of Section 3 Dosage Forms and Strengths. Additionally, we note the active ingredient and package type is not presented in Section 3. We recommend revising to read "Injection: 40 mg/5 mL (8 mg/mL) indigotindisulfonate sodium is a dark blue sterile solution available in 5 mL single dose ampules".

3. Section 16: How Supplied/Storage and Handling

a. We note the proposed Section 16 currently contains subheadings for "Storage" and for (b) (4) We recommend including one subheading for "How Supplied" and one subheading for "Storage". Additionally, we recommend removing (b) (4) and presenting this shelf-life information under the "Storage" subheading.

b. We note Section 16 How Supplied/Storage and Handling states that the proposed product will be supplied in (b) (4) We recommend revising the package type term to read (b) (4) for consistency with the rest of the PI and the carton and container labeling.

c. As currently presented, the symbol "-" is used to represent "to" in the storage temperature range. We recommend removing the use of the symbol and replacing it with its intended meaning of "to". Additonally, we note the proposed product should not be refrigerated or frozen and requires protection from light. We recommend including these statements are part of the storage information. Revise the storage information to read "Store at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59° to 86°F) in original carton to protect from light. Do not refrigerate or freeze. Use immediately after opening. Discard unused portion.".

d. We note Section 16 states (b) (4) We recommend removing this information from Section 16 as it is not required.

4.2 RECOMMENDATIONS FOR PROVEPHARM INC.

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

A. General Comments Regarding Vial Container Label and Carton Labeling

1. As currently presented, we note the proposed vial container label and carton labeling contain both [redacted] (b) (4) and "indigotindisulfonate sodium". Additionally, we note the established name for the proposed product is "indigotindisulfonate sodium". We recommend removing [redacted] (b) (4) from the proposed vial container label and carton labeling.
2. We recommend removing the use of the placeholder "Tradename" on the proposed vial container label and carton labeling and replacing it with the conditionally approved proprietary name "Bludigo".
3. As currently presented, the proposed vial container label and carton labeling contain a placeholder for the expiration information. However, the proposed format for the expiration information on the vial container label and carton labeling is not provided. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

B. Vial Container Label

1. We note the statement "Rx Only" is presented on the proposed vial container label after the package type description. We recommend presenting the statement "Rx Only" on its own line on the proposed vial container label.

C. Carton Labeling

1. We note the proposed prescribing information (PI) for Bludigo states that the proposed product should not be refrigerated or frozen, and the proposed product needs to be protected from light. We recommend including this storage information on the proposed carton labeling after the storage temperature requirements. Revise the storage information on the proposed carton labeling to read "Store at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59° to 86°F) in the carton to protect from light. Do not refrigerate or freeze.".
2. As currently presented, we note the proposed carton labeling for Bludigo does not include the amounts of each of the inactive ingredients. We recommend revising the back panel of the carton labeling to include the quantity for each of the inactive ingredients to be consistent with 21 CFR 201.100(b)(5).

3. We note the proposed principal display panel includes the statements “For Intravenous Use Only” and [redacted] (b) (4) We recommend removing the statement [redacted] (b) (4) as it is redundant.

4. As currently presented, the proposed carton labeling contains the statement [redacted] (b) (4) We recommend revising this statement to read “Recommended Dosage: See Prescribing Information”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bludigo received on December 8, 2021 from Provepharm Inc..

Table 2. Relevant Product Information for Bludigo	
Initial Approval Date	N/A
Active Ingredient	indigotindisulfonate sodium
Indication	Diagnostic dye indicated for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	40 mg/5 mL (8 mg/mL)
Dose and Frequency	Administer (b) (4) 5 mL intravenously over 1 minute.
How Supplied	TRADENAME (indigotindisulfonate sodium) 40 mg/5 mL solution for injection is supplied in 5 mL single-use amber ampoules. A box contains 5 ampules.
Storage	This product does not require any special storage conditions. Protect from light. Store at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59° to 86°F). Shelf Life: (b) (4) After opening: this product should be used immediately. Discard unused portion. Do not refrigerate or freeze.

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Bludigo labels and labeling submitted by Provepharm Inc..

- Vial Container Label received on September 9, 2021
- Carton Labeling received on September 9, 2021
- Prescribing Information (Image not shown) received on December 8, 2021, available from \\CDSESUB1\evsprod\nda216264\0006\m1\us\114-labeling\draft\labeling\prescribing-information-word.docx

G.2Label and Labeling Images

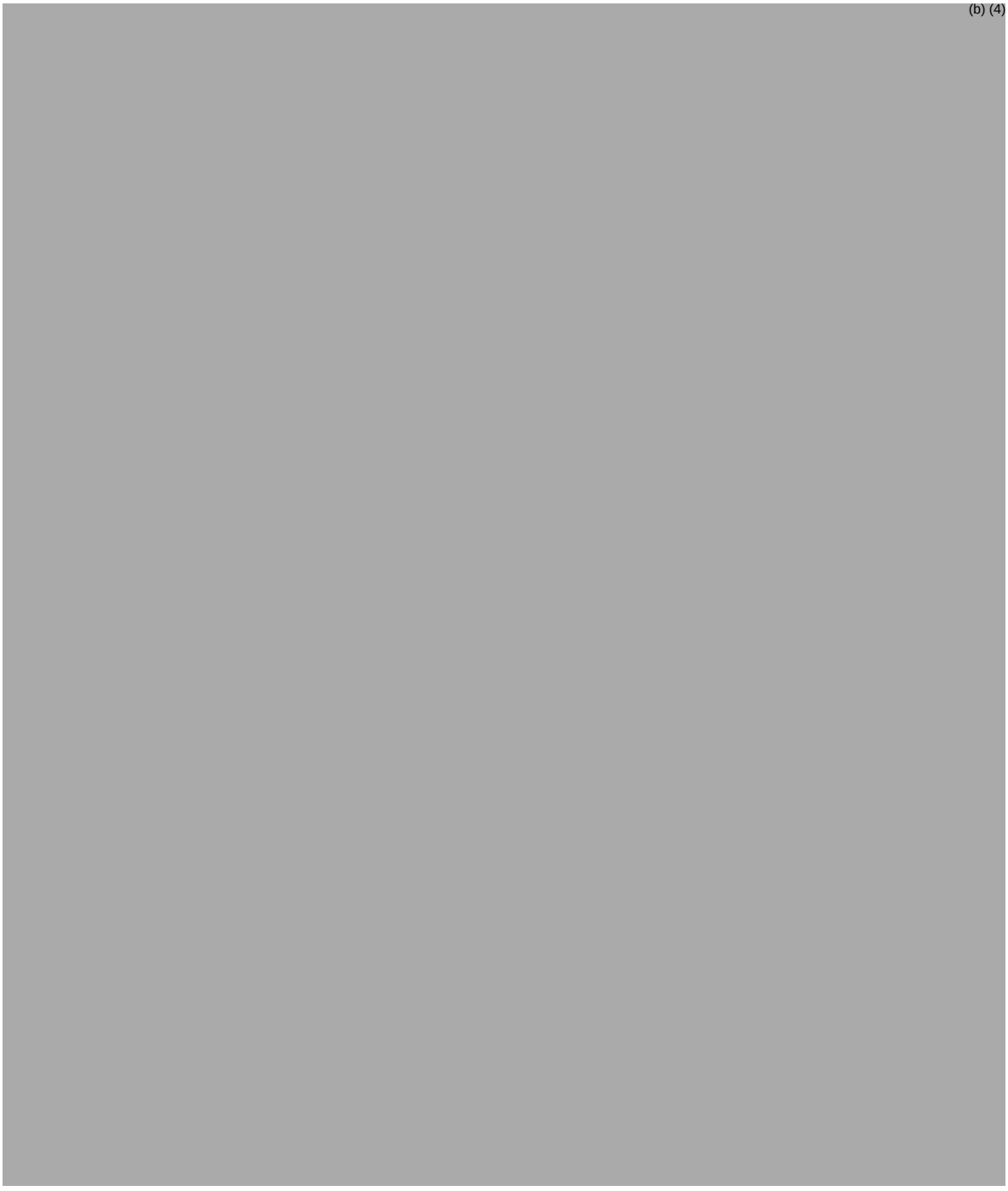
- Vial Container Label

(b) (4)

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

- Carton Labeling

(b) (4)



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/s/

DEVIN R KANE
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HINA S MEHTA
04/28/2022 03:51:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
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Division of Pediatric and Maternal Health Review

Date: 3/10/2022 **Date consulted:** 9/9/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Imaging and Radiation Medicine (DIRM)

Drug: Indigotindisulfonate Sodium Injection USP 0.8 % solution

NDA: 216264

Applicant: Provepharm SAS

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 216264
- DMIRM consult form for DPMH, DARRTS Reference ID 4874578

Consult Question:

Please review section 8 of the USPI.

INTRODUCTION AND BACKGROUND

On September 9, 2021, the applicant (Provepharm SAS) submitted a new NDA for (b) (4) (Indigotindisulfonate Sodium) Injection USP 0.8 % solution, NDA 216264 for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures. The Division of Medical Imaging and Radiation (DMIRM) consulted the Division of Pediatric and Maternal Health (DPMH) on October 19, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Indigotindisulfonate Sodium, or indigo carmine, is approved for used as a food colorant in the U.S.[1]
- Indigo carmine has been used as a contrast agent since the 1900s and is considered a marketed unapproved by the FDA. A marketed unapproved drug is exempted from the definition of "new drug" under FD&C Act of 1938; therefore, it is considered a new chemical entity (NCE).
- On September 9, 2021, Provepharm SAS submitted (b) (4) NDA 216263, indicated for use as a visualization aid in the (b) (4) of the integrity (b) (4) of the ureters (b) (4) urological and gynecological open, robotic, or endoscopic surgical procedures. This was submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Indigo carmine is a marketed unapproved drug. There is no drug that was relied upon as indigo carmine has not been approved for use in the U.S. The applicant is relying on the published literature to support the claim.[2]
- The proprietary name of (b) (4) was proposed by the applicant in May 2021, but unaccepted by the FDA.
- On October 19, 2021, DIRM consulted DPMH to assist with development of subsections 8.1 and 8.2 of the product's labeling.
- On October 22, 2021, FDA send an Information Request (IR) to the applicant to obtain supplemental information including
    - a review and summary of all available published literature regarding indigo carmine use in pregnant and lactating women and the effects of indigo carmine on male and female fertility,
    - a cumulative review and summary of relevant cases reported in your pharmacovigilance database,
    - a summary of drug utilization rates among females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval.
    - a revised labeling incorporating the above information that complies with PLLR.
- On November 4, 2021, the applicant replied to the IR with a Labeling Supplement Amendment.
- On February 15, 2022, the applicant requests the review of proprietary name Bludigo. The applicant also submitted an updated proposed labeling.

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[1] Summary of Color Additives for Use in United States in Foods, Drugs, Cosmetics, and Medical Devices, Food and Drug Administration. https://www.fda.gov/industry/color-additive-inventories/summary-color-additives-use-united-states-foods-drugs-cosmetics-and-medical-devices

[2] Personal Communication with DIRM RPM dated 11/17/21.

Drug Characteristics

Indigotindisulfonate Sodium (indigo carmine) Injection Characteristics[3]

Drug Class	Diagnostic dye
Mechanism of action	[redacted] excreted via kidney following intravenous administration visibly turning the urine blue. The dye coloring of the urine provides a visualization aid in the [redacted] of the integrity [redacted] of the ureters [redacted]
Molecular weight	466.35 g/mol
Half-life	12 min (following intravenous injection)
Protein Binding	Largely bound

Indigo carmine is a dye clinically used for diagnostic purposes. When it is intravenously administered, it causes dark blue discoloration of urine within [redacted] minutes of injection. It is actively excreted by the kidney. Clearance is mostly in urine (20% of total dose and more than half excreted as metabolite 5-sulfo-isatin). Other sources of elimination include [redacted] and stool (<2%). The oral bioavailability of indigo carmine is 3%.

Serious Adverse Effects[4]

- Heart rate and blood pressure changes: may cause a transient elevation of blood pressure and reflex bradycardia in patients under general anesthesia or under spinal anesthesia
- Exercise caution in treatment with patients with heart rate and conduction disorders as well as patients with high blood pressure.

REVIEW

Indigo Carmine Use

Indigo carmine has a long history of use in intraoperative cystoscopy to detect urinary tract injury as the standard of care following surgeries with high risk of injury to the urinary tract, such as in hysterectomies, pelvic organ prolapses, and incontinence operations.[5,6] Cystoscopy is a procedure that allows for the visual examination of the urinary tract where a cystoscope equipped with a lens is inserted into the urethra and advanced up to the bladder. Indigo carmine is administered intravenously [redacted] allow for better visualization. Sluggish or absent efflux of dye from ureteral orifices indicates a patency issue in the ureter.

Indigo carmine has been used in gynecologic laparoscopic procedures (by injection into the uterus via cervical opening and watch for spill into the peritoneal cavity) to visualize patency of the fallopian tubes. It has also been used in obstetrics procedures to mark the first-entered

[3] Based on applicant proposed labeling and discussion with DMIRM review team.

[4] Proposed by the Sponsor. See Sponsor's submitted package on September 9, 2021. See page 7 of "Summary of Clinical Safety." This was discussed and confirmed by DPMH Personal communication with DMIRM Clinical Team on 2/11/2022.

[5] Ribeiro S, et al. The value of intra-operative cystoscopy at the time of laparoscopic hysterectomy. Human Reproduction. 1999; 14 (7): 1727–1729.

[6] Kwon CH, et al. The use of intraoperative cystoscopy in major vaginal and urogynecologic surgeries. American Journal of Obstetrics and Gynecology. 2002;187(6):1466-71.

amniotic sac in twin amniocentesis[7] and to detect rupture of membrane (ROM).[8,9,10] In situations where ROM is indeterminate from the clinical exam and the standard test (pooling, nitrazine, fern and Valsalva maneuver), indigo carmine is injected into the amniotic cavity directly by amniocentesis and a tampon is inserted in the vaginal cavity to detect blue dye (usually 20-30 minutes later) in those with ROM.

Since June 2014, there has been a shortage of indigo carmine in United States due to a shortage of the active ingredient, manufactory delays, and an increased demand for the drug.[11,12,13] At this time, health care providers are using alternative agents as a surgical contrast dye described below.[14,15,16,]

Ureter and Bladder Identifications in Surgical Procedures[17]

Contrast dyes or solutions are often utilized for intraoperative identification of the bladder and ureter integrity. Commonly used dyes or solutions are:

- Intravesical Contrast or Solutions
    - Methylene blue- two or three drops in saline and used for intravesical distention.
    - Infant formula- used in obstetrical procedures for intravesical distention of the bladder and to assess bladder integrity.
    - Mannitol- intravesical instillation in hysteroscopic procedures to allow visualization of ureteral jets.
- Intravenous Contrast
    - Fluorescein- 2.5 ml or 25 mg of 10% solution administered intravenously to color urine fluorescent yellow. It is associated with rare anaphylactic reactions.
    - Indigo carmine – (b) (4) of a 0.8% solution used to color urine blue. Manufacturer of the product discontinued production in 2015 due to a shortage of

[7] Horger EO, et al. Use of indigo carmine for twin amniocentesis and its effect on bilirubin analysis. American Journal of Obstetrics and Gynecology 1984;150(7): 858-860. https://doi.org/10.1016/0002-9378(84)90462-9.
[8] ACOG Practice Bulletin Number 217 Prelabor Rupture of Membranes. Obstetrics & Gynecology 2020;135(3): e80-97.
[9] Guidelines for perinatal care 8th edition. ACOG, AAP. Accessed 10/26/2021. https://www.acog.org/clinical-information/physician-faqs/-/media/3a22e153b67446a6b31fb051e469187c.ashx
[10] Sosa CG, et al. Comparison of placental alpha microglobulin-1 in vaginal fluid with intra-amniotic injection of indigo carmine for the diagnosis of rupture of membranes. J. Perinat. Med. 2014; 42(5): 611–616.
[11]https://www.accessdata fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI5Indigotindisulfonate%20Sodium%20(Indigo%20 Carmine)%20Injection&st5c&tab5tabs-1#
[12] Ireland KE, et al. Intra-amniotic Dye Alternatives for the Diagnosis of Preterm Prelabor Rupture of Membranes. Obestrics & Gynecology 2017;129(6): 1040-1045.
[13] Integrated ASHP's Drug Shortage Database. Accessed 10/26/2021. https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=175&loginreturnUrl=SSOCheckOnly#:~:text=Reason%20for%20the%20Shortage%20American%20Regent%20launched%20indigo,indigo%20carmine%20due%20to%20shortage%20of%20raw%20material.
[14] Ostrosky, K, et al. Sodium Fluorescein Usage During Cystoscopy. Obstetrics & Gynecology. 2016(127):47S
[15] Hui JYC, Harvey MA, Johnston SL. Confirmation of ureteric patency during cystoscopy using phenazopyridine HCl: a low-cost approach. J Obstet Gynaecol Can. 2009 Sep;31(9):845-849. doi: 10.1016/S1701-2163(16)34303-1. PMID: 19941709.
[16] Luketic L, Murji A, Options to Evaluate Ureter Patency at Cystoscopy in a World Without Indigo Carmine, Journal of Minimally Invasive Gynecology. 2016;23(6):878-885. https://doi.org/10.1016/j.jmig.2016.06.009.
[17] Gilmour D. Urinary tract injury in gynecologic surgery: Identification and management. UpToDate. Accessed 2/7/22. https://www.uptodate.com/contents/urinary-tract-injury-in-gynecologic-surgery-identification-and-

raw material. This product is not recommended to be used in patient with history of anaphylaxis to sulfa medications due to cross reactivity.
    - Methylene blue- this is not recommended due to increased chance of postoperative urinary tract infection compared to normal saline, and cumulative dose of >7mg/kg can result in methemoglobinemia in susceptible individuals.
- Oral
    - Phenazopyridine- 100mg orally one hour prior to surgery colors the urine reddish-orange color. This is not recommended in patients with renal insufficiency. The change in urine color is inconsistent.

PREGNANCY

Nonclinical Experience

Animal reproduction studies using the intravenous route of administration have not been conducted. Oral administration of indigotindisulfoate sodium to pregnant rats and rabbits produced no evidence of fetal harm. However, oral availability is low (3%) so that the risk of intravenous administration of indigotindisulfonate sodium during pregnancy cannot be evaluated from the data available.

The reader is referred to the full Pharmacology/Toxicology report by Ronald Honchel, Ph.D. and Jonathan Cohen, Ph.D.

Review of Clinical Trials

Pregnant individuals were excluded from the clinical trials.

Review of Pharmacovigilance Database

The applicant conducted a search of indigo carmine exposure during pregnancy in their pharmacovigilance database including US clinical trials and reports in Europe. No cases were identified.

Federal Adverse Events Reporting System (FAERS) and EudraVigilance data analysis system (EVDAS)

The applicant conducted a search in FAERS and found three cases related to fetal exposure to indigo carmine during pregnancy. Two of these cases are also reported below under literature review (Mann C., 2016, Johari K, et al., 2018).

management?search=cystoscopy%20dye%20choice&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

Table 1. Applicant's Table of Indigo Carmine Exposure in Pregnancy in FAERS[18]

Case ID	Suspect Product Active Ingredients	Reason for Use	Reactions	Serious	Outcomes	Sex	Age (Years)
8179104	Indigotindisulfonate Sodium	Photodynamic Diagnostic Procedure	Vascular Resistance Systemic Increased; Hypertension; Cardiac Index Increased; Maternal/Foetal Exposure During Pregnancy	Serious	Other Outcomes	F	34
15496061	Indigotindisulfonate Sodium; Azithromycin Anhydrous; Acyclovir; Ampicillin; Penicillin; Oxacillin Sodium; Sodium Chloride; Betamethasone	Suspected PPROMs	Premature Baby; Low Birth Weight Baby; Maternal/Foetal Exposure During Pregnancy	Serious	Delivery of a healthy infant at 34 weeks; Other Outcomes	M	unk
12805762	Indigotindisulfonate Sodium; Sufentanil; Dexamethasone; Dexketoprofen; Midazolam Hydrochloride; Ranitidine; Propofol; Cefuroxime; Mivacurium	Product Used For Unknown Indication	Nervous System Disorder; Maternal/Foetal Exposure During Pregnancy; Brain Malformation; Microcephaly; Cerebellar Hypoplasia	Serious	Congenital Anomaly; Other Outcomes	unk	unk

[18] "0003-response-to-fda-information-request-dated-22-oct-2021" page 15.

Table 2. Applicant's Table of Indigo Carmine Exposure in Pregnancy from the EudraVigilance data analysis system (EVDAS)[19]

EU Local Number	Worldwide Unique Case Identification	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference	Patient Age	Patient Sex	Reaction List PT	Suspect/Interacting Drug List (Drug Char-Indication PT-Action Taken-[Duration-Dose-Route])	Concomitant/Not Administered Drug List (Drug Char-Indication PT-Action Taken-[Duration-Dose-Route])
EU-EC-10006202768	FR-AFSSAPS-RN20181988	Healthcare Professional (Physician)	EEA	Not Available	18-64 Years	Female	Abortion Spontaneous (n/a-Recovered/Resolved-Other Medically Important Condition)	[INDIGO CARMINE] (S-Hydrosalpinx-Not applicable-[n/a-n/a-Intrauterine]), [TRIPTORELIN ACETATE] (S-Laparoscopy-Not applicable-[n/a-3.75 mg-Subcutaneous])	Not Reported

[19] "0003-response-to-fda-information-request-dated-22-oct-2021" page 16.

The applicant concludes the following:

> A search of the US FAERS and EU EVDAS systems only identifies 4 reports related to maternal/fetal exposure during pregnancy. These exposures resulted in a spontaneous abortion, a child born with a brain malformation, and the birth of healthy but pre-mature /low birth weight child. The one case that reported effects on the mother included increased systemic vascular resistance and hypertension. These are known adverse events in non-pregnant women and men. As there are few reported events in pregnancy associated with decades of market availability and patient exposure, Provepharm believes the proposed labeling is sufficient.

Reviewer comment:
There are a total of four cases reported above, one case resulted in a low-birth-weight infant with premature delivery, one case resulted in cerebellar hypoplasia/microcephaly (unknown mode of indigo carmine administration), one case resulted in miscarriage and one case had an unknown pregnancy outcome. There is no additional information available for any of the four cases. No pattern of adverse effects was detected by his reviewer, and no conclusion can be drawn based on these limited cases.

Review of Literature

Applicant's Review of Literature

The applicant performed a search of the published literature in PubMed and EMBASE of indigo carmine use in pregnant females. The detailed search criteria can be found in Figure 1, "Indigo Carmine Pregnancy and Fertility Literature Search Schematic", submitted on November 4, 2021, by the applicant. The reader is referred to Appendix A for a list of the submitted articles.

The applicant found one case of intravenous administration of indigo carmine by intravenous route at 26^{+4} weeks' gestation. The patient delivered a healthy infant at 38^{+4} weeks' gestation.[20] The majority of the published literature consist of indigo carmine use during pregnancy via amino infusion during the second and third trimester. Four cases of small bowel atresia with intraamniotic instillation of indigo carmine in pregnancy have been reported in the published literature. These cases raised concern of association between indigo carmine use via amnioinfusion.

- Two cases of jejunal atresia were reported by a in the Netherlands (1980-1992) at the academic Hospital Rotterdam in a total of 306 twin amniocentesis. Both were exposed to indigo carmine.[21]
- One case of small bowel atresia (out of four cases that had amniocentesis, the other three were exposed to methylene blue) was exposed to indigo carmine from a review from the department of Pediatric Surgery in Hannover, Germany from 1977 to 1994. There were 31 children who had surgery for small bowel atresia (six were twins).[22]
- In a case report, amniocentesis was performed in a 35-year-old female with a triplet pregnancy at 16 weeks' gestation. Indigo carmine was instilled in the first two sacs. The

[20] Sekiguchi M, H. Y. (2014). Clinical manifestation of a calyceal diverticular abscess in a pregnant woman. Case Rep Obstet Gynecol, 975071.
[21] Brandenburg H. The use of synthetic dyes for identification of the amniotic sacs in multiple pregnancies. Prenat Diag 1997;17(3), 281-282.
[22] Glüer S. Intestinal atresia following intraamniotic use of dyes. Eur J Pediatr Sur 1995;5(4), 240-242.

mother delivered at 35 weeks' gestation. Triplet A was found to have small bowel atresia. Triple C had a single umbilical artery.[23]

Other studies did not report this finding.[24,25]A study involving 156 twin births in which indigo carmine was used to facilitate amniocentesis did not find an increased incidence of congenital defects. Among the defects uncovered, no infants had small bowel atresia.[24]

The applicant concludes:

> Individual case report(s) following intra-amniotic instillation of indigo carmine, suggest a possible association of indigo carmine to small bowel atresia presenting in the neonate and fetal death associated with premature rupture of membranes and amniopatching… There are no adequate and well-controlled studies of indigo carmine in pregnant women with pregnancy outcomes reported to inform a drug-associated risk… In animal reproduction studies, oral administration of indigo carmine to pregnant rats and rabbits… produced no evidence of fetal harm. However, oral availability is low (3%) so that the risk of intravenous administration of indigo carmine during pregnancy cannot be evaluated from the data available.

Reviewer comment:
Four cases of small bowel atresia with intraamniotic instillation of indigo carmine in pregnancy have been reported in the published literature. These reports of small bowel atresia raise concerns regarding use of indigo carmine in pregnancy. However, this reviewer notes that the route of administration in these four cases was intraamniotic. The proposed route of administration for the current NDA is intravenous (b) (4)*. Overall, there were limited cases of intravenous indigo carmine exposure in pregnancy and no cases of intramuscular administration of indigo carmine in the published literature.*

DPMH's Review of Literature
DPMH conducted a search of the published literature in Embase, Pubmed, Micromedex,[26] ReproTox,[27] TERIS,[28] and Shepard's.[29] Search terms used were "indigo carmine" AND "pregnancy" AND "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." The following articles were found:

- A possible association between the use of indigo carmine and small bowel atresia was suggested based on one case report.[30] A portion of this report described 67 newborns treated for small bowel atresia, 20 of whom were one of a set of twins. Of these latter

[23] Hausknecht RU, Y. H. (1981, Sep). Prenatal genetic diagnosis in a triplet gestation. Obstet Gynecol, 58(3), 382-385.
[24] Romero R, S. F. Infection and labor. VI. Prevalence, microbiology, and clinical significance of intraamniotic infection in twin gestations with preterm labor. Am J Obstet Gynecol 1990;163(3), 757-761.
[25] Cragan JD, Martin ML, Khoury MJ, Fernhoff PM: Dye use during amniocentesis and birth defects. Lancet 341:1352, 1993.
[26] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 10/26/2021.
[27] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/26/2021.
[28] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 10/26/2021.
[29] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 10/26/2021.
[30] Van Der Pol JG, Wolf H, Boer K et al: Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins. Br J Obstet Gynaecol 99:141-3, 1992.

cases, 2nd trimester amniocentesis had been performed with indigo carmine in one case and with methylene blue in 18 cases.[31]

- In a case series of 20 twin pregnancies (during the second trimester), amniocentesis using indigo carmine with ultrasound was performed in 19 pregnant patients with a minimal complication rate.[32] Of the 19 patients who were successfully sampled, all were cytogenetically normal. In one set of twins, one twin was stillborn at 40 weeks gestation; the case of the stillbirth was unknown. Another set of twins delivered prematurely at 28 weeks gestation.

- In a case series from 1988, amniocentesis with indigo carmine instillation was performed in 83 twin pregnancies during the second trimester for prenatal genetics. Amniotic fluid was successfully obtained from both amniotic sacs in 77 patients.[33]
    - In two pregnancies, elevated levels of alpha-fetoprotein (AFP) were found in both sacs. One of these pregnancies was electively terminated and the other continued until term (one infant died 8 days after birth due to renal failure, and the second infant was healthy).
    - One pregnancy miscarried 5 days after amniocentesis at 19 weeks' gestation. No congenital malformations were noted at autopsy.
    - Three women were delivered between 23- and 28-weeks' gestation, all resulted in stillbirths and no congenital abnormalities were noted at autopsy.
        - 1 patient had the diagnosis of incompetent cervix (with a Shirodkar cerclage) and chorioamnionitis.
        - 1 patient delivered at 24 weeks' gestation.
        - 1 had preterm labor (PTL) and delivered at 26 weeks gestation.
    - Thirty-six patients delivered preterm infants between 28- and 37-weeks' gestation. There were three perinatal deaths.
        - 1 perinatal death occurred in an infant who was delivered at 34 weeks gestation and who had intrauterine growth restriction (IUGR) and a diaphragmatic hernia; the co twin was normal and did well after birth.
        - 1 perinatal death occurred in an infant who was delivered at 29 weeks gestation and had respiratory distress syndrome (RDS). The co-twin was normal.
        - 1 perinatal death occurred in an infant with urethral stenosis and hydronephrosis. This was already described above under elevated AFP.
    - Forty-two patients delivered at term after 37 weeks.
    - The perinatal mortality rate was 55/1000 (9 of 164).

- A prospective controlled study compared placental alpha macroglobulin-1 (PAMG-1) in the vaginal fluid test to the reference standard, indigo carmine dye test, in 140 pregnant females between 21- and 42-weeks' gestation who reported signs, symptoms, or

[31] McFadyen I: The dangers of intra-amniotic methylene blue. Br J Obstet Gynaecol 99:89-90, 1992.
[32] Elias S, et al. Genetic amniocentesis in twin gestations. American Journal of Obstetrics and Gynecology. 2980;138(2): 169-173. https://doi.org/10.1016/0002-9378(80)90029-0.
[33] Pijpers L, Jahoda MG, Vosters RP, Niermeijer MF, Sachs ES. Genetic amniocentesis in twin pregnancies. Br J Obstet Gynaecol. 1988 Apr;95(4):323-6.

complaints suggestive of ROM without obvious leakage of fluid from the cervical os and confirmation of ROM by traditional methods. In all cases, PAMG-1 in the vaginal fluid test was obtained prior to indigo carmine dye test (1 mL of indigo carmine dye in 9 mL of sterile saline was transabdominally instilled into the amniotic cavity under ultrasound guidance). PAMG-1 was found to be sensitive and specific. Pregnancy outcomes were not reported.[34]

- Records of 34 pregnant women who underwent amniodye test using indigo carmine secondary to equivocal PROM on standard tests were reviewed. None of these pregnancies were complicated by fetal death, methemoglobinemia, and small intestinal atresia.[35]

According to ACOG, indigo carmine is indicated for use in the diagnosis of ROM.[36]

Indigo carmine was not found in Micromedex,[26] TERIS,[28] or Shepard.[29]

ReproTox[27] states "based on experimental animal studies and limited mid-trimester human experience, indigo carmine exposure is not anticipated to increase the risk of congenital anomalies."

- Indigo carmine is a dye used in foods and medical devices.
- Developmental toxicity was not observed when this compound was tested in rats and rabbits.
- Because of its ergot-like activity, the intravenous administration of this dye can increase total peripheral resistance, blood pressure, and central venous pressure with decreased cardiac output, stoke volume, and heart rate.

Reviewer comment:
Available data from case reports, case series, observational studies and experience with indigo carmine use in pregnant women over several decades have not identified a drug associated risk of adverse maternal and fetal adverse effect. Available data from case reports, case series, observational studies are insufficient to identify a drug-associated risk of miscarriage or congenital malformation because the majority of the published data are from intra-amniotic administration of indigo carmine during the second and third trimesters of pregnancy. There is one reports of indigo carmine use during the first trimester of pregnancy in a patient undergoing chromopertubation. There are limited reports of indigo carmine use in pregnancy though the intravenous or intramuscular routes.

Although early publications of intraamniotic injection of indigo carmine in pregnancy raised concerns for an increased risk of small bowel atresia in the exposed infants (n=5), recent studies have not confirmed this finding. Indigo carmine is indicated for use in the diagnosis of rupture of

[34] Sosa CG, et al. Comparison of placental alpha microglobulin-1 in vaginal fluid with intra-amniotic injection of indigo carmine for the diagnosis of rupture of membranes. J. Perinat. Med. 2014; 42(5): 611–616.
[35] Adekola H, Gill N, Sakr S, Hobson D, Bryant D, Abramowicz JS, Soto E. Outcomes following intra-amniotic instillation with indigo carmine to diagnose prelabor rupture of membranes in singleton pregnancies: a single center experience. J Matern Fetal Neonatal Med. 2016;29(4):544-9. doi: 10.3109/14767058.2015.1015982. Epub 2015 Feb 25. PMID: 25714481.
[36] ACOG Practice Bulletin Number 217.

membranes according to ACOG.

Because indigo carmine is often used for diagnosis of PPROM, pregnancy outcomes in these cases are often associated with increased rates of fetal loss, chorioamnionitis, and other adverse pregnancy outcomes. Such outcomes are confounded by indication. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

Nonclinical Experience

It is not known if indigo carmine is present in animal milk following intravenous and intramuscular administration. The applicant notes that when indigo carmine was administered by intramammary infusion to cows, indigo carmine was detected in milk samples.

The reader is referred to the full Pharmacology/Toxicology report by Ronald Honchel, Ph.D. and Jonathan Cohen, Ph.D.

Reviewer comment:
This example of administration of indigo carmine via intramammary infusion in cows is not a typical method of lactation study in animals, so it is unclear how relevant these data are for labeling.

Review of Literature

Applicant's Review of Literature

The applicant conducted a search of published literature and found no relevant clinical studies regarding use of indigo carmine during lactation.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms "indigo carmine" AND "lactation" and "indigo carmine" AND "breastfeeding."

- There are no articles on the use of indigo carmine during lactation.

ReproTox[27] has no information on indigo carmine and lactation.

Indigo carmine is not found in LactMed.[37]

Briggs[38] categorized indigo carmine as probably compatible with breastfeeding with no human data.

[37] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 10/26/21.

[38] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015.

Hales[39] notes the following

> While there are no published studies on breastfeeding compatibility or safety, available pharmacokinetic information suggests that this drug can be used safely in nursing women. With a rapid elimination half-life of just 4 to 5 minutes, the drug is readily and completely cleared by renal excretion. Given that the molecule is large (466.35 Daltons) and practically insoluble in organic solvents, it is unlikely that considerable drug would diffuse into the breast milk after administration. Consider waiting several half-lives after administration (or until the mother's urine is clear) to resume breastfeeding. Half-life may be longer following intramuscular injection.

Hales gives lactation rating of "L2-No Data-Probably Compatible."

Reviewer comment:
It is not known if indigo carmine is present in animal or human milk. There are no data on the effects of indigo carmine on the breastfed infant or on milk production. Indigo carmine has a half-life of 11 minutes and typically is used during surgery. The lactation exposure window following 5 half-lives is estimated to be one hour. Given the need for post-surgical monitoring in the recovery room, it is unlikely that a patient will be attempting to breastfeed within the first hour following a surgical procedure. Additionally, indigo carmine is approved for used as a food colorant in U.S.. The oral bioavailability of indigo carmine is low (3%); therefore, exposure of breastfed infant to indigo carmine is expected to be low. This was discussed and agreed upon by the Clinical Pharmacology Team. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Carcinogenicity

Carcinogenicity studies in animals have not been conducted with indigotindisulfonate sodium using the intravenous route of administration.

Long-term studies in mice with oral and subcutaneous administration of indigotindisulfonate sodium revealed no carcinogenic effects.

Mutagenesis

Although indigotindisulfonate sodium has been evaluated in a number of Ames assay studies, an Ames assay study that follows all currently recommended guidelines has not been performed. Indigotindisulfonate sodium was not genotoxic in all those Ames assays that did not follow current guidelines. The mutagenicity of indigotindisulfonate sodium was inconclusive in the in vitro mouse L5187Y Lymphoma TK +/- assay. Orally administered indigotindisulfonate sodium was not mutagenic in the in vivo mouse micronucleus test. An in vivo micronucleus test with indigotindisulfonate sodium using the intravenous route of administration has not been conducted.

[39] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

Fertility
Fertility studies with indigotindisulfonate sodium using the intravenous route of administration have not been conducted.

The reader is referred to the full Pharmacology/Toxicology report by Ronald Honchel, Ph.D. and Jonathan Cohen, Ph.D.

Review of Literature
Applicant's Review of Literature
The applicant conducted a search of published literature and found that indigo carmine is utilized for visualization of patency of fallopian tubes in infertility surgeries.

- There are no relevant clinical studies regarding adverse effect of indigo carmine on fertility.
- The applicant found an in-vitro study where sperm motility is assessed under solution of indigo carmine and other dyes. The authors did not find any significant adverse effect on sperm motility caused by indigo carmine.[40]

DPMH's review of literature
DPMH conducted a search of published literature using Embase, Pubmed, Micromedex,[41] ReproTox,[42] and TERIS.[43] Search terms used were "indigo carmine" AND "reproduction," "indigo carmine" AND "infertility," and "indigo carmine" AND "contraception."

- No articles of indigo carmine adversely affecting fertility were found.

ReproTox[42] notes indigo carmine may be used for chromopertubation as part of an infertility evaluation. This dye has not been shown to be toxic to human luteal cells in culture, suggesting acceptability for use in such tubal patency studies.[44]

- A 2013 study conducted in male mice found that giving indigo carmine in the diet for 6 weeks caused a significant increase in body weight but a significant decrease in testes weight.[45] Sperm motility and tubular diameter were reduced. A significant reduction in sperm density was found at the highest dose level (39 mg/kg/day).

Use in Females of Reproductive Potential
The applicant has not done any drug utilization review to date regarding this population.

Reviewer comment:
Indigo carmine is used in females of reproductive potential to determine tubal patency, amniocentesis, delineation of rupture of membrane, and in the assessment of ureter and bladder

[40] Sheynkin YR, S. C. Effect of methylene blue, indigo carmine, and Renografin on human sperm motility. Urology, 1999;53(1), 214-217.
[41] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 10/26/21.
[42] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/26/21.
[43] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 10/26/21.
[44] Mahadevan MM, Wietzman GA, Hogan S, Breckinridge S, Miller MM. Methylene blue but not indigo carmine is toxic to human luteal cells in vitro. Reprod Toxicol 1993; 7:631-3.
[45] Dixit A, Goyal RP. 2013. Evaluation of reproductive toxicity caused by indigo carmine on male Swiss albino mice. PharmacologyOnLine 1: 218-224.

integrity during urologic and gynecologic surgeries. There is no published literature on indigo carmine adversely affecting human fertility. Animal fertility studies have not been conducted with intravenous or intramuscular administration of indigo carmine. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Available data from case reports, case series, observational studies and experience with indigo carmine use in pregnant women over several decades have not identified a drug associated risk of adverse maternal and fetal adverse effects. Use of indigo carmine is uncommon in the first and second trimester of pregnancy and therefore there are insufficient data to evaluate for a drug associated risk of major birth defects and miscarriage. There was only one case report of first trimester indigo carmine exposure that was found in the literature.

Because intravenous administration of indigo carmine will be used for the visualization of the ureter (b) (4) urologic and gynecologic surgeries, (b) (4) (b) (4) Because there is a lack of first-trimester pregnancy data, a lack of information regarding the use of intravenous indigo carmine and potential use in females of reproductive potential, DPMH recommends a postmarketing requirement (PMR) for a descriptive pregnancy safety study.

Lactation

It is not known if indigo carmine is present in animal or human milk. There are no data on the effect of indigo carmine on the breastfed infant and milk production. Because indigo carmine is approved for used as a food colorant in U.S. and the oral bioavailability of indigo carmine is low (3%), (b) (4) (b) (4) .

There are no safety concerns of breastfeeding with indigo carmine use during lactation identified by this reviewer. DPMH does not recommend any postmarketing clinical lactation study at this time.

Females and Males of Reproductive Potential

There is no evidence in the literature to suggest that indigo carmine use adversely affects male or female fertility. An animal fertility study has not been conducted with the indicated route of administration. There is no anticipated drug-to-drug interaction between indigo carmine and hormonal contraceptives. DPMH recommends (b) (4) from the labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

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Appendix A. Applicant's List of Published Literature on the Use of Indigo Carmine in Pregnancy

- A case report described intravenous administration of indigo carmine to examine communication between a renal cyst and the renal collecting system in a pregnant patient at 26^{+4} weeks gestation. The patient went on to deliver a healthy infant at 38^{+4} weeks gestation.[46]

- The American College of Obstetricians and Gynecologist recommend use of indigo carmine to diagnose prelabor rupture of membranes (PROM) in pregnant women if the diagnosis of PROM remains unclear after a full evaluation, and if the benefits of the procedure outweigh the risk.[47]

- In a retrospective study, 34 pregnant females, carrying a singleton non-anomalous pregnancy, had an amniocentesis and intra-amniotic dye instillation with indigo carmine due to equivocal test for PROM. [48]
    - Nine patients tested positive for PROM, and they all delivered preterm. Seven patients had placental pathology consistent of chorioamnionitis.
    - Twenty-five patients tested negative for rupture of membrane.
    - Five (14.7%) neonates delivered to women in this study suffered perinatal death. The gestational age at delivery of these five women ranged between 22 and 24 weeks.

- In a prospective study, seven patients with iatrogenic preterm premature rupture of membrane underwent placement of an amniopatch, an intra-amniotic injection of platelets and cryoprecipitate, used to seal the amniotic sac. Indigo carmine was delivered (2mL) to aid in detection of amniotic fluid leakage.
    - Three patients delivered healthy infants- two at full term and one at 33^{+5} weeks.
    - One patient, who had undergone amniocentesis at 12 weeks gestation for diagnosis of fetal lower obstructive uropathy, developed preterm premature rupture of membranes three days after the amniocentesis. The fetus continued to have megacystitis and severe oligohydramnios, and the pregnancy was electively terminated at 21 weeks gestation.
    - One patient delivered twins prematurely at 22 weeks gestation.
    - Two patients experienced intrauterine fetal death.
        - One fetus was found to have trichothiodystrophy, which is associated with immunologic incompetence.
        - One patient had leakage of fluid at 15+2 weeks gestation after amniocentesis. An autologous amniopatch was placed at 16^{+4} weeks and

[46] Sekiguchi M, H. Y. (2014). Clinical manifestation of a calyceal diverticular abscess in a pregnant woman. Case Rep Obstet Gynecol, 975071.
[47] ACOG Practic Bulletin Number 2017 Prelabor Rupture of Membranes. Obstetrics & Gynecology 2020;135(3):e80-e97.
[48] Adekola H, et al. (2015) Outcomes following intra-amniotic instillation with indigo carmine to diagnose prelabor rupture of membranes in singleton pregnancies: a single center experience. J Matern Fetal Neonatal Med. Early Online:1–6.

leakage of fluid continued. A second amniopatch was placed 17^{+2} weeks gestation. No further leakage occurred. Five days after the second amniopatch the fetus was noted to have tachycardia of 190 to 200 beats/minute. Fetal death occurred at 19^{+3} weeks gestation. The cause for fetal death was not determined.

The authors speculated that the cause of spontaneous fetal death for the first patient may be due to the underlying fetal disease. For the second case of fetal death, the authors speculated that the death may be attributable to vasoactive effects of platelets or indigo carmine.[49]

Reviewer comment:
Although indigo carmine was used, the outcomes were confounded by indication and by use of amniopatch. Other studies have not reported intrauterine death related to intraamniotic indigo carmine use.

- In a case series, 13 patients (9 in the second trimester and 4 in the third trimester) underwent amnioinfusion (indigo carmine (3mL) was instilled along with saline infusion) to treat severe oligohydramnios. Premature rupture of membranes was confirmed in six patients and excluded in the remaining seven patients. Nine of the 13 pregnancies ended in loss of pregnancy or neonate (three induced abortions, two spontaneous abortions, one stillbirth, and three neonatal deaths). There were five cases of chorioamnionitis.[50]

[49] Quintero RA, Treatment of iatrogenic previable premature rupture of membranes with intra-amniotic injection of platelets and cryoprecipitate (amniopatch): Preliminary experience. Am J Obstet Gynecol 1999;181(3): 744-749.
[50] Quetel TA, Amnioinfusion: An aid in the ultrasonographic evaluation of severe oligohydramnios in pregnancy. Am J Obstet Gynecol 1992; 167:333-6.1992

Table 1: Post-Amnioinfusion Ultrasonographic Diagnosis and Pregnancy Outcome in 13 Patients with Severe Oligohydramnios				
Case No.	Maternal Age (year)	Gestational Age (Week)	Ultrasound Diagnosis	Pregnancy Outcome
(b) (6)	32	18	Premature rupture of membranes, choroid plexus cyst	Induced abortion
	28	31	Renal agenesis	Renal agenesis, pulmonary hypoplasia
	32	21	Intrauterine growth retardation	Delivered at 39 wk, 1640 gm; no anomalies; discharged home
	33	19	Premature rupture of membranes; no anomalies seen	Induced abortion
	39	14	Renal agenesis, intrauterine growth retardation	Delivered at 39 wk; neonatal death growth retardation day I, 1.4 kg; severe oligohydramnios and Potter's facies; kidneys reported seen at autopsy
	29	15	Renal agenesis	Chorioamnionitis; spontaneous abortion
	39	20	Premature rupture of membranes, no anomalies seen	Chorioamnionitis; delivery at 26 wk; discharged home
	26	23	Renal agenesis, intrauterine growth retardation	Stillborn at 38 wk; no autopsy
	34	21	Premature rupture of membranes, gross leakage	Chorioamnionitis; spontaneous abortion 21 wk
	29	25	Premature rupture of membranes, no anomalies seen	Chorioamnionitis; delivery 34 wk; neonatal death day I
	26	23	Premature rupture of membranes, no anomalies seen	Chorioamnionitis; delivery 34 wk; discharged home
	35	20	Intrauterine growth retardation	Delivered at 30 wk, 465 gm; discharged home
	23	20	Encephalocele, multicystic kidneys	Induced abortion; Meckel-Gruber syndrome confirmed

- In a case report, premature preterm rupture of membrane (PPROM) was diagnosed by indigo carmine instillation via amniocentesis. Chorioamnionitis was diagnosed two days later, and the patient delivered a female infant at 22 weeks' gestation who died 8 hours later. The amniotic fluid grew Hemophilus influenzae biotype 1.[51]

- In a case report, amniotic fluid was infused with indigo carmine instillation in a patient with PPROM at 21^{+6} weeks. Serial amnioinfusion was planned until 26 weeks gestation; however, the patient's amniotic membrane was confirmed to be resealed. The patient denied any leakage of fluid after 23^{+6} weeks gestation. She developed gestational hypertension at 27 weeks gestation and underwent successful induction of labor at 34^{+2}

[51] Pinar H, et al. Pathological Case of the Month. Arch Pediatr Adolesc Med 1998; 152:199-200

weeks gestation and delivered a healthy male infant.[52]

- In a case report of a pregnancy with twin-twin transfusion syndrome (TTTS), indigo carmine was infused intraamniotically to aid amino-reduction of fetus B. The fetus had persistent reverse-end-diastolic flow (REDF), and fetal demise (both) was reported at 23^{+6} weeks gestation due to TTTS.[53]

- In a prospective study, 46 patients with twin pregnancies (mean gestational age of 29-20 weeks) who had preterm labor and intact membranes had amniocentesis performed to evaluate for microbial invasion of the amniotic sacs. Indigo carmine was injected after amniotic fluid was retrieved to ensure sampling of both amniotic sacs. All pregnancies were delivered with live infants. No congenital malformations were reported.[54]

- A study involving 78 twin pregnancies (156 twin births) in which indigo carmine was used to facilitate amniocentesis did not find an increased incidence of any specific congenital malformations. Among the defects uncovered, no infants had small bowel atresia (a specific congenital malformation observed with use of methylene blue during amniocentesis).[55]

- In a case report, indigo carmine was used during laparoscopic chromo-perturbation in a 38-year-old woman undergoing a hysteroscopy and myomectomy for the treatment of fibroids and infertility. The women had an undetected pregnancy and was 2^{+6} weeks gestation at the time of the surgery. She delivered a child with congenital cerebellar vermis hypoplasia at 37 weeks gestation. The paternal age was 57-year-old.[56]

- A review of amniocentesis cases in the Netherlands (1980-1992) at the academic Hospital Rotterdam yielded two cases of jejunal atresia in a total of 306 twin amniocentesis. Both infants were exposed to indigo carmine intraamniotically.[57] The authors report that although indigo carmine appears less toxic than methylene blue when used to differentiate the amniotic sacs during amniocentesis evaluating a twin pregnancy, it can still be the cause of small intestinal atresia.

- A review from the department of Pediatric Surgery in Hannover, Germany from 1977 to 1994 yielded reports of 31 children who had surgery for small bowel atresia (six were

[52] Kohari K, et al. A Novel Approach to Serial Amnioinfusion in a Case of Premature Rupture of Membranes Near the Limit of Viability. Am J Perinatol Rep 2018;8:e180–e183.
[53] Hackney DN, et al. Twin-twin transfusion syndrome presenting as polyhydramnios in both fetuses secondary to spontaneous microseptostomy. AJP Rep 2013;3(2), 83-86.
[54] Romero R, S. F. Infection and labor. VI. Prevalence, microbiology, and clinical significance of intraamniotic infection in twin gestations with preterm labor. Am J Obstet Gynecol 1990;163(3), 757-761.
[55] Cragan JD, Martin ML, Khoury MJ, Fernhoff PM: Dye use during amniocentesis and birth defects. Lancet 341:1352, 1993.
[56] Mann C, K. K.-W. Laparoscopic Chromopertubation, Myomectomy with Opening of the Uterine Cavity and Hysteroscopy during the Early Implantation Phase of an Undetected Pregnancy: Delivery of a Child with a Complex Brain Malformation. Geburtshilfe Frauenheilkd 2016;76(8), 906-909.
[57] Brandenburg H. The use of synthetic dyes for identification of the amniotic sacs in multiple pregnancies. Prenat Diag 1997;17(3), 281-282.

twins). Of these 31 patients, four children had prenatal amniocentesis, which involved intra-amniotic infection of a dye. Of the four children, three received methylene blue and one received indigo carmine (exposed at 16 weeks gestation and born at 29 weeks gestation).[58]

- In a case report, amniocentesis was performed in a 35-year-old female with a triplet pregnancy at 16 weeks gestation. Indigo carmine 1mL (diluted in 15 ml of amniotic fluid) was instilled in the first two sacs. The mother delivered at 35 weeks' gestation. Triplet A was found to have small bowel atresia. Triple C had a single umbilical artery.[59]

[58] Glüer S. Intestinal atresia following intraamniotic use of dyes. Eur J Pediatr Sur 1995;5(4), 240-242.
[59] Hausknecht RU, Y. H. (1981, Sep). Prenatal genetic diagnosis in a triplet gestation. Obstet Gynecol, 58(3), 382-385.

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