

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216016Orig1s000

216017Orig1s000

OTHER REVIEW(S)

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)

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Date of This Review:	November 18, 2024
Requesting Office or Division:	Division of Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216016 and NDA 216017
Product Name, Dosage Form, and Strength:	Iomervu (iomeprol) Injection, 250 mg Iodine/mL, 300 mg Iodine/mL, 350 mg Iodine/mL and 400 mg Iodine/mL
Applicant Name:	Bracco Diagnostics Inc. (Bracco)
FDA Received Date:	November 7, 2024
TTT ID #:	2023-7438-2
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Bracco Diagnostics Inc. (Bracco) submitted revised container labels and carton labeling received on November 7, 2024 for Iomervu under NDA 216016 and NDA 216017. We reviewed the revised container labels and carton labeling for Iomervu (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 memo^a and via email on October 22, 2024.

2 CONCLUSION

Bracco Diagnostics Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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^a Kane, D. Review of Revised Label and Labeling for Iomervu (NDA 216016 and NDA 216017). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 03. TTT ID: 2023-7438-1.

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/s/

DEVIN R KANE
11/18/2024 08:15:25 AM

STEPHANIE L DEGRAW
11/18/2024 01:40:19 PM

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)

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Date of This Review:	October 3, 2024
Requesting Office or Division:	Division of Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216016 and NDA 216017
Product Name, Dosage Form, and Strength:	Iomervu (iomeprol) Injection, 250 mg Iodine/mL, 300 mg Iodine/mL, 350 mg Iodine/mL and 400 mg Iodine/mL
Applicant Name:	Bracco Diagnostics Inc. (Bracco)
FDA Received Date:	September 12, 2024
TTT ID #:	2023-7438-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Bracco Diagnostics Inc. (Bracco) submitted revised container labels and carton labeling received on September 12, 2024 for Iomervu under NDA 216016 and NDA 216017. We reviewed the revised container labels and carton labeling for Iomervu (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 container labels and carton labeling are unacceptable from a medication error perspective. For the container labels and carton labeling, we recommend removing the hyphen symbol “-” and replacing it with its intended meaning of “to”, revising the presentation of the established name to present the dosage form outside of the parentheses, and including the appropriate units after all numeric values presented. We provide our recommendations below. We ask that the Division convey Section 2.1 in its entirety to Bracco Diagnostics Inc. so that recommendations are implemented prior to approval of this NDA.

2.1 RECOMMENDATIONS FOR BRACCO DIAGNOSTICS INC.

A. General Comments (Container Labels and Carton Labeling)

1. As currently proposed, each container label and carton labeling includes a colored box containing (b) (4) in addition to a complete strength statement (e.g., 300 mg Iodine/mL). However, the units are not presented in the colored box next to the numeric value. We recommend adding the appropriate units after all numeric values in order to avoid confusion. You may consider removing (b) (4) and placing a colored box around the strength and units that is located below the established name. Alternatively, consider revising the information in the colored box to include the numeric strength and appropriate units (i.e., revise (b) (4) to read “300 mg iodine/mL”).
2. As currently presented, the container labels and carton labeling include the hyphen symbol “-” to represent the word “to”. We recommend replacing the hyphen with its intended meaning of “to” in order to avoid confusion. For example, in the pH statement on the container labels and carton labeling revise “6.5 – 7.2” to read “6.5 to 7.2”.
3. The established name and dosage form are presented together inside parentheses below the proprietary name on the proposed container labels and carton labeling. However, the proposed Iomervu prescribing information (PI) presents “Iomeprol” in parentheses with the dosage form, “injection” presented

^a Kane, D. Label and Labeling Review for Iomervu (NDA 216016 and NDA 216017). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 07. TTT ID: 2023-7438.

after outside of the parentheses. We recommend revising the presentation of the established name and dosage form such that it is consistent across all labels and labeling.

B. Carton Labeling

1. As currently proposed, the fill volume is prominently displayed on each carton labeling in bold font and in an increased font size. We recommend de-bolding the fill volume to decrease prominence and decreasing the font size to be consistent with the font size used for the “10 bottles” statement.

C. 50 mL Carton Labeling (300 mg Iodine/mL, 350 mg Iodine/mL and 400 mg Iodine/mL)

1. The proposed carton labeling for the 50 mL package sizes states (b) (4). However, the Iomervu PI and container labels state the 50 mL fill volume will be supplied in vials. Thus, we recommend revising the package type on the 50 mL carton labeling to read “single-dose vials” and “10 vials 50 mL each” to align with the PI and container labels.

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/s/

DEVIN R KANE
10/03/2024 11:08:24 AM

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10/03/2024 01:16:13 PM

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)

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Date of This Review:	August 7, 2024
Requesting Office or Division:	Division of Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216016 and NDA 216017
Product Name, Dosage Form, and Strength:	Iomervu (iomeprol injection), 250 mg Iodine/mL, 300 mg Iodine/mL, 350 mg Iodine/mL and 400 mg Iodine/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bracco Diagnostics Inc. (Bracco)
FDA Received Date:	NDA 216016: December 14, 2023 and January 17, 2024 NDA 216017: November 30, 2023 and January 17, 2024
TTT ID #:	2023-7438
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

Bracco Diagnostics Inc. (Bracco) submitted a 505(b)(2) application for Iomervu (iomeprol injection) on November 30, 2023 and December 14, 2023, under NDA 216016 and NDA 216017. Iomervu is a radiographic contrast agent indicated for intravenous and intraarterial procedures in adult and pediatric patients. We evaluated the proposed Iomervu prescribing information (PI), container labels, 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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

Bracco Diagnostics Inc. (Bracco) submitted a 505(b)(2) application to obtain marketing approval of Iomervu (iomeprol injection) under NDA 216016 and NDA 216017 relying on medical literature. We performed a risk assessment of the proposed PI, container labels and carton labeling for Iomervu to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

Our evaluation of the proposed PI, container label, and carton labeling for Iomervu identified areas of vulnerability that may lead to medication errors. We note in the request for proprietary name review (PNR) for Iomervu Bracco states (b) (4)

The request for PNR was for “Iomervu” (b) (4), as such, we did not consider the (b) (4) as part of the PNR or this review. We consulted the Division of Imaging and Radiation Medicine (DIRM) regarding the name presentation with the

use of the (b) (4). Ultimately, it was determined to present the proprietary name as “lomervu” throughout the labels and labeling without the (b) (4) and presenting the individual strengths as “250 mg Iodine/mL”, “300 mg Iodine/mL”, “350 mg Iodine/mL” and “400 mg Iodine/mL”. We include our recommendations below for the presentation of the proprietary name and individual product strengths. In addition, for the PI we recommend including the appropriate units after all numeric values, removing the strength presentations for lomervu in terms of (b) (4) from Sections 3 and 16, removing trailing zeros, and replacing the term “saline” with the official USP name “0.9% Sodium Chloride Injection”. For the container labels and carton labeling, we recommend removing the strengths in terms of (b) (4), including the appropriate units after all numeric values, presenting the established name in parentheses, and revising the storage information statement to align with the storage information in the PI. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed lomervu PI, container labels 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 the Applicant. We ask that the Division convey Section 4.2 in its entirety to Bracco Diagnostics Inc. so that recommendations are implemented prior to approval of this NDA.

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

A. General Comments for Highlights of Prescribing Information and Full Prescribing Information

1. We note reference is made throughout the PI to drug product as (b) (4). However, we note the proposed proprietary name submitted for review was (b) (4) reviewed and found unacceptable on February 28, 2024; however, the proposed name, lomervu, (b) (4) was found conditionally acceptable on August 7, 2024. Thus, we recommend removing (b) (4) throughout the PI, presenting the product name as “lomervu” and including the appropriate units after all numeric values. For example, revise (b) (4) to read “lomervu 250 mg Iodine/mL”.
2. We note use of the term “saline” to refer to “0.9% Sodium Chloride Injection”. We recommend removing “saline” and replacing it with the proper USP name “0.9% Sodium Chloride Injection” (without the “USP” descriptor) throughout the PI.

B. Highlights of Prescribing Information

1. Highlights of Dosage and Administration
 - a. Revise highlights of dosage and administration to read:

- Individualize the volume and concentration according to the specific dosing tables accounting for factors such as age, body weight, size of the vessel, the rate of blood flow within the vessel, and structures or areas to be examined.
- See full prescribing information for complete dosage and administration information.

2. Highlights of Dosage Forms and Strengths

- Revise highlights of dosage forms and strengths to read: “Injection: 250 mg Iodine/mL, 300 mg Iodine/mL, 350 mg Iodine/mL and 400 mg Iodine/mL in single-dose vials or bottles”.

C. Prescribing Information

1. Section 2: Dosage and Administration

- As currently presented, the original second bullet under Section 2.1 Important Dosing and Administration Information states “(b) (4)”. We recommend including the appropriate temperature range for body temperature in terms of degrees Celsius followed by the Fahrenheit equivalent values in parentheses.
- We note the tables in Section 2 include the units “(b) (4)”. We recommend revising the units in the table headers to read “mg Iodine/mL” to avoid confusion.
- We note use of the hyphen symbol “-” in numeric ranges to represent the word “to”. We recommend removing the hyphen symbol and replacing it with its intended meaning of “to”. Additionally, we note there are numeric values that are not immediately followed by the appropriate units. We recommend including the appropriate units after all numeric values to avoid confusion. For example, in Table 1, revise “100-190 mL” to read “100 mL to 190 mL” and in the footnote under Table 1 in Section 2.2, revise “6-8 minutes” to read “6 minutes to 8 minutes”.
- As currently presented, there are numeric values with trailing zeros included throughout Section 2. We recommend removing trailing zeros to avoid misinterpretation of the numeric values. For example, in Table 1 under “Injection Rate” we recommend revising “(b) (4)” to read “(b) (4)” and in Table 2 under “(b) (4) Volume”, revise “1.0-2.0 mL/kg” to read “1 mL/kg to 2 mL/kg”.
- We note Table 3 under Section 2.4 Intraarterial Procedures in Adults includes the units “(b) (4)”. We recommend revising the units to read “g of Iodine” to avoid confusion.

2. Section 3: Dosage Forms and Strengths

- a. We recommend revising Section 3: Dosage Forms and Strengths to read:
Injection: clear, colorless to pale yellow solution available in the following iodine concentrations and configurations:

Concentration (mg iodine/mL)	Package Size	Package Type
250	100 mL	Single-dose bottles
300	50 mL	Single-dose vials
	100 mL, 150 mL, 200 mL	Single-dose bottles
350	50 mL	Single-dose vials
	100 mL, 150 mL, 200 mL	Single-dose bottles
400	50 mL	Single-dose vials
	100 mL, 150 mL, 200 mL	Single-dose bottles

3. Section 16: How Supplied/Storage and Handling

- a. We recommend presenting the various package types in table format to improve readability of Section 16.1. Revise Section 16.1 to read:
IOMERVU is a clear, colorless to pale yellow solution supplied in single-dose vials or bottles in the following configurations:

Concentration (mg iodine/mL)	Package Size	Package Type	Sale Unit	NDC
250	100 mL	Single-Dose Bottle	Carton of 10	0270-7015-14
300	50 mL	Single-Dose Vial	Carton of 10	0270-7016-15
	100 mL	Single-Dose Bottle	Carton of 10	0270-7016-17
	150 mL	Single-Dose Bottle	Carton of 10	0270-7016-18
	200 mL	Single-Dose Bottle	Carton of 10	0270-7016-19
350	50 mL	Single-Dose Vial	Carton of 10	0270-7017-20
	100 mL	Single-Dose Bottle	Carton of 10	0270-7017-21
	150 mL	Single-Dose Bottle	Carton of 10	0270-7017-24
	200 mL	Single-Dose Bottle	Carton of 10	0270-7017-25
400	50 mL	Single-Dose Vial	Carton of 10	0270-7018-26
	100 mL	Single-Dose Bottle	Carton of 10	0270-7018-27
	150 mL	Single-Dose Bottle	Carton of 10	0270-7018-28
	200 mL	Single-Dose Bottle	Carton of 10	0270-7018-29

4.2 RECOMMENDATIONS FOR BRACCO DIAGNOSTICS INC.

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

A. General Comments (Container Labels and Carton Labeling)

1. The proposed name, lomervu, was found conditionally acceptable on August 7, 2024. Please revise all labels and labeling to replace (b) (4) with the proprietary name “lomervu”.
2. As currently presented, the proposed container labels and carton labeling include the following strength statements: “XX% organically bound iodine”, “Iomeprol Injection XX%”, and the milligrams of iodine per mL strength prominently displayed in a colored box. We recommend removing the strengths in terms of percentages to avoid confusion, and only presenting the strength in terms of milligrams of iodine per mL on the container labels which aligns with the dosing in the prescribing information (PI). Additionally, we recommend including the units “mg Iodine/mL” next to the strength. For example, revise “250” to read “250 mg iodine/mL”.
3. We note the established name and dosage form are presented below the proposed proprietary name, but are not presented inside parentheses. This is inconsistent with the PI which presents this information inside parentheses. Revise the established name and dosage form on the proposed container labels and carton labeling to be presented within parentheses as “(Iomeprol injection)”.
4. We note the statement “For intravascular use only” is presented in a red box at the bottom of the proposed container labels and carton labeling. We recommend revising this statement to read “For intravenous or intraarterial use only” to align with the more specific routes of administration described in the PI.
5. We note use of the hyphen symbol “-” to represent the word “to” in numeric value ranges. We recommend replacing the hyphen symbol with its intended meaning of “to” to prevent misinterpretation. Additionally, we note there are numeric values presented on the proposed container label that are not immediately followed by the appropriate units. We recommend including the appropriate units after all numeric values presented on the proposed container label. For example, revise the storage information statement to read “Store at room temperature between 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]”. If space is limited, “[see USP Controlled Room Temperature]” can be omitted.
6. We note the storage information presented on the container labels and carton labeling lacks the statement “do not freeze”. We recommend including the statement “Do not freeze” to align with the full storage information presented in the PI.
7. We note the proposed container labels and carton labeling include the statement (b) (4) This terminology

is inconsistent with the terminology in the PI. Therefore, we recommend revising this statement to read “Recommended Dosage: See Prescribing Information”.

8. As currently presented, the proposed container labels and carton labeling include a placeholder for the expiration information but the proposed format for the expiration is not provided. We are unable to assess the proposed expiration date format from a medication safety perspective. 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 hyphen or forward slash be used to separate the portions of the expiration date.

B. Container Labels

1. As currently presented, the bottom of the proposed container label contains the proposed proprietary name and the strength presented without the appropriate units. We recommend including the units “mg Iodine/mL” after each strength presentation to avoid confusion. For example, revise “(b) (4)” to read “Iomervu 250 mg Iodine/mL”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Iomervu received on December 14, 2023 from Bracco Diagnostics Inc.

Table 2. Relevant Product Information for Iomervu	
Initial Approval Date	N/A
Active Ingredient	iomeprol injection
Indication	Iomervu (iomeprol injection) is a radiographic contrast agent indicated for: <u>Intravenous Procedures</u> - Adults - Computed tomography (CT) of head and body - Computed tomography angiography (CTA) - Coronary computed tomography angiography (CCTA) (b) (4) - Computed tomography (CT) urography - Pediatric Patients - Computed tomography (CT) of head and body - Computed tomography angiography (CTA) - Coronary computed tomography angiography (CCTA) (b) (4) - Computed tomography (CT) urography <u>Intraarterial Procedures</u> - Adults - Coronary arteriography and ventriculography; (b) (4) - Cerebral, peripheral and visceral angiography, and aortography, including digital subtraction angiography - Pediatric Patients (b) (4) - Cerebral, peripheral, and visceral angiography, including digital subtraction angiography
Route of Administration	Intravenous and Intraarterial
Dosage Form	injection
Strengths	250 mg Iodine/mL, 300 mg Iodine/mL, 350 mg Iodine/mL and 400 mg Iodine/mL
Dose and Frequency	Individualize dose and concentration. Use the lowest effective dose necessary to obtain adequate visualization. See full prescribing information for additional information.

How Supplied	IOMERVU is supplied in (b) (4) clear glass vials or bottles with elastomeric closures and flip-off caps. IOMERVU is supplied in the following configurations: • IOMERVU 250 mg Iodine/mL - o Ten 100 mL single dose bottles (NDC 0270-7015-14) • IOMERVU 300 mg Iodine/mL - o Ten 50 mL single dose vials (NDC 0270-7016-15) - o Ten 100 mL single dose bottles (NDC 0270-7016-17) - o Ten 150 mL single dose bottles (NDC 0270-7016-18) - o Ten 200 mL single dose bottles (NDC 0270-7016-19) • IOMERVU 350 mg Iodine/mL - o Ten 50 mL single dose vials (NDC 0270-7017-20) - o Ten 100 mL single dose bottles (NDC 0270-7017-21) - o Ten 150 mL single dose bottles (NDC 0270-7017-24) - o Ten 200 mL single dose bottles (NDC 0270-7017-25) • IOMERVU 400 mg Iodine/mL - o Ten 50 mL single dose vials (NDC 0270-7018-26) - o Ten 100 mL single dose bottles (NDC 0270-7018-27) - o Ten 150 mL single dose bottles (NDC 0270-7018-28) - o Ten 200 mL single dose bottles (NDC 0270-7018-29)
Storage	Store at 20° to 25°C (68° to 77°F) [See USP controlled room temperature]. Protect from light. Do not freeze.

APPENDIX F. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Iomervu labels and labeling submitted by Bracco Diagnostics Inc..

- Container Labels received on January 17, 2024
- Carton Labeling received on January 17, 2024
- NDA 216016 Prescribing Information (Image not shown) received on December 14, 2023, available from <\\CDSESUB1\EVSPROD\nda216016\0007\m1\us\114-labeling\1141-draft-labeling\11413-draft-label-text\11413-draft-labeling-text-0007.pdf>
- NDA 216017 Prescribing Information (Image not shown) received on November 30, 2023, available from <\\CDSESUB1\EVSPROD\nda216017\0009\m1\us\114-labeling\1141-draft-labeling\11413-draft-label-text\11413-draft-labeling-text-0009.pdf>

G.2 Label and Labeling Images



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

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/s/

STEPHANIE L DEGRAW on behalf of DEVIN R KANE
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STEPHANIE L DEGRAW
08/07/2024 06:18:56 PM

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

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

Memorandum

Date: August 2, 2024

To: Sharon Thomas, Regulatory Project Manager, Division of Imaging and Radiation Medicine (DIRM)

Hayoung Koo, Clinical Reviewer, DIRM

Younsook Kim, Associate Director for Labeling, DIRM

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for (b) (4) (iomoprol) injection, for intravenous or intra-arterial use

NDA: 216016

Background:

In response to DIRM's consult request dated February 20, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for (b) (4)

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on July 26, 2024, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on July 26, 2024, and we do not have any comments at this time.

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

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**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: July 19, 2024

Reviewer: Danielle Molnar, PharmD, BCPS, Safety Evaluator
Division of Pharmacovigilance (DPV) II

Team Leader: Mallika Mundkur, MD, MPH
DPV II

Division Director: S. Christopher Jones, PharmD, MPH, MS
DPV II

Product Name: (b) (4) (iomeprol)

Subject: All Adverse Events

Application Type/Number: NDA 216016 (intraarterial)
NDA 216017 (intravenous)

Applicant: Bracco, Inc.

TTT Record ID: 2024-8035

**** 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.****

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EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) database, published medical literature, Vigibase, and Applicant submissions for adverse events (AEs) reported with iomeprol. The Division of Imaging and Radiation Medicine (DIRM) requested this review on January 26, 2024, to help inform the evaluation of New Drug Applications (NDAs) for iomeprol injection (NDA 216016 for intraarterial administration; NDA 216017 for intravenous administration) and potential eventual product labeling.

DIRM requested that DPV perform a high-level broad assessment of adverse events reported with iomeprol from available postmarketing data. To perform this assessment, DPV:

- 1) Gathered event-level safety data from postmarketing sources, including 897 FAERS reports, 62 medical literature publications, and the 50 most frequently reported events in reports with serious outcomes in Vigibase.
- 2) Screened reported events to identify those not represented in applicant-proposed iomeprol labeling.
- 3) Assessed unlabeled events by screening available content from postmarketing data sources to determine whether available data suggests safety signals^a for iomeprol. To identify signals, DPV focused on unlabeled adverse events with the potential for serious outcomes, labeled adverse events with unexpected characteristics such as an increase in severity than what is proposed in labeling, and other important findings that inform the safety of the product.

DPV did not identify any safety signals unrepresented in proposed iomeprol labeling from this high-level broad assessment of adverse events reported with iomeprol from available postmarketing data.

Based on this review, DPV does not have any recommendations at this time.

^a We considered potential safety signals to be events that that meet the Center for Drug Evaluation and Research (CDER) Newly Identified Safety Signal (NISS) criteria: information that represents a serious adverse event; medication error; or an adverse event that suggests therapeutic inequivalence or product quality issue; AND the information indicates a likely safety signal that warrants further investigation into whether there is a causal association or a new aspect of a known association.

1 INTRODUCTION

This review evaluates the FDA Adverse Event Reporting System (FAERS) database, published medical literature, VigiBase, and Applicant submissions for adverse events (AEs) reported with iomeprol. The Division of Imaging and Radiation Medicine (DIRM) requested this review on January 26, 2024, to help inform the evaluation of New Drug Applications (NDAs) for iomeprol injection (NDA 216016 for intraarterial administration; NDA 216017 for intravenous administration) and potential eventual product labeling.

DIRM requested that DPV perform a high-level broad assessment of adverse events reported with iomeprol from available postmarketing data. To perform this assessment, DPV:

- 1) Gathered event-level safety data from postmarketing sources.
- 2) Screened reported events to identify those not represented in applicant-proposed iomeprol labeling.
- 3) Assessed unlabeled events by screening available content from postmarketing data sources to determine whether available data suggests safety signals^b for iomeprol. To identify signals, DPV focused on unlabeled adverse events with the potential for serious outcomes, labeled adverse events with unexpected characteristics such as an increase in severity than what is proposed in labeling, and other important findings that inform the safety of the product.

1.1 BACKGROUND

Iomeprol is a drug in the class of iodinated contrast media (ICM) which are widely used in conjunction with X-ray and computed tomography for imaging modalities including angiography, arteriography, venography, and urography. ICM may be subcategorized based on certain properties, such as osmolality, ionicity, and the number of tri-iodinated rings in the compound (monomeric versus dimeric) (Spampinato et al. 2017). Iomeprol is a low-osmolar nonionic monomer which are characteristics also shared by several approved ICM: iohexol, iopamidol, iopromide, and ioversol (Bracco 2023a; Spampinato et al. 2017).

Iomeprol has never been approved for marketing in the United States, although FDA granted temporary importation of iomeprol in 2022 to address ICM shortages (ACR 2022). In contrast, iomeprol's presence in the foreign marketplace spans more than three decades. Iomeprol was first approved by the United Kingdom in 1992 and is currently approved for marketing (under the tradename Iomeron) in 50 countries (Bracco 2023a). The Applicant estimates that more than 160 million patients have been exposed to iomeprol (Bracco 2023a), of which an estimated 0.8% was pediatric patient exposure (< 18 years of age) (Bracco 2024a).

^b We considered potential safety signals to be events that that meet the Center for Drug Evaluation and Research (CDER) Newly Identified Safety Signal (NISS) criteria: information that represents a serious adverse event; medication error; or an adverse event that suggests therapeutic inequivalence or product quality issue; AND the information indicates a likely safety signal that warrants further investigation into whether there is a causal association or a new aspect of a known association.

1.2 REGULATORY HISTORY

NDA 216016 and 216017 are being reviewed after resubmission. FDA issued a Refusal to File (RTF) letter after the initial 2021 NDA submissions because the applications were not sufficiently complete to permit a substantive review. The RTF letter identified Chemistry, Manufacturing, and Controls (CMC) filing issues pertaining largely to insufficient data for product strengths and presentations proposed with the NDAs (submitted data appeared to be for iomeprol products marketed outside the United States) (FDA 2022).

Note that the indications and strengths proposed by the Applicant for U.S. marketing (shown in Table 1) are a subset of strengths and indications approved by one or more foreign countries. For example, while intrathecal and intracavitary administration for certain indications are approved elsewhere, as are strengths such as 150 milligrams of iodine (mg I)/milliliter (mL), the Applicant is not currently seeking U.S. approval for these indications or strengths (Bracco 2023a).

Table 1. Summary of Indications and Strengths Proposed for Iomeprol with NDAs 216016 and 216017*	
<u>Intravenous procedures (adult and pediatric patients)</u>	
CT of head and body	
CTA of intracranial, visceral, (b) (4)	
Coronary CTA	
(b) (4)	
CT urography	
<u>Intraarterial procedures</u>	
Coronary arteriography, ventriculography, (b) (4)	
interventions (adult patients)	
Cerebral, peripheral, and visceral arteriography, and aortography, including digital subtraction angiography (adult and pediatric patients)	
(b) (4)	
<u>Strengths (mg I/mL) † ‡</u>	
250, 300, 350, 400	
* Table assembled from data in proposed product labeling (Bracco 2023b)	
† Strengths are shown in milligrams of organically bound iodine (mg I) per milliliter (mL) of product. Sections 3 and 11.1 of proposed product labeling contains a more thorough description of product strengths (e.g., mg of iomeprol/mL, percent of iodine per mL of product).	
‡ Proposed strengths vary by indication (e.g., only 300, 350, and 400 strengths are proposed for (b) (4)	
(b) (4)	
Abbreviations: CT=computed tomography, CTA=computed tomography angiography, NDA=New Drug Application	

1.3 RELEVANT PRODUCT LABELING

Table 2 summarizes relevant safety sections from the Applicant-proposed product labeling for iomeprol. (Appendix A contains the full content of these safety sections.)

(b) (4)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*	
Date of search	April 17, 2024
Time period of search	All reports through April 16, 2024

Table 3. FAERS Search Strategy*	
Search type	RxLogix DPV Surveillance Summary Alert [†]
Product terms	Product Active Ingredient: iomeprol
MedDRA search terms (Version 26.1)	All adverse events
* See Appendix A for a description of the FAERS database. † The following reports were added to the standard alert template: Case Count by System Organ Class & Preferred Term; Complete PT List. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

2.2 DATA MINING SEARCH STRATEGY

DPV used the Empirica Signal software with the strategy described in Table 4 to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., “potential signals”). If a drug-event combination has an EB05 ≥ 2 , this indicates with 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining results do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Table 4. Data Mining Search Strategy*	
Data refresh date	May 19, 2024
Product terms	Product Active Moiety (PAM): iomeprol
Empirica Signal run name	PAM(S)
MedDRA search terms (Version 27.0)	All events
* See Appendix B for description of Data Mining of FAERS using Empirica Signal. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

2.3 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in Table 5.

Table 5. Literature Search Strategy	
Date of search	April 5, 2024
Years included in search	All
Database	Embase, PubMed

Table 5. Literature Search Strategy	
Search terms	Embase: ('iomeprol'/exp/'adverse drug reaction','drug toxicity','drug interaction','special situation for pharmacovigilance' OR 'iomeprol-induced':de,ab,ti) AND [humans]/lim AND [english]/lim AND (('case finding'/de OR 'case report'/de OR 'case study'/de) OR ('case series' OR 'case report' OR 'case')) PubMed: (iomeprol OR iomeron) AND ((casereports[Filter]) OR (case series OR case report OR case))
Other criteria	Humans, English

2.4 VIGIBASE SEARCH STRATEGY

DPV searched the VigiBase database (description in Appendix C) with the strategy described in Table 6, which was modeled after the FAERS search strategy. VigiBase reports lack narrative information, hindering clinical assessment, so we provide aggregate MedDRA preferred term (PT)-level data from VigiBase for descriptive purposes. Preliminary searches revealed that there are more than 50,000 reports, containing more than 1200 PTs, in VigiBase for iomeprol. We focused our search on reports with serious outcomes in attempt to narrow the results to events that may represent the greatest safety risks.

Table 6. VigiBase Search Strategy*	
Date of search	May 31, 2024
Time period of search	All reports as of May 28, 2024 (dataset date)
Search type	Qualitative search
Product terms	Active Ingredient: iomeprol
MedDRA search terms (Version 27.0)	All events
Other criteria	Reports with serious outcomes [†]
*See Appendix C for a description of the VigiBase database. [†] Reports may have more than one serious outcome. Serious outcomes: death, life threatening, caused/prolonged hospitalization, disabling/incapacitating, congenital anomaly/birth defect, other medically important condition. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

2.5 RELEVANT APPLICANT SUBMISSIONS

DPV screened the following documents for the Applicant's assessment of adverse events reported with iomeprol use, particularly its assessment of postmarketing data, and its evaluation of safety signals we identified (if any) during the course of our review.

- Integrated Summary of Safety (ISS) (Bracco 2023a)
- 120 Day Safety Update (Bracco 2024a)

3 RESULTS

3.1 FAERS

The FAERS search on April 17, 2024, yielded 897 reports. For the purposes of this review, a case-level analysis was not performed on all reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes; causality and the role of the product in the coded outcome have not been determined for all reports (see Appendix B for FAERS limitations).

Table 7 provides the descriptive characteristics of the FAERS reports retrieved by the search strategy described in Table 3.

Table 7. Descriptive Characteristics of FAERS Reports with Iomeprol, Received by FDA Through April 16, 2024		
N=897*		
Sex	Male	420
	Female	404
	Unknown	73
Age	< 1 year	0
	1 to <3 years	1
	3 to < 7 years	0
	7 to <17 years	14
	17 to <65 years	426
	≥ 65 years	382
Country	Null	74
	United States	8 [†]
	Foreign	889
Report type	Expedited	887
	Periodic	10
Serious outcomes[‡] (n=895)	Death	63
	Life-threatening	114
	Hospitalization	580
	Disability	3
	Congenital anomaly	1
Other serious		415
* May include duplicates.		
† The country for these eight reports appears to have been miscoded; all described patients were in France or Finland per narrative content.		
‡ For the purposes of this document, 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 report can have one or more outcome.		

Reviewer comments: The descriptive characteristics of FAERS reports in Table 7 did not reveal unexpected trends or outcomes. Serious outcomes are not unexpected for iomeprol given proposed labeled events, such as life-threatening or fatal hypersensitivity reactions, acute kidney

injury (AKI), severe cutaneous adverse reactions (SCAR) which are also labeled for other iodinated contrast agents.

Deaths (N=63)

There were 36 fatal reports (after accounting for 27 duplicates).

Reviewer comments: Based on a manual review of the 36 fatal reports, the death outcome in 21 reports appeared to have an alternate explanation other than iomeprol (e.g., disease-related or concomitant medication-related), and could not be assessed in 2 reports that lacked temporal information. Death outcomes in the remaining 13 reports appeared to be attributable to events that are the subject of proposed warnings (i.e., hypersensitivity reaction, AKI, SCAR, or thyroid storm) and could be causally related to iomeprol. However, concomitant medications may have played contributing roles in 5 of the 13 reports and confounding roles in at least 9 of the 13 reports. Manual review of fatal reports did not suggest event outcomes or severity that were inconsistent with proposed labeling for iomeprol.

3.1.1 Reported Preferred Terms

Table 8 lists the most frequently reported MedDRA preferred terms (PTs) and the labeling status of each PT. Although only PTs with a frequency ≥ 10 are listed in the table, we reviewed all PTs for new potential safety signals. These PTs are derived from individual case safety reports (ICSRs) identifying iomeprol as a suspect drug and reporting varying strengths, indications, and routes of administration.

Table 8. Most Frequently Reported MedDRA PTs with N ≥ 10 with Iomeprol Received by FDA Through April 16, 2024, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT	Number of FAERS Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
Drug reaction with eosinophilia and systemic symptoms ‡	161	Yes, W/P (5.10)
Acute kidney injury‡	125	Yes, W/P (5.4)
Rash (b) (4)	123	Yes, AR (6.1; rash, rash (b) (4))
Acute generalized exanthematous pustulosis‡	80	Yes, W/P (5.10)
Toxic skin eruption	79	Yes, W/P (5.10; toxic epidermal necrolysis)
Eosinophilia	71	Yes, W/P (5.10; DRESS§)
(b) (4)	48	Yes, AR (6.1)
Erythema	39	Yes, AR (6.1)
Pyrexia	36	No, Alt Ex
Anaphylactic reaction‡	31	Yes, W/P (anaphylaxis ¶)
Rash	31	Yes, AR (6.1)
Urticaria	30	Yes, AR (6.1)
Dermatitis bullous	25	Yes, W/P (5.10; SCAR)

Table 8. Most Frequently Reported MedDRA PTs with N ≥ 10 with Iomeprol Received by FDA Through April 16, 2024, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT	Number of FAERS Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
Drug interaction	24	Yes, W/P (concomitant nephrotoxic drugs) and DI (metformin)
Anaphylactic shock‡	21	Yes, W/P (5.3; circulatory collapse)
Rash pruritic	20	Yes, AR (6.1; rash, pruritis)
Off label use	19	Not applicable (reports described off-label use of concomitant drug)
Hepatic cytolysis	17	No, Alt Ex
Renal failure	16	Yes, W/P (5.4; acute kidney injury)
Angioedema	15	Yes, W/P
Hypotension	15	Yes, AR 6.1
Lactic acidosis	15	Yes, DI (7.1)
Neutrophil count increased	15	No, Alt Ex
Rash (b) (4)	15	Yes, W/P (SCAR)
Toxic epidermal necrolysis‡	15	Yes, W/P (5.10)
Hypertension	14	Yes, AR (6.1)
Overdose	14	Yes, OVERDOSAGE (10)
Condition aggravated	12	No, U
Diarrhea	12	Yes, AR (6.1)
Dyspnea	12	Yes, W/P (5.3)
Hypersensitivity	12	Yes, W/P (5.3)
Multiple organ dysfunction syndrome	12	No, Alt Ex
Headache	11	Yes, AR (6.1)
Stevens-Johnson syndrome‡	11	Yes, W/P (5.10)
Abdominal pain	10	Yes, AR (6.1)
(b) (4)	10	Yes, W/P (5.3)
Fixed eruption	10	No, Alt Ex
Edema	10	Yes, W/P (5.3; diffuse or facial edema)
* A report can contain more than one MedDRA PT. † See Appendix A for proposed labeling. If the event is included in multiple sections of labeling, only the section of highest importance is listed. ‡ Designated medical event (DME). DMEs are defined below this table. § Reports of eosinophilia were co-reported with PTs indicative of rash or with the PT DRESS. Anaphylaxis and angioedema were added to the proposed hypersensitivity reactions warning by the DIRM clinical team based on their review of the applicant submission (FDA 2024).		

Table 8. Most Frequently Reported MedDRA PTs with N ≥ 10 with Iomeprol Received by FDA Through April 16, 2024, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT	Number of FAERS Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
Abbreviations: Alt Ex = Alternative explanation (disease-related, indication-related, procedure-related, or concomitant medication-related), AR = Adverse Reactions, DI = Drug Interactions, DRESS=drug reaction with eosinophilia and systemic symptoms, MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, SCAR=severe cutaneous adverse reactions, W/P = Warnings/Precautions, U = Uninformative		

Reviewer comments: We identified five unlabeled PTs among those listed in Table 8 (b) (4)

After screening the associated reports, we found that the events could be attributable to alternative explanations other than (b) (4) exposure (e.g., concomitant medication or disease-related), or the role of (b) (4) in the events could not be clinically assessed (e.g., absent temporal information, confounding by one or more concomitant medications).

We did not identify safety signals unrepresented in proposed iomeprol labeling from our screening of the PTs reported with iomeprol in FAERS.

3.1.2 Designated Medical Events

Designated Medical Events (DMEs) are adverse events that are considered serious and, from a pharmacovigilance perspective, may often be caused by exposure to drugs from many pharmacological or therapeutic classes. Identification of these events is a priority, even when the number of cases is small, and before there is evidence of disproportional reporting. DMEs are not intended to include events with a high prevalence in the general population. See Appendix D for a list of the Office of Surveillance and Epidemiology's (OSE) DMEs.

Table 9 lists the reported DMEs that were not captured above in Table 8 and the labeling status of each.

Table 9. Reported DMEs (Not Captured in Table 8) Received by FDA Through April 16, 2024, Sorted by Decreasing Number of FAERS Reports per PT		
DME MedDRA PT	Number of FAERS Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
Rhabdomyolysis	6	No, Alt Ex
Generalised tonic-clonic seizure	5	Yes, AR (6.2; convulsion)
Agranulocytosis	2	No, Alt Ex
Anaphylactoid reaction	2	Yes, W/P (5.3; hypersensitivity reactions)
Pancreatitis necrotising	2	No, Alt Ex
Pancytopenia	2	No, Alt Ex
Acute hepatic failure	1	No (<i>see below</i>)

Table 9. Reported DMEs (Not Captured in Table 8) Received by FDA Through April 16, 2024, Sorted by Decreasing Number of FAERS Reports per PT		
DME MedDRA PT	Number of FAERS Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
Electrocardiogram QT prolonged	1	No, Alt Ex
Status epilepticus	1	No, Alt Ex
Thrombotic thrombocytopenic purpura	1	No (<i>see below</i>)
* A report can contain more than one MedDRA PT. † See Appendix A for proposed labeling. If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: DME = Designated Medical Event, MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, W/P = Warnings/Precautions, AR = Adverse Reactions, Alt Ex = Alternative explanation (disease-related, indication-related, procedure-related, or concomitant medication-related)		

Reviewer comments:

The role of iomeprol in the single report of acute hepatic failure was not clinically assessable because the report lacked temporal information (time from iomeprol and co-suspect to event onset), and any explanation or context around reported events. The role of iomeprol in the single undetailed report of thrombotic thrombocytopenic purpura (TTP) was feasible but was confounded by concomitant drug clopidogrel which carries a warning for TTP. Thus, the report was not adequate to suggest the need for more specific labeling than thrombocytopenia which appears in 6.2 of proposed labeling.

We did not identify safety signals unrepresented in proposed iomeprol labeling from our screening of reported DMEs.

3.2 DATA MINING

Empirica Signal disproportionality results are displayed in Appendix E because two-thirds of the PTs were redundant of PTs addressed in Section 3.1.1.

Thirty drug-event combinations had an $EB05 \geq 2^c$ reported with iomeprol use, of which:

- 26 appear in proposed labeling for iomeprol; and
- 3 were unlabeled but captured above in Section 3.1.1 and were found to have alternate explanations other than iomeprol for the events (PTs fixed eruption, hepatic cytolysis, and multiple organ dysfunction syndrome).

The one remaining unlabeled drug-event combination with $EB05 \geq 2$ was mixed liver injury (n=5).

^c An $EB05 \geq 2$ indicates with 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background “expected.”

Reviewer comments: Our manual review of the five FAERS reports with the PT mixed liver injury revealed one unique report (FAERS ID 13467941 plus duplicates) that described two potential alternative etiologies (i.e., disease-related, concomitant medication-related) for the reported mixed liver injury.

We did not identify safety signals unrepresented in proposed iomeprol labeling from Empirica Signal data mining results.

3.3 LITERATURE

The literature search described in Section 2.3 identified 156 articles. We screened article titles (and abstracts or full text if the title was ambiguous) for mention of any adverse events and relevance to iomeprol safety, which narrowed the results to 62 articles. Table 10 summarizes the events with iomeprol reported in the 62 articles.

Table 10. Summary of Events with Iomperol Reported in the Medical Literature Through April 4, 2024		
(N=62 articles)		
Reported Events	Number of Articles	Reflected in Applicant's Proposed Labeling (Yes/No), Location* or Other Category
Hypersensitivity reactions (various)	18	Yes, W/P (5.3)
Nervous system disorders (various)	13	Yes, AR (6.1, 6.2)
Cutaneous adverse reactions (various)	11	Yes, W/P (5.10), AR (6.1) (<i>see below</i>)
Hemolytic anemia	4	Yes, AR (6.2)
Acute kidney injury	3	Yes, W/P (5.4)
Transient blindness	3	Yes, AR (6.2)
Salivary gland enlargement	2	Yes, AR (6.2)
Laboratory test interference	2	Yes, AR (6.2)
Hypothyroidism	1	Yes, W/P (5.8)
Thrombocytopenia	1	Yes, AR (6.2)
Pulmonary edema	1	Yes, AR (6.1)
Renal fornix rupture	1	No, Alt Ex
Rhabdomyolysis	1	No, Alt Ex
* See Appendix A for proposed labeling. If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: W/P = Warnings/Precautions, AR = Adverse Reactions, Alt Ex = Alternative explanation (disease-related, indication-related, procedure-related, or concomitant medication-related)		

Reviewer comments: After screening the 62 articles relevant to iomeprol safety, we found that 2 provided an alternative explanation for the event (i.e., concomitant medications), and the remaining 60 articles described adverse events consistent with proposed labeling for iomeprol.

Among the 11 publications describing cutaneous reactions to iomeprol were single case reports of fixed drug eruption (FDE) (n=1) and symmetrical drug-related intertriginous and flexural

exanthema (SDRIFE) (n=1).^d Both described cutaneous symptoms that could reasonably be attributed to iomeprol, based on our manual review of the publications (Watanabe et al. 1999; Arnold et al. 2007). Patients in both cases were diagnosed and treated (oral [FDE case] or topical [SDRIFE case] steroids) on an outpatient basis and recovered without sequelae. FDE and SDRIFE are not specifically named in proposed iomeprol labeling. However, because of the described non-serious manifestations and small number of cases we identified (n=1 each), we believe they are adequately represented within the mild to severe spectrum of skin and subcutaneous tissue disorders described in proposed language in Section 6.2 (see Appendix A).

We did not identify safety signals unrepresented in proposed iomeprol labeling from the medical literature.

3.4 VigiBASE

The VigiBase search on May 31, 2024, yielded 954 MedDRA PTs from a total of 8937 reports with iomeprol as a suspect drug, and with one or more serious outcomes.

We reviewed the labeling status for each of the 50 most frequently reported PTs (shown in Appendix F because many PTs are redundant of PTs in Section 3.1) and found that all are in proposed labeling for iomeprol, except for the 3 PTs shown in Table 11. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports (see Appendix C for VigiBase limitations).

Table 11. Unlabeled MedDRA PTs from the Top 50 Most Frequently Reported MedDRA PTs with Iomeprol in Reports with Serious Outcomes Received by VigiBase Through May 28, 2024, Sorted by Decreasing Number of VigiBase Reports per PT		
MedDRA PT	Number of VigiBase Reports*	Reflected in Applicant's Proposed Labeling[†] (Yes/No)
Tachycardia	180	No
Hyperhidrosis	129	No
Oxygen saturation decreased	87	No
* A report can contain more than one MedDRA PT. † See Appendix A for proposed labeling. Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term		

^d FDE presents as one or more erythematous and edematous plaques with a grayish center or frank bullae and characteristically recurs in the same locations upon re-exposure to the offending drug. After drug discontinuation, FDE typically resolves without treatment in a few days leaving postinflammatory hyperpigmentation, but corticosteroids and antihistamines may be used to relieve pruritis (Shiohara 2024).

SDRIFE presents as a sharply demarcated, V-shaped erythema in the gluteal/perianal or inguinal/perigenital areas, often with involvement of at least one other flexural or intertriginous fold, in the absence of systemic symptoms. Treatment includes stopping the suspected drug and topical or systemic corticosteroids (Samel 2023).

Reviewer comments: Lack of report narratives from Vigibase hindered our clinical assessment of the above unlabeled PTs reported with iomeprol. However, each unlabeled PT in Table 11 could be explained by one or more labeled events. For example, tachycardia is not unexpected in the setting of labeled severe hypersensitivity reactions (W/P) or cardiovascular adverse reactions (W/P); hyperhidrosis is not unexpected in the setting of hypersensitivity reactions or feeling hot (6.1); and oxygen saturation decreased is not unexpected in the setting of severe hypersensitivity reactions, pulmonary edema (6.1), or acute respiratory distress syndrome (6.2).

Based on the limited information available from Vigibase, we did not identify safety signals unrepresented in proposed iomeprol labeling from the top 50 most frequently reported PTs with iomeprol in Vigibase.

3.5 RELEVANT APPLICANT SUBMISSIONS

DPV's screening of the Applicant's ISS (Bracco 2023a) and 120 Day Safety Update (Bracco 2024a) did not identify safety signals unrepresented in proposed iomeprol labeling.

Applicant's Summary of Postmarketing Data

Collectively across the two documents, the Applicant summarized postmarketing data (spontaneous reports and reports identified from its literature surveillance) from its integrated global safety database from July 1, 1997, through December 31, 2023. The Applicant's summary of postmarketing data included report counts of serious versus non-serious events, certain events in the overall and in pediatric patients (e.g., number of cases with PTs in Standardized MedDRA Query [SMQ] hypersensitivity, SMQ anaphylactic reaction, SMQ Acute Renal Failure), and a listing of "adverse drug reactions" (ADRs) by System Organ Class (SOC) without report counts. The Applicant concluded that postmarketing data "demonstrates the good safety profile of iomeprol in routine clinical use" (Bracco 2023a). The Applicant did not describe an evaluation of causal relationship for any of the ADRs it identified from postmarketing data.

Applicant Evaluation of Safety Signals DPV Identified from Other Data Sources

Not applicable. Based on the information we reviewed, we did not identify safety signals for iomeprol that are unrepresented in proposed labeling.

Reviewer comments: The postmarketing ADRs identified by the Applicant align with its proposed labeling for the ADVERSE REACTIONS, Postmarketing Experience section. Our review of postmarketing data did not identify apparent omissions by the Applicant in its proposed labeling for iomeprol.

4 CONCLUSION

DPV reviewed multiple postmarketing data sources to identify safety signals for iomeprol, including FAERS reports received by FDA for iomeprol, Vigibase, the medical literature, and Applicant submissions. DPV did not identify any safety signals unrepresented in proposed iomeprol labeling from this high-level broad assessment of adverse events reported with iomeprol from available postmarketing data.

5 RECOMMENDATIONS

Based on this review, DPV does not have any recommendations at this time.

6 REFERENCES

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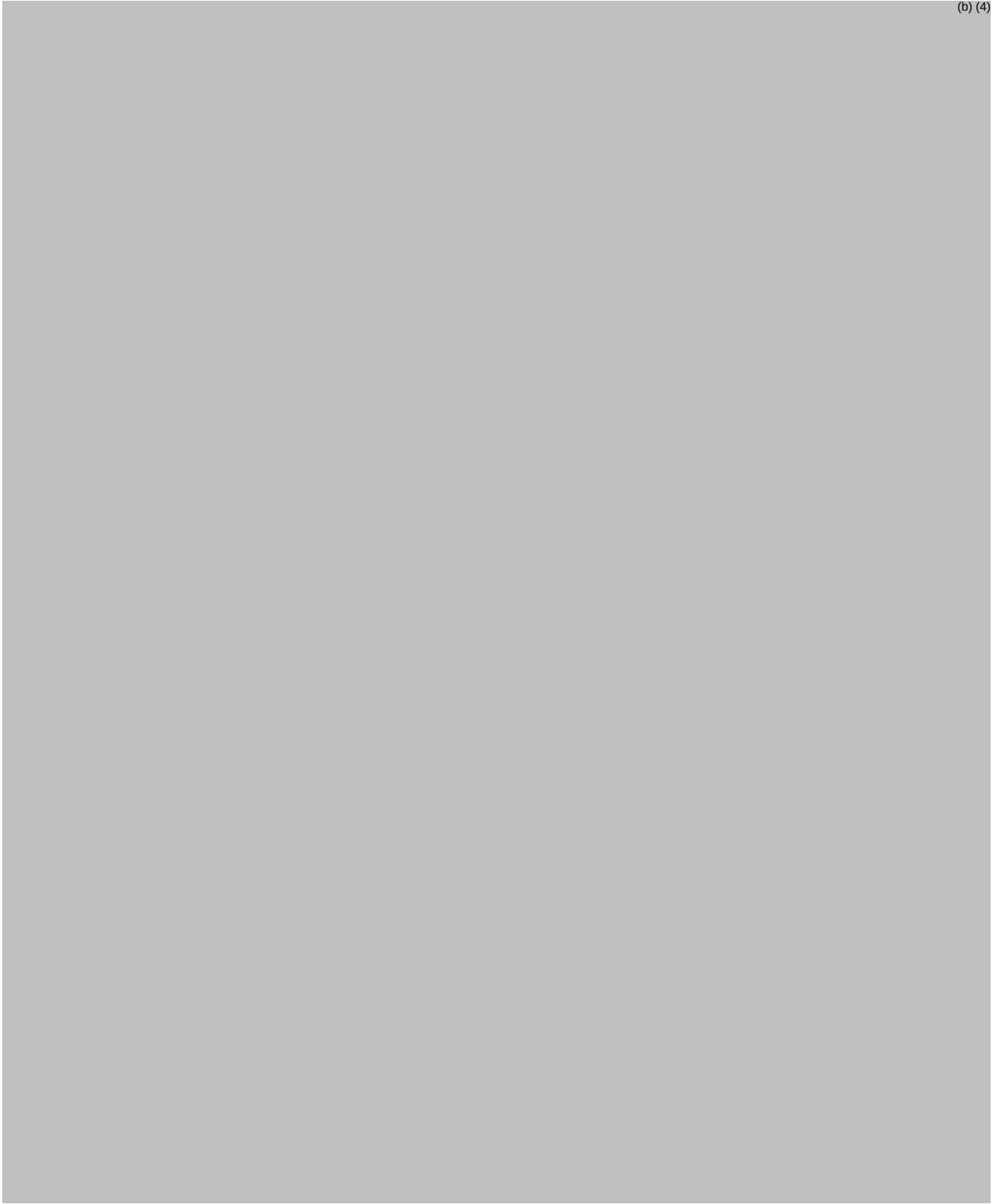
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7 APPENDICES

7.1 APPENDIX A. FULL TEXT OF RELEVANT PRODUCT LABELING

(b) (4)



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

7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether 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.

Data Mining of FAERS Using Empirica Signal

Empirica Signal refers to the software that the Office of Surveillance and Epidemiology (OSE) uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.3 APPENDIX C. VigiBASE DATABASE DESCRIPTION

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 approximately 150 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.

7.4 APPENDIX D. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA version 27.0)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Haemolytic uraemic syndrome
	Microangiopathic haemolytic anaemia
	Pancytopenia
	Thrombotic microangiopathy
	Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye disorders	Blindness
	Blindness transient
	Blindness unilateral
	Optic ischaemic neuropathy
	Sudden visual loss
	Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant
Immune system disorders	Anaphylactic reaction

System Organ Class	Preferred Terms (MedDRA version 27.0)
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock
	Immunotoxicity
Infections and infestations	Progressive multifocal leukoencephalopathy
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	New onset refractory status epilepticus
	Seizure
	Serotonin syndrome
	Status epilepticus
Product issues	Product compounding quality issue
	Product contamination
	Product contamination chemical
	Product contamination microbial
	Product contamination physical
	Product sterility issue
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	AGEP-DRESS overlap
	Drug reaction with eosinophilia and systemic symptoms
	Generalised bullous fixed drug eruption
	Severe cutaneous adverse reaction
	SJS-TEN overlap
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

7.5 APPENDIX E. FAERS DATA MINING DISPROPORTIONALITY RESULTS

Table 12 summarizes the Empirica Signal disproportionality results for drug-event combinations with $EB05 \geq 2$, sorted by descending EB05.

Table 12. Data Mining Results Using Empirica Signal for Events with $EB05 \geq 2$ Reported with Iomeprol Use, Sorted by Descending EB05			
MedDRA Preferred Term	N*	EB05†	Reflected in Applicant's Proposed Labeling (Yes/No) Location‡ or Other Category
Acute generalised exanthematous pustulosis	44	141.51	Yes, W/P
Rash (b) (4)	71	88.72	Yes, AR (rash; rash (b) (4))
Toxic skin eruption	35	87.50	Yes, W/P (SCAR)
Symmetrical drug-related intertriginous and flexural exanthema	7	76.71	Yes, AR (6.2; skin and subcutaneous tissue disorders: mild reactions... to severe...)
Drug reaction with eosinophilia and systemic symptoms	79	75.35	Yes, W/P
Eosinophilia	37	56.47	Yes, W/P (DRESS)
Contrast media allergy	6	42.38	Yes, W/P (hypersensitivity)
Rash (b) (4)	7	37.57	Yes, W/P (SCAR)
(b) (4)	10	20.86	Yes, W/P (SCAR)
Anaphylactic reaction	27	10.36	Yes, W/P (anaphylaxis [§])
Anaphylactic shock	17	10.10	Yes, W/P (circulatory collapse)
Acute kidney injury	71	7.65	Yes, W/P
(b) (4)	9	4.36	Yes, W/P
Dermatitis (b) (4) generalised	6	4.07	Yes, W/P (SCAR)
Toxic epidermal necrolysis	8	3.93	Yes, W/P
Erythema	27	3.57	Yes, AR 6.1
(b) (4)	7	3.47	Yes, W/P (acute kidney injury)
Eosinophil count increased	6	3.25	Yes, W/P (DRESS)
Rash (b) (4)	5	2.90	Yes, W/P (SCAR)
Rash pruritic	10	2.68	Yes, AR 6.1 (rash, pruritis)
Hyperthyroidism	6	2.63	Yes, W/P (thyroid storm)
Fixed eruption	4	2.43	No, Alt Ex
Urticaria	16	2.37	Yes, AR 6.1
(b) (4)	8	2.34	Yes, AR 6.1 (rash, erythema)
Mixed liver injury	4	2.33	No, Alt Ex
Hepatic cytolysis	6	2.23	No, Alt Ex
(b) (4) hypersensitivity	4	2.16	Yes, W/P
Multiple organ dysfunction syndrome	8	2.12	No, Alt Ex
Pruritus	29	2.01	Yes, AR 6.1

Table 12. Data Mining Results Using Empirica Signal for Events with EB05 $\geq$ 2 Reported with Iomeprol Use, Sorted by Descending EB05

MedDRA Preferred Term	N*	EB05†	Reflected in Applicant's Proposed Labeling (Yes/No) Location‡ or Other Category
Drug interaction	16	2.01	Yes, W/P (concomitant nephrotoxic drugs) and DI (metformin)

* A report can contain more than one MedDRA PT.

† An EB05 $\geq$ 2 indicates with 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background “expected.”

‡ See Appendix A for proposed labeling. If the event is included in multiple sections of labeling, only the section of highest importance is listed.

§ Anaphylaxis and angioedema were added to the proposed hypersensitivity reactions warning by the DIRM clinical team based on their review of the applicant submission (FDA 2024).

|| Reports of eosinophilia were co-reported with PTs indicative of rash or with the PT DRESS.

Abbreviations: Alt Ex = Alternative explanation (disease-related, indication-related, procedure-related, or concomitant medication-related), AR = Adverse Reactions, DI = Drug Interactions, DRESS=drug reaction with eosinophilia and systemic symptoms, MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, SCAR=severe cutaneous adverse reactions, W/P = Warnings/Precautions

7.6 APPENDIX F. VigiBASE – TOP 50 MOST FREQUENTLY REPORTED PREFERRED TERMS

We reviewed the labeling status for each of the 50 most frequently reported PTs for iomeprol in VigiBase as shown in Table 13. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports (see Appendix C for VigiBase limitations).

PTs in **bold font** were not captured by FAERS data summarized in Sections 3.1 and 3.2. PTs identified as unlabeled in Table 13 are discussed in Section 3.4.

Table 13. Top 50 Most Frequently Reported MedDRA PTs with Iomeprol in Reports with Serious Outcomes Received by VigiBase Through May 28, 2024, Sorted by Decreasing Number of VigiBase Reports per PT		
MedDRA PT	Number of VigiBase Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
Urticaria	1,296	Yes, AR 6.1 [‡]
Dyspnoea	1,155	Yes, W/P [‡]
Anaphylactic shock	1,114	Yes, W/P [‡] §
Pruritus	904	Yes, AR 6.1 [‡]
Erythema	814	Yes, AR 6.1 [‡]
Rash	698	Yes, AR 6.1 [‡]
Anaphylactic reaction	660	Yes, W/P [‡] §
Hypotension	550	Yes, AR 6.1 [‡]
Nausea	483	Yes, AR 6.1
Hypersensitivity	472	Yes, W/P [‡]
Vomiting	413	Yes, AR 6.1
(b) (4) hypersensitivity	401	Yes, W/P [‡]
Cough	323	Yes, AR 6.1
Angioedema	283	Yes, W/P [‡] §
(b) (4)	250	Yes, W/P [‡]
Contrast media reaction	249	Yes, W/P (hypersensitivity) [‡]
Dizziness	235	Yes, AR 6.1
Loss of consciousness	232	Yes, AR 6.2
Blood pressure decreased	231	Yes, AR 6.1 (hypotension) [‡]
Laryngeal oedema	208	Yes, W/P
Acute kidney injury	207	Yes, W/P [‡]
Cardiac arrest	201	Yes, AR 6.2
Rash (b) (4)	182	Yes, AR 6.1 (rash, rash (b) (4)) [‡]
Tachycardia	180	No
Flushing	174	Yes, AR 6.1
Malaise	173	Yes, AR 6.1
Sneezing	159	Yes, AR 6.1
Bronchospasm	149	Yes, W/P
Shock	145	Yes, W/P (circulatory collapse) [‡]

Table 13. Top 50 Most Frequently Reported MedDRA PTs with Iomeprol in Reports with Serious Outcomes Received by Vigibase Through May 28, 2024, Sorted by Decreasing Number of Vigibase Reports per PT		
MedDRA PT	Number of Vigibase Reports*	Reflected in Applicant's Proposed Labeling (Yes/No), Location† or Other Category
(b) (4)	142	Yes, W/P (b) (4)
Cardio-respiratory arrest	132	Yes, W/P (respiratory arrest)
Hyperhidrosis	129	No
Rash (b) (4)	129	Yes, AR (rash, pruritis) ‡
Anaphylactoid reaction	128	Yes, W/P (hypersensitivity) ‡
Throat irritation	118	Yes, AR 6.1
Respiratory distress	109	Yes, W/P (dyspnea, respiratory arrest) ‡
Chest (b) (4)	106	Yes, AR 6.1
Chills	106	Yes, AR 6.1
Syncope	103	Yes, AR 6.2
Feeling hot	100	Yes, AR 6.1
Chest pain	99	Yes, AR 6.1
Dysphonia	97	Yes, AR 6.2
(b) (4)	97	Yes, W/P (facial edema/angioedema) ‡ §
Headache	96	Yes, AR 6.1 ‡
Cyanosis	95	Yes, AR 6.2
(b) (4) of consciousness	95	Yes, AR 6.2 (loss of consciousness)
Throat tightness	93	Yes, W/P (laryngeal edema)
(b) (4)	88	Yes, W/P (b) (4) /angioedema) ‡ §
Oxygen saturation decreased	87	No
Oedema	81	Yes, W/P (b) (4) edema) ‡
* A report can contain more than one MedDRA PT. † See Appendix A for proposed labeling. If the event is included in multiple sections of labeling, only the section of highest importance is listed. ‡ Event also identified on FAERS reports with iomeprol (see sections 3.1 and 3.2). § Anaphylaxis and angioedema were added to the proposed hypersensitivity reactions warning by the DIRM clinical team based on their review of the applicant submission (FDA 2024). Abbreviations: AR = Adverse Reactions, MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, SCAR=severe cutaneous adverse reactions, W/P = Warnings/Precautions		

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/s/

DANIELLE M MOLNAR
07/19/2024 12:53:58 PM

MALLIKA L MUNDKUR
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STEVEN C JONES
07/19/2024 08:28:12 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Date: 06/25/24 **Date consulted:** 04/15/24

From: Sarah Sheikh, DO Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS Team Leader, Maternal Health, DPMH

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

To: Frank Lutterodt, Regulatory Project Manager (RPM)
Division of Imaging and Radiation Medicine (DIRM)

Drug: (b) (4) (iomprol injection) for intravascular administration
(iomprol injection) for intraarterial administration

NDA 216017; 216016

Applicant: Bracco Diagnostics Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication:

(b) (4) (iomprol) is a radiographic contrast agent for:
Intravenous Procedures
Adult and Pediatric patients

- Computed tomography (CT) of head and body
- Computed tomography angiography (CTA)
- Coronary computed tomography angiography (CCTA)
- (b) (4)
- Computed tomography (CT) urography

Intra-arterial Procedures

Adults

- Coronary arteriography and ventriculography
- Cerebral, peripheral and visceral arteriography, and aortography

Pediatric patients

- (b) (4)
- Cerebral, peripheral and visceral arteriography, and aortography including digital subtraction angiography

Materials Reviewed:

- DPMH consult request dated 4/15/2024, DARRTS Reference ID: 5364265
- Applicant's submitted background package and proposed labeling for NDA 216017, Sequence Number (SN) 009
- Applicant's submitted background package and proposed labeling for NDA 216016, Sequence Number (SN) 007
- Prior DPMH PLLR Review of Isovue and Isovue-M (iopamidol injection) NDA 018735/Seq 0068; 018735/Seq 0075 by Kristie Baisden, DO dated 3/18/24, DARRTS reference ID: 5348304¹
- Information request (IR), sent on 05/28/24
- Applicant's response to IR submitted on 5/31/2024

Consult Question:

DIRM requests DPMH review the Prescribing Information (PI), specifically subsections 8.1 Pregnancy and 8.2 Lactation

INTRODUCTION

On December 14, 2023, the applicant, Bracco Diagnostics, submitted a New Drug Application (NDA) as a 505 (b)(2) submission for iomeprol IV and IA with the proposed indications for intravenous (IV) use with CT examinations and intraarterial (IA) use with diagnostic interventional procedures requiring radiographic contrast.

DIRM consulted DPMH on April 15, 2024, to review the PI or the *Pregnancy* and *Lactation* subsections of labeling.

BACKGROUND

Regulatory History

- (b) (4) is a water-soluble, non-ionic radiopaque contrast imaging agent which has not been previously approved in the US. It was first approved in the United Kingdom on

¹ DPMH did not rely on data in the Isovue and Isovue-M (iopamidol injection) NDA or the Agency's finding of safety and effectiveness for Isovue and Isovue-M (iopamidol injection) to support labeling sections of this (b) (4) NDA. Rather, the cross-reference to the above-mentioned DPMH consult is included to avoid duplicating background information relevant to this class of products.

December 1, 1992, for intravenous, intraarterial, and intrathecal, and intracavitary procedures. It is currently approved in 50 countries worldwide.

- On November 23, 2021, and December 10, 2021, the applicant, Bracco Diagnostics, submitted two new drug applications (NDAs) for (b) (4) (iomeprol injection) with the proposed indications for intravenous (IV) use with CT examinations and intraarterial (IA) use with diagnostic interventional procedures requiring radiographic contrast. FDA issued a Refusal to File letter on January 21, 2022, after preliminary review, finding Bracco's applications not to be sufficiently complete for a substantive review.
- On December 14, 2023, the applicant, Bracco Diagnostics, resubmitted a New Drug Application (NDA) as a 505 (b)(2) submission for iomeprol IV and IA for indications as listed above. The applicant is relying upon both clinical studies performed by or on behalf of the applicant, as well as literature articles based on studies not conducted by the applicant. There is no listed drug (LD).
- DIRM consulted DPMH on April 15, 2024, to review the PI or the Pregnancy and Lactation subsections of labeling.
- On May 28, 2024, the Agency sent the applicant an information request (IR) for a clarification on whether their pharmacovigilance database included iomeprol-exposed patients in pregnancy or lactation during clinical trials.

Drug Characteristics²

- *Description:* iomeprol is a tri-iodinated, non-ionic radiographic contrast agent that is highly water-soluble
- *Dosage and administration:* varies by procedure and age, body weight, size of the vessel, the rate of blood flow within the vessel, and structures or areas to be examined.
- *Mechanism of action:* opacifies the vessels and body structures where the contrast agent is present following intravenous or intra-arterial administration, permitting their radiographic visualization of internal structures through attenuation of X-ray photons.
- *Half-life:* 1.8 ± 0.33 hours
- *Protein binding:* Does not bind to plasma proteins
- *Bioavailability:* 100 %
- *Contraindications:* None
- *Severe adverse events:* severe adverse events with inadvertent intrathecal administration, life threatening hypersensitivity reactions, acute injury including renal failure, increased risk of severe adverse reaction with history of cardiovascular disease, thyroid dysfunction in pediatric patients 0 to 3 years of age, hypertensive crisis in patient with pheochromocytoma, sickle cell crisis in patients with sickle cell disease, severe cutaneous adverse reactions, aggravation of myasthenia gravis, and interference with protein-bound iodine lab test.

² From working draft labeling (b) (4) IV IA and email correspondence with Clinical Pharmacology, Clinical, and Pharmacology/Toxicology teams

REVIEW

PREGNANCY

Nonclinical experience

According to the applicant, no adverse developmental outcomes were observed with IV administration of iomeprol to rats and rabbits at doses up to 3.3 (rat) and 1.7 (rabbit) times the maximum recommended human dose. Reproduction studies were performed with IV administration of iomeprol to rats at daily doses of 0.6, 1.5, or 4.0 g iodine/kg and to rabbits at daily doses of 0.3, 0.8, or 2.0 g iodine/kg. The treatment was continued until completion of embryogenesis. Iomeprol did not have adverse effects on gestation, did not affect fetal development and did not induce teratogenic changes in the offspring.

An animal study with intravenous administration of 1g iodine/kg of radiolabelled iomeprol to pregnant rats showed that iomeprol crosses the placenta. The labelled compound was more prone to cross the placenta during the first half of pregnancy than towards the end. No accumulation of radioactivity in fetal tissues occurred.

The reader is referred to the full Pharmacology/Toxicology review by Drs. Yanli Ouyang and Jonathan Cohen.

Applicant's Review of Pharmacovigilance Database

The applicant reviewed cases from their global pharmacovigilance database cumulatively up to June 30, 2023, and found 21 cases of exposure to iomeprol during pregnancy. Refer to the Appendix: Applicant's Table A for details regarding the list of the 21 cases.³ In 12 cases, no information on the pregnancy outcome was given. In the remaining 9 cases, the outcomes include: 7 live births (5 full-term and 2 pre-term births), 1 pregnancy termination, and 1 spontaneous abortion.

Reviewer comment: Although the applicant has stated no congenital anomalies/perinatal complications were reported in any of the 21 cases, there are only 7 cases that were evaluable for congenital abnormalities. Outcomes were unknown in 12 cases. In addition, miscarriage was reported at 8 weeks in a 40-year-old patient with Sjogren's syndrome and voluntary termination was reported at 6 weeks in a 23-year-old patient with unknown medical history. Finally, a premature delivery due to preeclampsia was reported in a 38-year-old patient after 30 weeks gestation, which is considered a perinatal complication.

Applicant's Review of Published Literature

The applicant performed a cumulative literature search with the following strategy:

- Databases: BIOSIS Previews, Derwent Drug File, Embase, MEDLINE;
- Search terms: (pregnancy or "fetation" or "gestation" or "gravidism" or "graviditas" or "pregnancies") AND (Iomeron or iomeprol or imeron);
- Limits: up to 30 June 2023

³ Applicant's submission document titled, "Information in Support of Proposed Language Regarding Pregnancy Lactation Labeling Rule (PLLR)."

A total of 16 publications were retrieved, including 14 publications in humans and 2 in animals. Among the 14 publications in humans, only 7 publications were relevant. These included 2 case reports involving administration of iomeprol to pregnant or lactating female patients for clinical reasons, 1 systematic review of papers with use of iodinated contrast agents before or during pregnancy, 3 guidelines from scientific societies reporting on recommendations on the use of iodinated contrast agents in pregnant women and 1 guideline on use in lactating women.

The publications relevant to pregnancy exposure are briefly summarized below.

Case studies (n = 1)

- **Akpinar E, et al.**⁴ describes a case report involving an 18-year-old at 29 weeks gestation, who was admitted with dyspnea and edema, along with no fetal movement for 3 weeks. Fetal cardiac activity was confirmed on ultrasound on admission. Chest CT with iomeprol was performed and findings were indicative of pulmonary embolism. The patient's clinical status rapidly deteriorated, despite intubation and sedation, as she developed cardiac arrest and expired. The baby was delivered via cesarean section with an Apgar score of 0 at birth. The baby was pronounced dead after 20 minutes of CPR. No pathologic diagnosis was available due to declined autopsy by the patient's family.

Reviewer's comment: Although iomeprol was administered to a pregnant patient in the described case report, no conclusion can be drawn on the safety of the drug given the clinical scenario of fetal demise and no fetal autopsy performed.

Systematic review (n =1)

- **Van Welie N, et al.**⁵ conducted a systematic review of published studies reporting on the impact of iodinated contrast agents prior to or during pregnancy on the neonatal thyroid function. From a total of twenty-six (26) publications identified, 6 studies involved maternal exposure to iodinated contrast media preconceptionally during a hysterosalpingogram (HSG) and 20 studies included maternal exposure during pregnancy for amniotography, urography, or CT scanning. The selected publications included a variety of iodinated contrast media such as oil-based agents, water-soluble ionic, and non-ionic agents. As summarized by the authors, cohort studies included in the review show that the proportion of (transient) neonatal thyroid dysfunction is low after exposure to iodinated contrast agents before or during pregnancy, with the exception of amniotography. Amniotography involves direct injection of iodinated contrast into the fetal compartment.

Guidelines/Position papers from Scientific Societies (n=3)

- The European Society of Urogenital Radiology (ESUR) conducted a literature review and derived guidelines in 2005 for use of iodinated contrast agents in pregnancy, concluding

⁴ Akpinar E, Akpinar B, Turkbey B, Deren O, Ariyurek M. PVOD suggested by MDCT and clinical findings in a pregnant woman. *Emerg Radiol.* 2008;15:193-95.

⁵ Van Welie N, et al. Iodine contrast prior to or during pregnancy and neonatal thyroid function: a systematic review. *Eur J Endocrinol* 2021; 184:189-198.3

there is no evidence that exposure of the fetus to water soluble iodinated agents is associated with hypothyroidism⁶. An updated on the guidelines released in March 2018⁷ made no changes to their recommendations, stating “*in exceptional circumstances, when radiographic examination is essential, iodine-based contrast media may be given to the pregnant mother. Following administration of iodine-based contrast media to the mother during pregnancy, thyroid function should be checked in the neonate during the first week.*”

- The applicant noted guidelines from The American College of Radiology (ACR)⁸ are aligned with ESUR regarding use of iodinated contrast agents in pregnancy and lactation. ACR recommendations state,
“*We do not recommend withholding the use of iodinated contrast agents in pregnant or potentially pregnant patients when it is needed for diagnostic purposes. Given the current available data and routine evaluation of all newborns for congenital hypothyroidism by measurement of TSH levels at the time of their birth, no extra attention is felt to be necessary.*”
- The American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice recommended the following about use of iodinated contrast media in pregnancy⁹:
“*Although iodinated contrast media can cross the placenta and either enter the fetal circulation or pass directly into the amniotic fluid, animal studies have reported no teratogenic or mutagenic effects from its use. Additionally, theoretical concerns about the potential adverse effects of free iodide on the fetal thyroid gland have not been borne out in human studies. Despite this lack of known harm, it generally is recommended that contrast only be used if absolutely required to obtain additional diagnostic information that will affect the care of the fetus or woman during the pregnancy.*”

Reviewer comment:

The applicant stated there are no available clinical data of iomeprol in pregnant women to inform about the drug associated risk of miscarriage or major congenital malformations. There are no completed or ongoing pregnancy registries with iomeprol; however, the applicant concludes the available post-marketing data suggests no harm to the fetus following maternal exposure to Iomeprol during pregnancy. This reviewer concludes more information is needed to inform on the safety of Iomeprol use in pregnant women and the fetus; however, diagnostic

⁶ Webb JA, et al. The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol* 2005; 15:1234-1240.4

⁷ European Society of Uroradiology (ESUR) guidelines, version 2019. Available at: [https://www.esur.org/fileadmin/content/2019/ESUR Guidelines 10.0 Final Version](https://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version). Accessed on October 16, 2023.

⁸ ACR Manual on Contrast Media.2023. Administration of contrast media to pregnant or potentially pregnant patients, pages103-104; Administration of contrast media to women who are breast-feeding, page 107.

⁹ Copel J, El-Sayed Y, Heine RP, et al. Guidelines for diagnostic imaging during pregnancy and lactation. Committee Opinion No. 723. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017; 130: e210-216

studies which require administration of Iomeprol should not be withheld in pregnant women based on the existing published data.

DPMH's Review of Published Literature

This Reviewer performed a published literature search in PubMed, Embase, Micromedex¹⁰ TERIS¹¹, and Reprotox¹² to find relevant articles not cited by the applicant.

Search terms included “Iomeprol” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” OR “miscarriage.”

- No new literature was found other than the literature presented by the applicant.

LACTATION

Nonclinical Experience

According to the applicant, intravenous administration of 0.5 g iodine/kg of radiolabeled iomeprol to nursing rats showed that the contrast agent distributed into the milk. Iomeprol levels in the milk peaked at 6 hours after administration with mean values corresponding to approximately 6% of the highest concentration found in plasma of nursing dams.

For further details, the reader is referred to the full Pharmacology/Toxicology review by Drs. Yanli Ouyang and Jonathan Cohen.

Review of Pharmacovigilance Database

The applicant searched the Bracco global safety database up to June 30, 2023, and cumulatively identified seven reports of exposure to Iomeron during lactation. Six reports were not associated with any other adverse events (AEs) in the mother or the child. In the seventh case, transient neonatal hypothyroidism was reported in a 17-day-old preterm infant after the lactating mother underwent a CT examination with Iomeron. This case was retrieved from the literature and will be presented below under *Applicant's Review of Literature*.

Applicant's Review of Literature

The applicant performed a cumulative literature search with the following strategy:

- Databases: BIOSIS Previews, Derwent Drug File, Embase, MEDLINE;
- Search terms: (lactation or “prolonged lactation”) AND (Iomeron or iomeprol or imeron);
- Limits: up to 30 June 2023

The applicant identified one case report in which Iomeprol was given to a lactating female patient for clinical reasons. The case study is summarized below:

- ***Themelin C et al.*¹³** describes a 33-year-old female patient who delivered a preterm male infant by cesarean section due to preeclampsia at 31 weeks. The mother had a history of

¹⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 05/20/2024.

¹¹ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 05/20/2024.

¹² Reprotox Website: www.Reprotox.org. Accessed 05/20/2024.

¹³ Themelin C, Pierron C, Calafat JF, de Beaufort C. Transient neonatal hypothyroidism secondary to postnatal maternal exposure to contrast medium. *BMJ Case Rep*. 2019 Oct 15;12:e230854.

subclinical hypothyroidism and was taking L-thyroxin for the previous 8 years. The mother underwent CT pulmonary angiography four days after delivery with administration of Iomeprol to exclude pulmonary embolism. She discontinued breastfeeding for 24 hours as advised. Neonatal screening tests performed day 4 of life showed an elevated 17-hydroxy-progesterone (17-OH-P) and a normal thyrotropin (TSH). Screening tests were repeated at postnatal day 17 and showed normal levels of 17-OH-P, increased levels of TSH, and decreased levels of free T4 (FT4). After normal thyroid imaging confirmed, the neonate was started on thyroid replacement treatment. Thyroid function rapidly normalized after 35 days of treatment and a 7 month follow up visit confirmed normal levels of TSH and FT4. The authors conclude “although the risk of neonatal transient hypothyroidism during breastfeeding seems rare, current timelines for lactation interruption may need adjustment if the lactating mother of preterm infants has to undergo imaging with contrast administration”.

Reviewer’s comment:

In the case report described above, the timing of the transient neonatal hypothyroidism development and administration of iodinated contrast to the lactating mother raise concern about the effects of iodine in the preterm neonate. The lactating mother discontinued breastfeeding for 24 hours after iodinated contrast administration. Given the short half-life of iomeprol (about 2 hours), the neonate did not receive breastmilk for more than 5 elimination half-lives after Iomeprol administration, which would indicate low probability of free iodine causing the transient neonatal hypothyroidism. Another factor to consider as a cause for the transient neonatal hypothyroidism could be the preterm status of the infant, leading initially to normal thyroid testing followed by abnormal testing due to the immaturity of the neonatal hypothalamic-pituitary-thyroid axis.

Guidelines/Position papers from Scientific Societies

- Webb JA, et al.’s¹⁴ publication states there is evidence indicating only a very small amount of contrast reaches the infant’s blood when a lactating mother is given iodinated contrast agents intravascularly. Based on this information, ESUR members conclude “breastfeeding may be continued normally when iodine-based contrast media are given to the mother during lactation”.
- ACR’s¹⁵ position on administration of contrast during lactation is as follows:

“The plasma half-life of intravenously administered iodinated contrast medium is approximately 2 hours, with nearly 100% of the media cleared from the bloodstream in patients with normal renal function within 24 hours. Because of its low lipid solubility, less than 1% of the administered maternal dose of iodinated contrast medium is excreted into the breast milk in the first 24 hours.

¹⁴ Webb JA, et al. The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol 2005; 15:1234-1240.4

¹⁵ ACR Manual on Contrast Media.2023. Administration of contrast media to pregnant or potentially pregnant patients, pages103-104; Administration of contrast media to women who are breast-feeding, page 107.6

Therefore, the expected systemic dose absorbed by the infant from the breast milk is less than 0.01% of the intravascular dose given to the mother... it is safe for the mother and infant to continue breast-feeding after receiving such an agent.”

- A joint working group comprised of the The Italian Society of Radiology (SIRM), the Italian Society of Pediatrics (SIP), the Italian Society of Neonatology (SIN), and Task Force on Breastfeeding, Italian Ministry of Health published a position paper on the safety profile of radiologic contrast media in breastfeeding women in 2014.¹⁶ The paper summarized published medical literature on the use of contrast agents during breastfeeding, which included a comprehensive review of clinical trials, reviews, guidelines, case reports, commentaries/letters/editorials, original studies, and textbooks. Although relative to different classes of contrast media, reported data for iodinated contrast agents share similar pharmacokinetic parameters, with a negligible excretion into breast milk after administration to the breastfeeding mother. Iodine-based agents are poorly absorbed from breast milk by the gastrointestinal tract of the nursing infant. Based on the available evidence, the working group concluded,
“Breastfeeding is safe for the nursing infant of any post-conception age after administration to the mother of all iodine-based contrast media. There is no need to discontinue breastfeeding for 24-48 hours after the administration of contrast media or to express and discard breast milk.”
- ACOG Committee on Obstetric Practice¹⁷ advises the following regarding use of iodinated contrast media during lactation:
“Traditionally, lactating women who receive intravascular iodinated contrast have been advised to discontinue breastfeeding for 24 hours. However, because of its water solubility, less than 1% of iodinated contrast administered to a lactating woman is excreted into the breast milk, and less than 1% of this amount of contrast will be absorbed through the infant’s gastrointestinal tract. Therefore, breastfeeding can be continued without interruption after the use of iodinated contrast.”

DPMH Review of Literature:

DPMH conducted an updated search of literature in PubMed and Embase, Micromedex¹⁸, Hale’s *Medications and Mothers’ Milk*¹⁹, Reprotox, the Drugs and Lactation Database (LactMed)²⁰, and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*²¹, using the search terms “ioimeprol” and “lactation” or “breastfeeding.”

¹⁶ Cova MA et al. Radiological contrast media in the breastfeeding woman: A position paper of the Italian Society of Radiology (SIRM), the Italian Society of Paediatrics (SIP), the Italian Society of Neonatology (SIN) and the Task Force on Breastfeeding, Ministry of Health. Eur Radiol 2014; 24:2012-2022.7

¹⁷ Copel J, El-Sayed Y, Heine RP, et al. Guidelines for diagnostic imaging during pregnancy and lactation. Committee Opinion No. 723. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017; 130: e210-216

¹⁸ Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 5/24/24.

¹⁹ Hale, Thomas W. Hale’s Medications & Mothers’ Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com

²⁰ Drugs and Lactation Database (LactMed). Accessed 5/24/24

²¹ Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

- No new literature was found other than the literature presented by the applicant.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

According to applicant proposed draft labeling, nonclinical data reveal no special hazard for humans based on conventional studies of genotoxicity or fertility studies in rats. At the writing of this review, the Pharmacology Toxicology review was ongoing. For further details and conclusion regarding nonclinical studies, the reader is referred to the full Pharmacology/Toxicology review by Drs. Yanli Ouyang and Jonathan Cohen.

Review of Pharmacovigilance Database

The applicant performed a comprehensive search in the Bracco global safety database to identify reports related to fertility in male and female patients exposed to Iomeprol. One single non serious case with 2 associated events in Preferred Terms (PTs) was found: Menstruation delayed and Ovulation disorder.

The applicant concluded the findings suggest no adverse association between iomeprol administration and infertility.

Applicant's Review of Literature

The applicant performed a cumulative literature search with the following strategy:

- Databases: BIOSIS Previews, Derwent Drug File, Embase, MEDLINE;
- Search terms: (fertility) AND (Imeron or iomeprol or imeron);
- Limits: up to 30 June 2023

The applicant stated no articles were identified that reported on potential effects of Iomeprol upon fertility in male or female subjects.

DPMH Review of Published Literature

DPMH conducted a literature search in Micromedex, Reprotox, and TERIS²², using the search terms “iomeprol” AND “fertility,” “contraception,” “oral contraceptives,” OR “infertility.”

- No relevant published literature was found.

DISCUSSION AND CONCLUSIONS

Pregnancy

DPMH reviewed published literature and applicant's pharmacovigilance case reports regarding iomeprol use during pregnancy. There is over 30 years of post-marketing experience outside of the US and nine pregnancy cases with known outcomes reported in pharmacovigilance, which are insufficient to evaluate the potential for congenital malformation or other adverse maternal or fetal outcomes. Post-marketing data provided by the applicant are limited but the available published information does not identify adverse effects in the fetus following maternal exposure to iomeprol during pregnancy. In addition to the limited quantity of the data, a majority of postmarketing case reports by the applicant included unknown pregnancy outcomes.

Both ESUR and ACR do not recommend withholding use of iodinated contrast agents for diagnostic purposes in pregnancy. ACOG acknowledges the theoretical fetal risk of neonatal

²² TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 4/23/24.

hypothyroidism but, due to the lack of known harm, advises iodinated contrast agents should be used only if necessary for diagnostic purposes during pregnancy. Therefore, DPMH recommends including a statement in subsection 8.1 Pregnancy labeling based on the available ex-US data from postmarketing reports that iomeprol use in pregnant females from decades of use have not identified a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Regarding postmarketing requirements (PMRs), iomeprol is anticipated to be widely used in females of reproductive potential, including pregnant women. Given the available human pregnancy data from outside the US over several decades of use of iomeprol, DPMH does not recommend issuing a PMR for a pregnancy safety study but would recommend routine pharmacovigilance to report on any pregnancy exposures.

Lactation

There are no data on the presence of iomeprol in human milk following maternal IV or IA administration. Iomeprol is present in animal milk. There are no data on the effects of iomeprol on the breastfed infant or milk production. Although iomeprol is not currently available in the US, ACOG notes that other iodinated contrast agents are excreted unchanged in human milk in low amounts and are poorly absorbed from breast milk by the gastrointestinal tract of the nursing infant.²³ Clinical guidelines and position papers do not recommend withholding breastfeeding after use of other iodinated contrast agents.

DPMH recommends including the standard benefit/risk statement in Subsection 8.2 labeling. In addition, for consistency with PLLR labeling for other iodinated contrast media, DPMH recommends adding the following under Clinical Consideration specific to breastfeeding recommendations:

“Interruption of breastfeeding after exposure to iodinated contrast agents is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 elimination half-lives) after (b) (4) administration in order to minimize drug exposure to a breast fed infant.”

DPMH does not recommend issuing a PMR for a clinical lactation study but would recommend routine pharmacovigilance to report on any lactational exposures.

Females and Males of Reproductive Potential

There were no adequately designed and conducted reproductive toxicity studies in animals to evaluate the effects of iomeprol on fertility. There are no available human data to suggest iomeprol adversely effects male or female fertility. Therefore, DPMH recommends omitting labeling subsection 8.3 Females and Males of Reproduction Potential.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 06/14/2024. DPMH refers to the final NDA action for final labeling.

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

APPENDIX

Table A –Applicant’s Pharmacovigilance data in pregnancy

Table A: Cumulative Reports of Exposure to Iomeron During Pregnancy from (b) (6)

Case ID / Country	Safety Date, Follow-up Date	Mother's Age	Length of Pregnancy at Time of Exposure	Procedure and Indication as Reported	Route of Administration	Event MedDRA PT	Clinical Event as Reported	Type of Birth	Pregnancy Outcome
(b) (6)		---	2 trimester (24 Weeks)		Cutaneous	Accidental exposure to product, No adverse event, Pregnancy	Inadvertent exposure to drug, No adverse reaction during or after the procedure, Pregnancy	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		---	1 trimester (12 Weeks)	CT scan	Intravenous (not otherwise specified)	Pregnancy	Pregnancy	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		25 years	3 trimester (32 Weeks)	CT angiogram	---	No adverse event, Pregnancy	No adverse effect during or after the procedure, Pregnancy	Full-term	Normal birth of a baby on (b) (6) (b) (6) unknown gender and weight of the newborn
(b) (6)		23 years	1 trimester (6 Weeks)	Abdomino-pelvic CT scan	Intravenous (not otherwise specified)	Maternal exposure during pregnancy	Maternal exposure during pregnancy	Elective Termination	Elective Termination
(b) (6)		29 years	2 trimester (21 Weeks)	Pulmonary CT angiography for suspected pulmonary embolism	Intravenous (not otherwise specified)	Maternal exposure during pregnancy, No adverse event	Maternal exposure during pregnancy, No adverse event during or after the procedure	Full-term	Normal birth of a male baby on (b) (6) (b) (6) No congenital abnormality or birth defect was diagnosed. No complications, infections or illnesses during pregnancy.

Case ID / Country	Safety Date, Follow-up Date	Mother's Age	Length of Pregnancy at Time of Exposure	Procedure and Indication as Reported	Route of Administration	Event MedDRA PT	Clinical Event as Reported	Type of Birth	Pregnancy Outcome
(b) (6)		24 years	1 trimester (7 Weeks)	CT scan	Intravenous (not otherwise specified)	Maternal exposure during pregnancy, No adverse event	Injection of Iomeron® 400 at seven weeks of amenorrhea, No adverse event during or after the procedure	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		---	1 trimester (11 Weeks)	CT scan for unknown indication	---	Maternal exposure during pregnancy, No adverse event	Maternal exposure during pregnancy, No adverse event during or after the procedure	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		---	---	CT scan for unknown indication	Intravenous (not otherwise specified)	Maternal exposure during pregnancy, No adverse event	Maternal exposure during pregnancy, No adverse event during or after the procedure	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		43 years	3 trimester (29 weeks)	Scan with contrast due to unknown indication	Intravenous (not otherwise specified)	Infusion site extravasation ; Maternal exposure during pregnancy	Contrast media extravasation, Maternal exposure during a twin pregnancy at 29 weeks of gestation	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		22 years	---	Diagnostic procedure NOS due to abdominal pain	---	Maternal exposure during pregnancy	Injection of Iomeron® in a pregnant female patient	Information not made available to Bracco	Information not made available to Bracco
(b) (6)		24 years	3 trimester (35 weeks)	Pulmonary angiogram due to an urgent emergency of pulmonary embolism	---	Maternal exposure during pregnancy, No adverse event	Injection of contrast media Iomeron® in a pregnant woman, No associated adverse drug reaction during or after the procedure	Full-term	Male, born alive without anomaly, unknown birth weight.

Case ID / Country	Safety Date, Follow-up Date	Mother's Age	Length of Pregnancy at Time of Exposure	Procedure and Indication as Reported	Route of Administration	Event MedDRA PT	Clinical Event as Reported	Type of Birth	Pregnancy Outcome
(b) (6)		29 years	3 trimester (37 Weeks)	Contrast Enhancement	Intravenous (not otherwise specified)	Discomfort, Exposure during pregnancy	Drug exposure during pregnancy, Feeling discomfort	Full-term	Patient delivered a healthy full-term male baby of 3376 g.
		30 years	---	Diagnostic procedure	Intravenous (not otherwise specified)	Erythema, Exposure during pregnancy, Pruritus	Drug exposure during pregnancy, itching, redness	Information not made available to Bracco	Information not made available to Bracco
		40 years	5 days	Uro-CT due to urinary tract infection	Unknown	Abortion spontaneous, Exposure during pregnancy	Drug exposure during pregnancy, Miscarriage	Spontaneous Abortion	Spontaneous Abortion
		30 years	18 Weeks	Computerized tomography due to pulmonary embolism	---	Contrast media reaction, Extravasation, Maternal exposure during pregnancy	Contrast media reaction, Extravasation, Maternal exposure during pregnancy	Information not made available to Bracco	Information not made available to Bracco

Case ID / Country	Safety Date, Follow-up Date	Mother's Age	Length of Pregnancy at Time of Exposure	Procedure and Indication as Reported	Route of Administration	Event MedDRA PT	Clinical Event as Reported	Type of Birth	Pregnancy Outcome
(b) (6)		27 years	3 trimester (33 weeks)	Angio CT thorax due to unknown indication	---	Maternal exposure during pregnancy, No adverse event	Injection of Iomeron® 350 contrast media in a pregnant woman, No AE during or after the procedure	Information not made available to Bracco	Information not made available to Bracco
		---	3 trimester (33 weeks)	Thoracic angio-CT due to unknown indication	---	Maternal exposure during pregnancy, No adverse event	Administration of Iomeron® 350 in a patient who was 33 weeks pregnant	Information not made available to Bracco	Information not made available to Bracco
		40 years	3 trimester (39 weeks)	CT scan angiothoracic due to suspicion of pulmonary embolism	Intravenous (not otherwise specified)	Maternal exposure during pregnancy, No adverse event	Maternal exposure during pregnancy, No adverse event	Full-term	Full-term birth; other information not made available to Bracco
		38 years	3 trimester (34 weeks)	Thoracic angiography CT scan due to unknown indication	---	Maternal exposure during pregnancy, No adverse event	Drug exposure during pregnancy, no adverse event	Preterm	Female baby was born without congenital defect/birth defect detected at birth at gestational age of 36 weeks and 6 days; unknown birth weight
		34 years	3 trimester 30 weeks	Arterial hypertension, CT pulmonary angiogram due to an unknown indication	Intravenous (not otherwise specified)	Maternal exposure during pregnancy, Pre-eclampsia, Early onset of delivery	Maternal exposure during pregnancy, Pre-eclampsia (21 days after the administration of Iomeron®), Early onset of delivery	Premature	The delivery occurred on an unknown date, which was reported as premature other information not made available to Bracco
		14 years	3 trimester	Investigation	Intravenous (not otherwise specified)	Maternal exposure during pregnancy, Rash	Maternal exposure during pregnancy, Worsening skin rash from suprapubic region to chest	Information not made available to Bracco	Information not made available to Bracco

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/

TAMARA N JOHNSON

06/30/2024 11:50:16 AM

Signing as self and as proxy for primary reviewer, Sarah Sheikh, DO.

LYNNE P YAO

07/01/2024 07:09:33 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: April 30, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Frank Lutterodt, RPM
DRIM

Subject: QT Consult to NDA 216016 / 216017 (SDN 007/009)

Note: Any text in the review with a light background should be inferred as copied from the Applicant's document.

This memo responds to your consult to us dated 2/6/2024 regarding the Division's QT related question. We reviewed the following materials:

- Proposed label for both IV and IA use (NDA 216016 / SN0007; [link](#));
- QT report for Study IOM-103 (NDA 216017 / SN0001; [link](#));
- Integrated summary of safety (NDA 216017 / SN0009; [link](#));
- QT evaluation checklist including highlights of clinical pharmacology and cardiac safety (NDA 216017 / SN0013; [link](#)).

1 Responses for the Division

Question: DIRM requests QT-IRT consult for NDA 216017(IV)-NDA 216016 (IA) for (b) (4) (Iomeprol) radiographic contrast agent. Per the summary of clinical safety, a prospectively designed, off-site, blinded analysis (Study IOM-103) of 12-lead and 2-lead ECG data collected during 4 double-blind, prospective, Phase III clinical studies (Studies 48,848-001A, -001B, -002A and -002B) was conducted.

IRT's response: Applicant's QTc assessment of safety ECGs collected from 12- and 2-lead ECGs showed mean time-average increases from baseline QTc interval > 6 msec with Iomeprol-400 and Iomeprol-300 as well as with the active controls ISOVUE-370 and OPTIRAY-320. Patients with maximum Δ QTcF > 60 msec or maximum QTcF > 500 msec were observed in all four treatment groups (see section 3.6). A search of AEs using broad SMQ "Torsade de pointes/QT prolongation" identified 7 cases, including 6 cases among the 4739 adult patients

(0.1%) who received Iomeprol intravascularly. Four of the 6 cases were serious, of which three were ventricular fibrillations in patients undergoing cardioangiography (see section 3.5).

The Applicant has not conducted a thorough QT/QTc (TQT) study. The Applicant's QTc evaluation report PR-IOM-103 included a blinded evaluation of standard 12-lead and 2-lead "rhythm strip" ECGs obtained during 4 multicenter, double-blind, randomized studies of Iomeprol (Studies 48848-001A, -OOIB, -002A, and -002B). This evaluation is not adequate as a substitute for TQT study as described in the ICH E14 Q&A. The timing of the 12-lead ECGs did not capture Tmax of Iomeprol and the ECGs obtained from the 2-lead "rhythm strip" are not adequate for QTc characterization (see section 3.6).

Nonclinical studies indicate that the potential for QTc prolongation due to direct inhibition of hERG current cannot be ruled out. In vitro hERG assay showed that Iomeprol inhibited the hERG current by 11% at 40 mgI/mL (safety margin > 6). In vivo dog study showed QTcF prolongations at all dose levels with significant increases in heart rate, which could have confounded the correction of QT for heart rate (see section 3.4).

Iomeprol is an imaging product that will be used in a highly-monitored setting. Similar products such as OMNIPAQUE (initially approved in 1985, [label](#)), ISOVUE (initially approved in 1985, [label](#)), and OPTIRAY (initially approved in 1988, [label](#)) do not appear to have TQT studies, and neither QTc prolongation nor torsade de pointes has been reported in the post-marketing section of USPIs. However, the safety ECG data collected in Studies 48848-001A, -OOIB, -002A, and -002B showed increases in the QTc interval for Iomeprol, ISOVUE and OPTIRAY. Because there was no placebo in these studies, it's unclear if the increases in QTc are related to the patients' medical condition, the administration procedures, or the drug products. Nonclinical studies showed potential for QTc prolongation due to direct inhibition of hERG current for Iomeprol and OMNIPAQUE.

If the Division would like a dedicated clinical QTc characterization for Iomeprol, the Applicant should conduct a TQT study in healthy subjects, if possible. We defer the timing of the TQT study to the Division.

2 PROPOSED LABEL

No QT labeling language was proposed by the Applicant in the label submitted to NDA 216016 SN0007 ([link](#)). If the Division requires QTc characterization for Iomeprol, we proposed QT labeling language consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance ([link](#)). Our changes are highlighted ([addition](#), ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

[Cardiac Electrophysiology](#)

[There is insufficient information to characterize the effect of IOMERON on the QTc interval.](#)

Reviewer's comment: *The Applicant has not conducted a thorough QT/QTc (TQT) study and the analysis in report PR-IOM-103 of pooled ECG data from 4 studies is not adequate as a substitute for TQT study.*

3 BACKGROUND

3.1 Product Information

(b) (4) (Iomeprol injection) is a radiographic contrast agent used in radiological examinations through intravenous (NDA 216017) or intraarterial (NDA 216016) injection for both adult and pediatric patients. The active substance is iomeprol, a nonionic, water-soluble compound containing three iodine (I) atoms responsible for the contrast effect in radiographic procedures.

The proposed Iomeprol doses vary for the different routes of administration and for the different clinical indications. The maximum proposed dose of Iomeprol for **IA** administration is **86 gI** in the indication “Coronary arteriography and ventriculography; (b) (4) (b) (4) The maximum proposed dose of Iomeprol for **IV** administration is 150 mL of Iomeprol 400, which corresponds to **60 gI**.

3.2 Applicant’s Position Related to the Question

Applicant did not conduct a thorough QT (TQT) study. The Applicant’s QT evaluation report PR-IOM-103 was a blinded evaluation of standard 12-lead and 2-lead "rhythm strip" ECGs obtained during 4 multicenter, double-blind, randomized studies of Iomeprol (Studies 48848-001A, -001B, -002A, and -002B). The original trials were conducted prior to the development of current regulatory concerns regarding potential effects of contrast agents on cardiac conduction; therefore, they were not designed in compliance with current FDA guidance with respect to ECG data collection.

3.3 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety.

The maximum proposed dose of Iomeprol is 86 gI through IA administration. The maximum tested dose of Iomeprol in pharmacokinetic clinical studies was 80 gI (Study 87020) with mean C_{max} (CV%) = 6.6 mgI/mL (21%) corresponding to 13.5 mg iomeprol/mL. Since PK parameters demonstrated linear behavior within the tested dose range and calculated AUC and C_{max} are proportional to the dose administered (20, 40 and 80 gI), C_{max} was predicted to be 7.0 mgI/mL (corresponding to 14.3 mg Iomeprol/mL) for 86 gI. T_{max} is achieved immediately prior to stopping administration of the agent. $t_{1/2\alpha}$ = 0.37 hours (CV% = 64) and $t_{1/2\beta}$ = 1.83 hours (CV% = 18).

Iomeprol does not undergo biotransformation. The agent is excreted unchanged into urine with no known metabolites. C_{max} was not elevated for subjects with renal impairment.

Table 1: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	86 gI, IA injection, single dose	7.0 mgI/mL (predicted $C_{max,ss}$)
Applicant’s High clinical exposure scenario	No high clinical exposure identified	Not applicable

Highest dose in QT
assessment

Not exceeding exceed 86 gI

PK not collected

C_{max} Ratio

Not applicable

3.4 Nonclinical Cardiac Safety

An in vitro study showed that the inhibitory effect of Iomeprol 400 mgI/mL on hERG tail current was equivalent to that of OMNIPAQUE 350, with changes attributed to increased osmolarity (Study No. DGMH1007). In a separate study, no significant effects were detected on dog Isolated Purkinje fibers in the range of Iomeprol concentrations from 5 to 40 mgI/mL. The changes seen were almost superimposable to those caused by the addition of equiosmolar mannitol (Study No. DGMH1008).

Reviewer's Comment: The GLP hERG study report (DGMH1007; [link](#)) describes the effects of Iomeprol on the hERG current in HEK293 cells, in comparison with Omnipaque. The hERG current was assessed at room temperature, using a step-step voltage protocol (from a holding potential of -80 mV to a depolarizing pulse of + 20 mV for 4.8 second, followed by a repolarizing pulse to -50 mV for 5 seconds) that is different from the recommended hERG current protocol by the FDA ([link](#)). The full hERG blocker (E-4031 at 0.1 µM) inhibited hERG potassium currents by 95.7%. No drug concentration verifications were performed in the assay.

Iomeprol inhibited (corrected with control) the hERG currents by -2.2 %, 15.2%, 16.4%, and 37.1% at 1, 4, 10, 40 mgI/mL, respectively. The Applicant also observed that Iomeprol caused concentration-dependent increase in the osmolarity of the external solution. Further study showed that mannitol (to increase the osmolarity of the external solution) decreased the hERG current by -3.9%, 6.5%, 15.5% and 26.4 %, at 1.7, 6.8, 17, and 68 mM, respectively. The osmolarities of the external solution at 1.7, 6.8, 17, and 68 mM mannitol approximately matched the osmolarities of the external solution of Iomeprol at 1, 4, 10 and 40 mgI/mL, respectively. Therefore, the osmolarity-corrected inhibition of hERG current by Iomeprol are 1.7%, 8.7%, 0.9%, and 10.7%, at 1, 4, 10 and 40 mgI/mL, respectively. The estimated IC₅₀ of Iomeprol inhibiting the hERG current is expected to be > 40 mgI/mL (11% inhibition). The estimated hERG safety margin over free (protein binding 0%) clinical exposure is > 6-fold (11% inhibition). Similar to Iomeprol 400, Omnipaque 350 inhibited (corrected with osmolarity) the hERG currents by 0.1%, 4.8%, 0.5%, and 12.7 % at 1, 4, 10, 40 mgI/mL, respectively.

In summary, the hERG assay showed deviations (e.g. room temperature; no drug concentration verification; no positive control drug) from the best practice recommendation from the S7B Q&As 2.1. The results showed that Iomeprol inhibited the hERG current by 11% at 40 mgI/mL (safety margin > 6), suggesting the direct interaction of Iomeprol on hERG channel cannot be ruled out.

In an in vivo study, intravenous administration of 4, 6 and 8 gI/kg of Iomeprol did not show evident effects on pressure parameters, heart rate and ECG intervals in conscious dogs (Study No. 6030).

Reviewer's comments: In the in vivo study 6030 ([link](#)), Iomeprol given at 4, 6, 8 gI/kg in conscious instrumented dogs induces minor changes in systolic and diastolic blood pressures. Iomeprol as well as mannitol and OMNIPAQUE induces a transient increase in heart rate during the IV infusion period up to 15 min after infusion. Heart rates were increased by 23 bpm,

29 bpm and 36 bpm at 5 min post- IV at dose levels of 4, 6 and 8 gI/kg, respectively. QTcF were increased by 19 ms, 25 ms and 24 ms at dose levels of 4, 6, and 8 gI/kg, at 5 min post-IV. Similar to Iomeprol, Omnipaque at 8 gI/kg also increased the heart rate (+22 bpm) and prolonged the QTcF (+20 ms) at 5 min post-IV. PK data was not collected in this study. No positive control was included in the study.

QTcF prolongations were observed in the in vivo dog study at all dose levels. However, significant increases in heart rate were also observed in all dose levels.

3.5 Clinical Cardiac Safety

A search using broad SMQ “Torsade de pointes/QT prolongation” identified 7 cases, including 6 cases among the 4739 adult patients (0.1%) who received Iomeprol intravascularly. Four of the 6 identified cases were serious ([narratives](#)), of which 2 were considered related. In addition, a 7th case was identified in 1 patient who received intrathecal administration of Iomeprol (Study B16880/013; Pt. (b) (6)); this case was nonserious and was considered related to the study agent. None of the adverse events resulted in the patient discontinuing from the study. No AEs were reported with QTc > 500 msec.

Table 2. Cases Identified using Broad SMQ “Torsade de pointes/QT prolongation”

Protocol #	Patient #	Iomeron concentration	Iodine dose (gI) / ROA	MedDRA PT	Serious	Related	Death Indicator
B16880/036	(b) (6)	350 mgI/mL	35 / IV	Cardio-respiratory Arrest *	Yes	No	Yes
B16880/034		400 mgI/	80 / IA	Cardiac Arrest	No	No	No
B16880/034		400 mgI/	80 / IA	Cardiac Arrest	No	No	No
B16880/034		400 mgI/mL	120 / IA	Ventricular Fibrillation	Yes	No	No
B16880/034		400 mgI/mL	70 / IA	Ventricular Fibrillation	Yes	Yes	No
B16880/034		400 mgI/mL	60 / IA	Ventricular Fibrillation	Yes	Yes	No
B16880/013		200 mgI/mL	3.6 / IT	Loss of consciousness #	No	Yes	No
* Patient experienced cardio-respiratory arrest 20 days after the study urography procedure with Iomeron, resulting in the death of the patient. This event was considered related to progressive disease (not related to Iomeron administration). ROA = route of administration [IV=intravenous, IA = intraarterial, IT=intrathecal]							

Source: QT evaluation checklist

Cardio-respiratory arrest: Subject (b) (6) was a 52-year-old, white male with a relevant medical history of renal cancer with widespread metastases, impaired renal function, and hepatomegaly who underwent excretory urography with IOMEPROL 350 mgI/mL for a suspected right kidney neoplasm. No concomitant or procedural medications were recorded. Following surgery (exploratory laporotomy), the subject’s clinical condition deteriorated. Approximately 3 weeks

after receiving Iomeprol, the subject experienced cardiac arrest and died. The cause of death was attributed to progressive disease.

Ventricular fibrillation: Subject (b) (6) was a 65-year-old white male with a relevant medical history of hypertension, hypercholesterolemia, unstable angina, and coronary artery disease who underwent cardioangiography with Iomeprol 400 mgI/mL for unstable angina. Concomitant medications included atenolol, acetylsalicylic acid with magnesium/aluminum hydroxide, nifedipine, captopril, heparin, nitroglycerin, ranitidine, and ticlopidine; procedural medications included diazepam and subcutaneous lidocaine. The subject experienced moderate ventricular fibrillation after the 4th injection of Iomeprol during the procedure, and electrocardioconversion was performed. The event resolved after 1 minute, and the subject recovered without sequelae. The subject completed the procedure. The event was described as life threatening.

Reviewer's comment: *The subject had multiple predisposing conditions such as unstable angina and coronary artery disease.*

Ventricular fibrillation: Subject (b) (6) was a 55-year-old white male with a relevant medical history of hypertension who underwent cardioangiography with Iomeprol 400 mgI/mL. Concomitant medications included Eliten (converting enzyme blocker) and Cemirit (platelet aggression inhibitor). The subject received lidocaine prior to the procedure. The subject experienced severe ventricular fibrillation after the second injection of Iomeprol 400 mgI/mL in the left coronary artery and was immediately treated with DC shock. The fibrillation lasted for approximately 1 minute. The subject recovered without sequelae.

Reviewer's comment: *The Investigator described the event as life threatening and related (definite) to the investigational product according to the [SAE report form](#) but the narrative described it as probably related to IP.*

Ventricular fibrillation: Subject (b) (6) was a 56-year-old white male with a relevant medical history of coronary heart disease who underwent cardioangiography with Iomeprol 400 mgI/mL. Concomitant medications including captopril, isosorbide mononitrate, acetylsalicylic acid, hydrocortisone hemisuccinate, and calcic eparina; procedural medications included diazepam and mepivacaine. The subject experienced severe ventricular fibrillation after the last injection in the right coronary artery and was immediately treated with electrocardioconversion. Normal rhythm was restored, and the subject recovered without sequelae. The fibrillation lasted for about 15 to 20 seconds.

Reviewer's comment: *Same as the previous ventricular fibrillation, the Investigator described the event as life threatening and related (definite) to the investigational product according to the [SAE report form](#) but the narrative described it as probably related to IP. The subject had predisposing condition of coronary heart disease.*

3.6 Summary results of prior QTc assessments

Study PR-IOM-103 was a retrospective, blinded evaluation of standard 12-lead and 2-lead "rhythm strip" ECGs obtained during 4 multicenter, double-blind, randomized studies of Iomeprol (Studies 48848-001A, -001B, -002A, and -002B). A total of 237 patients (118 Iomeprol, 119 comparator agent) who had a documented cardiac history or diagnosis that necessitated cardioangiography for diagnostic purposes or preoperative evaluation were enrolled in these studies. Isovue 370 (iopamidol) and Optiray 320 (ioversol) were used as comparator

agents (Table 3). The volume and rate of injection depended on the region of interest (Table 4). The recommended total dose of iodine should not exceed 86 grams for adult patients.

Table 3. Patient Population

Number of patients dosed:		
IOMERON 400 mgI/mL:		59
ISOVUE 370 mgI/mL:		58
IOMERON 300 mgI/mL:		59
OPTIRAY 320 mgI/mL:		61
Number of patients included in the ECG analyses:		
IOMERON 400 mgI/mL:		55
ISOVUE 370 mgI/mL:		54
IOMERON 300 mgI/mL:		57
OPTIRAY 320 mgI/mL:		59

Source: Study report PR-IOM-103

Table 4. Administration Guidelines

<u>Type of Angiography</u>	<u>Dose (mL)</u>	<u>Rate of Injection (mL/sec)</u>
Right Coronary Artery	3-6	2-3
Left Coronary Artery	4-7	2-3
Bypass Grafts	4-7	2-3
Left Ventricle	30-45	10-15
Aorta	30-60	15-30
Right Ventricle	30-45	10-15
Pulmonary Artery	30-60	15-30

Source: Study report PR-IOM-103

ECG measurements were obtained in triplicate. 12-lead ECGs were collected at 24 hours predose and 1, 4, and 24 hours postdose. 2-lead ECG "rhythm strip" monitoring, which was performed at the time of cardioangiography, using data acquired at the following time points:

- the last analyzable three-beat complex immediately prior to the first injection of study agent for formal diagnostic imaging, defined as the baseline for the acute ECG analysis using just the rhythm strip data;
- the first analyzable three-beat complex immediately after each diagnostic injection;
- the analyzable three-beat complex closest to the midpoint of the monitoring performed after each diagnostic injection (approximately 90 seconds after each RCA, LCA, and coronary bypass graft diagnostic injection; and approximately 60 seconds after each LV injection);
- the last analyzable three-beat complex obtained after each diagnostic injection and before the next injection (ie, end of injection monitoring);
- one additional analyzable three-beat complex obtained between the immediate post-injection time point and the monitoring midpoint;
- one additional analyzable three-beat complex obtained between the monitoring midpoint and the end of injection monitoring.

There was no placebo control. PK data were not collected in these studies.

The Applicant calculated the mean change from baseline of ECG parameters averaged across all time points for all subjects based on combined 12-lead and 2-lead ECG data (Table 5). Mean QTcF was increased from baseline for all treatments. The Applicant also summarized the number of subjects with ECG parameters with potential clinical importance (Table 6). Subjects with maximum Δ QTcF > 60 msec or maximum QTcF > 500 msec were observed in all treatment

arms. In addition, the Applicant conducted these analyses on 2-lead ECG data only and results were consistent with the combined 12-lead and 2-lead data.

Table 5. Mean (SD) Change from Baseline, Overall Analysis Including 12-Lead and 2-Lead ECG Data

Parameter (units)	Study Agent Group (Doses in mgI/mL)			
	IOMERON-400 (N=55)	ISOVUE-370 (N=54)	IOMERON-300 (N=56)	OPTIRAY-320 (N=59)
Heart rate (bpm)	1.1 (6.8)	1.4 (5.5)	2.5 (9.1)	2.1 (7.4)
PR (msec)	3.7 (10.2)	3.8 (14.5)	1.4 (10.1)	0.4 (8.7)
QRS (msec)	2.3 (7.5)	1.9 (6.2)	2.6 (4.8)	3.5 (8.3)
QT (msec)	10.3 (19.9)	7.1 (19.5)	1.7 (22.7)	3.3 (19.4)
QTcB (msec)	15.9 (18.1)	12.9 (19.1)	8.5 (16.2)	10.4 (22.8)
QTcB Max (msec)	53.1 (24.7)	42.9 (26.6)	35.8 (25.3)	38.7 (38.8)
QTcF (msec)	14.0 (16.3)	10.8 (18.0)	6.2 (15.9)	8.0 (18.6)
QTcF Max (msec)	46.0 (22.1)	36.7 (21.3)	30.6 (26.6)	32.8 (33.7)
SD = standard deviation; Max = maximum value obtained post-injection. Table data derived from <i>End-of-Text Table 1.1</i> .				

Source: Study report PR-IOM-103 Table C

Notes: In this table, QTcF shows the mean change from baseline QTcF, averaged across all time points for all subjects. QTcF Max shows the mean maximum change from baseline QTcF, averaged for all subjects.

Table 6. Number of Patients with Potentially Clinical Important 12-Lead and 2-Lead ECG Values

Finding	Study Agent Group (Doses in mgI/mL)			
	IOMERON-400 (N=54)	ISOVUE-370 (N=49)	IOMERON-300 (N=34)	OPTIRAY-320 (N=36)
QTcF Max increase:				
31-60 msec	33 (60)	26 (48)	14 (25)	17 (29)
≥ 61 msec	10 (18)	7 (13)	9 (16)	9 (15)
New mean QTcF:^c				
≥ 500 msec	0	1 (2)	0	0
> 450 msec (M)/> 470 msec (F)	1 (2)	4 (7)	3 (5)	5 (9)
New QTcF Max:^c				
≥ 500 msec	2 (4)	4 (7)	3 (5)	8 (14)
> 450 msec (M)/>470 msec (F)	20 (36)	15 (28)	15 (27)	14 (24)
Max = maximum value obtained post-injection; M = males; F = females ^a Bradycardia = decrease ≥ 25% and ≤ 50 bpm ^b Tachycardia = increase ≥ 25% and ≥ 100 bpm ^c New = value below cut point at baseline and above cut point post-injection Table data derived from <i>End-of-Text Tables 3.1, 3.2 and 3.3</i> .				

Source: Study report PR-IOM-103 Table D

Notes: In this table, New mean QTcF shows the number of subjects with mean QTcF exceeding a threshold. New QTcF Max shows the number of subjects with maximum QTcF exceeding a threshold.

Reviewer's comment: *Tmax of Iomeprol is achieved immediately prior to stopping administration of the agent. Administration of Iomeprol takes a few seconds based on injection volume and rate (Table 4). The first post-dose 12-lead ECG was performed at 1-hour postdose, which would not capture Tmax. The 2-lead "rhythm strip" had more dense time points. However, it was designed to monitor arrhythmia therefore are not adequate for QTc characterization.*

The Applicant's analysis in Table 5 does not reflect the mean effect of Iomeprol well. The Applicant calculated either the mean change from baseline QTcF averaged across all time points, which could underestimate the mean effect, or the mean change from baseline of maximum QTcF, which could overestimate the mean effect. We usually summarize mean change from baseline QTcF by time points. In Table 6, "QTcF Max increase" and "New QTcF Max" are the outlier analysis we usually perform.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: Sharon Thomas, Regulatory Project Manager
Division of Imaging and Radiation Medicine in the Office of Specialty Medicine

FROM: Evangela Covert, B.S., Senior Regulatory Project Manager,
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine (DRO-RDPURM)

SUBJECT: Division of Imaging and Radiation Medicine (DIRM) maternal and pediatric
consult to the Division of Pediatric and Maternal Health (DPMH) requesting a
PLLR review and PeRC preparation for a NDA submission

DRUG: (b) (4) (iomiprol) injection

NDA: 216017

DIRM submitted a consult to DPMH dated December 1, 2021, requesting DPMH assistance with the maternal and pediatric labeling review and PeRC preparation for the NDA submission.

On January 27, 2022 the Division informed DPMH they issued a refusal to file (RTF) letter to the Applicant on January 21, 2022.

Therefore, DPMH has no further comments at this time. This memorandum will close out the consult request.

RPM for DPMH – Evangela Covert
Chief Project Manager for DPMH – George Greeley
DPMH Maternal MO Reviewer – Jeannie Limpert
DPMH Pediatric MO Reviewer – Sonaly McClymont
DPMH Maternal Team Leader – Tamara Johnson
DPMH Pediatric Team Leader – Shetarra Walker
DPMH Division Deputy Director – John Alexander
DPMH Division Director – Lynne Yao

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/s/

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RPM Close Out Memo