CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216016Orig1s000
216017Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	216016 and 216017
PDUFA Goal Date	November 30, 2024
Nexus TTT #	2023-7439
Reviewer Name(s)	Timothy Bernheimer, Pharm.D
Team Leader	Carolyn Tieu, Pharm.D, MPH
Division Director	Cynthia LaCivita, Pharm.D
Review Completion Date	November 25, 2024
Subject	Evaluation of Need for a REMS
Established Name	Iomervu
Trade Name	Iomeprol injection
Name of Applicant	Bracco Diagnostic Inc.
Therapeutic Class	Radiographic contrast agent
Formulation(s)	250 mg iodine/ml, 300 mg iodine/ml, 350 mg iodine/ml, and 400 mg iodine/ml in single-dose vials or bottles
Dosing Regimen	Individualize the volume and concentration according to the specific dosing tables accounting for factors such as age, body weight, vessel size, rate of blood flow within the vessel, and structures or areas to be examined. See full prescribing information for complete dosage and administration information.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Iomervu (iomeprol) is necessary to ensure the benefits outweigh its risks. Bracco Diagnostic Inc. submitted New Drug Applications (NDA) 216016 and 216017 for Iomervu with the proposed indication for use in adults and pediatric patients for intra-arterial procedures (cerebral arteriography, including digital subtraction angiography (IA-DSA); visceral and peripheral arteriography, including (IA-DSA); coronary arteriography and cardiac ventriculography; and radiographic evaluation of cardiac chambers and related arteries) and intravenous procedures (computed tomography (CT) of the head and body; CT angiography of intracranial, visceral, and lower extremity arteries; coronary CT angiography; and CT urography). Iomervu's labeling will communicate the risks associated with intrathecal administration in the boxed warning and the risks of hypersensitivity reactions; acute kidney injury; cardiovascular adverse reactions; thromboembolic events; extravasation and injection site reactions; thyroid storm in patients with hyperthyroidism; thyroid dysfunction in pediatric patients 0 years to 3 years of age; hypertensive crisis in patients with pheochromocytoma; sickle cell crisis in patients with sickle cell disease; severe cutaneous adverse reactions; and interference with laboratory tests, in the *Warnings and Precautions* section of labeling. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Iomervu outweigh its risks. The risks identified with the use of Iomervu are described in other labels for other approved radiographic contrast agents commonly used for imaging and none of these products are approved with a REMS. The likely healthcare providers that perform imaging studies should be familiar with managing the risks.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Iomervu (iomeprol) is necessary to ensure the benefits outweigh its risks. Bracco Diagnostics, Inc. submitted a New Drug Application (NDA) 216016 and 216017 for Iomervu with the proposed indication in adults and pediatric patients for intra-arterial procedures (cerebral arteriography, including digital subtraction angiography (IA-DSA); visceral and peripheral arteriography, including (IA-DSA); coronary arteriography and cardiac ventriculography; and radiographic evaluation of cardiac chambers and related arteries) and intravenous procedures (computed tomography (CT) of the head and body; CT angiography of intracranial, visceral, and lower extremity arteries; coronary CT angiography; and CT urography). The application is under review in the Division of Imaging and Radiation Medicine (DIRM) The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Iomervu (iomeprol), a new molecular entity,[a] is a radiographic contrast agent. Iomervu is proposed as 250 mg iodine/ml, 300 mg iodine/ml, 350 mg iodine/ml, and 400 mg iodine/ml in single-dose vials or bottles by intraarterial (IA) injection or an intravenous (IV). Iomervu will likely be administered one-time[b] in a hospital or radiology center for an imaging study. Iomervu is not approved in the United States, however, in July 2022 FDA granted temporary importation of Iomervu into the U.S market to address iodinated contrast shortages.[1] Iomervu was first approved in the United Kingdom (1992) and is currently approved in 50 countries worldwide. Radiographic contrast agents carry similar class-wide boxed warning of risks associated with intrathecal administration.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216016 and NDA 216017 relevant to this review:

- 11/23/2021: Submission of NDA 216017 for IV indications, containing complete CMC, nonclinical, and clinical data
- 12/10/21: Submission of NDA 216016 containing data specific to IA indications and cross-referencing data in NDA 216017
- 01/21/2022: Refuse to file letter sent to the Applicant for NDA 216016 and NDA 216017 due mostly to product quality concerns
- 11/30/2023: NDA 216017 resubmission for use with CT examinations requiring intravenous administration of radiographic contrast agent or with diagnostic interventional angiography procedures requiring intra-arterial administration of radiographic contrast in adult and pediatric patients received
- 12/14/2023: NDA 216016 resubmission for use with CT examinations requiring intravenous administration of radiographic contrast agent or with diagnostic interventional angiography procedures requiring intra-arterial administration of radiographic contrast in adult and pediatric patients received
- 05/06/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS at this time.
- 05/09/2024: Applicant submits correspondence requesting change of product name from (b) (4) and requests review of proposed proprietary name, Iomervu
- 08/07/2024: The Agency finds the proposed proprietary name, Iomervu, conditionally acceptable

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 09/12/2024: A Late Cycle Meeting was held between the Agency and the Applicant via teleconference. The Agency inquired about the differences in the UK Summary of Product Characteristics (SmPC) included with each bottle of Iomeprol imported under tradename Iomeron into the US during the temporary importation discretion in 2022 and the currently proposed labeling. Notably, myelography is indicated in the SmPC for the 300 mg iodine/mL strength, but there is a boxed warning for intrathecal administration in the USPI. The Agency requested an assessment of risks related to the differences in labeling, particularly with regard to intrathecal use, and if applicable a proposal for risk mitigation. The Applicant stated that they conducted an assessment and did not identify any increased risk and stated that the boxed warning is a needed risk minimization measure.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Iomervu is a radiographic contrast agent and does not have a proposed indication to treat any disease, however, it is proposed for various CT, arteriography, ventriculography, and aortography procedures (see section 2.1). Generally, these procedures provide clinicians a detailed image of internal organs and structures.[2,3] Imaging is a vital tool that aids clinicians in the detection, diagnosis, and treatment of disease.[4,c] Millions of radiologic examinations requiring the use of iodinated contrast agents are performed yearly in the United States.[5,d]

3.2. Description of Current Treatment Options

Iodinated based contrast agents can be categorized by different properties, including ionization in solution (ionic vs nonionic), osmolarity, iodine content, and viscosity.[6] Iodinated based contrast agents can be subdivided into 4 major classes (ionic monomers, ionic dimers, nonionic monomer, and non ionic dimers) with differing properties which may influence the type of agents that are used for certain clinical applications.[5]

Iodinated contrast agents similar to Iomervu include Conray (iothalamate meglumine) approved 1962,[7] Isovue (Iopamidol)[8] approved 1985, Omnipaque (iohexol) approved 1985,[9] Optiray (ioversol) approved 1988,[10] Ultravist (iopromide) approved 1995,[11] and Visipaque (iodixanol) approved 1996.[12] These products share a class risk of risks with inadvertent intrathecal administration, which is communicated through a box warning. These products also share the class risks of hypersensitivity reactions, contrast-induced acute kidney injury, cardiovascular adverse reactions, and thyroid dysfunction in pediatric

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

patients zero to three years of age, which are communicated through the *Warnings and Precautions* section of labeling. None of these products have a REMS.

Although not approved in the US, on July 6, 2022, iomeprol (as Iomeron) received temporary importation discretion to address drug shortage issues with iodinated contrast media.[1] The prescribing information provided with each bottle of Iomeron was in the form of the Summary of Product Characteristics (SmPC) document approved for the United Kingdom, which included an indication for myelography (300 mg iodine/mL strength), which is administered by intrathecal administration. Additionally, the SmPC for all Iomeron strengths do not include a warning for risk of inadvertent intrathecal administration.[13] Although the importation discretion has ended, Iomeron product imported has a shelf life of 5 years and may still be present in the US until 2027 if not disposed or returned. Other US approved contract agents are labeled with a box warning of serious risks associated with intrathecal administration.

4. Benefit Assessment

The Applicant submitted two NDAs for Iomervu, NDA 216016 and NDA 216017. NDA 216016 contains information regarding use of Iomervu by IA administration and NDA 216017 contains information regarding use of Iomervu by IV administration.

The clinical review team's efficacy review is focused on the assessment of 19 key primary efficacy studies. See Table 1 in the Appendix for a summary of the studies. For more details, refer to the Review of Relevant Individual Trials Used to Support Efficacy subsection in the Statistical and Clinical and Evaluation section of the Unireview.[14]

The clinical reviewer concludes that the Applicant has submitted substantial evidence of the effectiveness of Iomervu for use in arteriography and CT imaging (coronary arteriography and cardiac ventriculography, cerebral arteriography, visceral and peripheral arteriography, intra-arterial digital subtraction angiography, CT head and body, CT angiography, coronary CT angiography, and CT urography).[e] (b) (4)

(b) (4)

5. Risk Assessment & Safe-Use Conditions

The clinical review team reviewed safety data for Iomervu used in IA and IV procedures for adults and pediatric patients collected from 88 clinical studies and post marketing surveillance. Studies in the safety database that varied in completeness of safety reporting were not included in the pooled safety analysis but collected information on serious adverse events (SAEs) and fatal outcomes.

The overall pooled safety population (n=4,923) consisted of 4,739 adult patients and 184 pediatric patients who were administered Iomervu intra-atrial or intravenously in clinical trials. The data was

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

further analyzed for adult (n=4,621) and pediatric (n=183) patients who received only up to the maximum recommended total iodine dose of 86 grams (n=4,804) to account for the possibility of adverse events with doses that were higher than intended. The adult population is the safety population that will be described in Section 6 of the label. Iomervu was administered during one single procedure in all studies.

Seven deaths were reported for adult patients in the pooled population, none of which were considered related to Iomervu by the investigator. The SAEs resulting in death observed were cardiogenic shock, cardiorespiratory arrest, intestinal ischemia, melena, cerebrovascular accident, acute kidney injury and circulatory collapse. Narratives for these deaths attribute these cases to underlying comorbidities and/or lack of temporal association, with most occurring after expected elimination of Iomervu.

A total of 27 SAEs were reported for 28 patients (0.6%) in the overall safety population of which three patients received a total iodine dose exceeding 86 grams. There were nine SAEs in seven patients (0.1%) that were considered related to Iomervu by the investigator. Serious adverse events include cardiac failure, myocardial infarction, ventricular fibrillation, pain, cerebrovascular disorder, chronic kidney disease, respiratory arrest, hypotension, and hypersensitivity. Most of these events are consistent with those observed with other iodinated contrast agents and have been observed in post marketing.

The comparison of safety data from clinical studies was assessed for consistency with post marketing surveillance of Iomervu as well as the adverse reactions described in the prescribing information for other iodinated contrast agents. The adverse reactions observed for Iomervu that were unique were primarily various non-serious vital sign related adverse reactions that are not unexpected for blood pressure and heart rate, as well as a range of less frequent cardiovascular adverse reactions that are related to class-wide warnings. The clinical reviewer states that these adverse reactions do not suggest an increased potential for serious outcomes than other iodinated contrast agents.

Overall, the clinical reviewer concludes that the major safety issues for Iomervu are the potential for hypersensitivity reactions, severe cutaneous adverse reactions, and acute kidney injury. The clinical reviewer concludes that given the similar safety issues for iodinated contrast agents, the safety profile of Iomervu is acceptable.

Similar to other iodinated contrast agents (described in section 3.2), labeling will contain a box warning of risks associated with intrathecal administration and the *Warnings and Precautions* section of the labeling for Iomervu will contain the risks of hypersensitivity reactions; acute kidney injury; cardiovascular adverse reactions; thromboembolic events; extravasation and injection site reactions; thyroid storm in patients with hyperthyroidism; thyroid dysfunction in pediatric patients 0 years to 3 years of age; hypertensive crisis in patients with pheochromocytoma; sickle cell crisis in patients with sickle cell disease; severe cutaneious adverse reactions; and interference with laboratory tests.[f] Sections 5.1-5.4 below provide details of the risks that are further characterized by the safety review of Iomervu.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.1. Risks Associated with Intrathecal Administration

The box warning advises healthcare providers that Iomervu is for IA or IV use only and must not be administered intrathecally. Intrathecal administration can cause death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema.

5.2. Hypersensitivity Reactions

Due to the class-wide risk for adverse reactions in patients with hypersensitivity, the incidence of adverse reactions experienced in patients with and without known history of hypersensitivity in clinical studies was assessed. In the safety population of adult patients (n=4,739), presence or absence of a history of hypersensitivity or allergy was assessed in 3,801 patients. A history of hypersensitivity or allergy was present in 415 patients (8%) and absent in 3,386 (69%). Of the patients with a history of hypersensitivity or allergy, 72 patients (17%) experienced adverse reactions. In patients with no known hypersensitivity or allergy, 200 patients (6%) experienced adverse reactions. One patient (0.2%) with a history of hypersensitivity or allergy and three patients (<0.1%) without known hypersensitivity or allergy experienced serious adverse reactions. As explained in section 5, no deaths were attributed to hypersensitivity reactions.

The Applicant's summary of post marketing data identified 25,620 patients (0.02%) from over 160 million exposed patients experienced hypersensitivity reactions (Standardized MedDRA Query). The evaluation of the FDA Adverse Event Reporting System (FAERS) database by the Division of Pharmacovigilance (DPV) identified similar reports of preferred terms related to hypersensitivity reactions. The clinical reviewer concludes that the data demonstrates evidence of risk for hypersensitivity reactions with administration of Iomervu, however, the data did not identify inconsistencies with the risks for hypersensitivity reactions between Iomervu and other nonionic low-osmolar iodinated contrast agents.

The label advises healthcare providers that Iomervu can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis and advises to obtain a history of allergy, hypersensitivity, and hypersensitivity reactions to iodinated contrast agents, and to always have emergency resuscitation equipment and trained personnel available before use.

5.3. Acute Kidney Injury

In the clinical trials the association of Iomervu and potential class-wide risk for acute kidney injury could not be ruled out for patients in the overall safety population who were generally within the normal range of serum creatinine at baseline. In addition to adverse reactions of acute kidney injury that occurred for two patients (<0.1%) in clinical trials, the evaluation of the FAERS data by DPV identified reports of the preferred terms "acute kidney injury" (n=125) and "renal failure" (n=16), and reports in

the literature (n=3). The Applicant's summary of post marketing data also identified reports of preferred terms "acute kidney injury" (n=214), "renal failure" (n=38), and "renal injury" (n=2).

The label advises healthcare providers that acute kidney injury, including renal failure, may occur after Iomervu administration. The label advises healthcare providers to use the lowest necessary dose of Iomervu in patients with renal impairment; to adequately hydrate patients prior and following administration; and to not use laxatives, diuretics, or preparatory dehydration prior to Iomervu administration.

5.4. Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions are another known class-wide risk with iodinated contrast agents that manifest most commonly as delayed reactions. Severe skin and subcutaneous AEs were not observed in clinical trials.

DPV was consulted for review of adverse events reported with Iomervu from available post marketing data. Several reports were identified for severe cutaneous reactions that are described in the class-wide warnings for iodinated contrast agents. These included preferred terms "drug reaction with eosinophilia and systemic symptoms" (n=161), "acute generalized exanthematous pustulosis" (n=80), "toxic skin eruption" (n=79), "eosinophilia" (n=71), "toxic epidermal necrolysis" (n=15), and "Stevens-Johnson syndrome" (n=11).

The Applicant's summary of post marketing data also identified reports of the same preferred terms "drug reaction with eosinophilia and systemic symptoms" (n=46), "acute generalized exanthematous pustulosis" (n=62), "toxic skin eruption" (n=53), "eosinophilia" (n=84), "toxic epidermal necrolysis" (n=3), and "Stevens-Johnson syndrome" (n=8).

The label advises healthcare providers that severe cutaneous adverse reactions may develop from 1 hour to several weeks after intravascular contrast agent administration. Healthcare providers are advised that prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions and to avoid administering Iomervu to patients with a history of severe cutaneous adverse reaction to Iomervu.

6. Expected Postmarket Use

Iomervu will likely be administered as a one-time injection in a hospital or radiology center for an imaging study.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Iomervu beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Iomervu on the basis of the efficacy and safety information currently available.

The major risks associated with the use of Iomervu are the risks associated with intrathecal administration, hypersensitivity reactions; acute kidney injury; cardiovascular adverse reactions; thromboembolic events; extravasation and injection site reactions; thyroid storm in patients with hyperthyroidism; thyroid dysfunction in pediatric patients 0 years to 3 years of age; hypertensive crisis in patients with pheochromocytoma; sickle cell crisis in patients with sickle cell disease; severe cutaneious adverse reactions; and interference with laboratory tests. Iomervu is a single dose expected to be administered in a hospital or radiology center by a healthcare provider.

The risks identified with the use of Iomervu are described in the labels for other approved radiographic contrast agents commonly used for imaging and none of these are approved with a REMS. The likely healthcare providers that perform imaging studies should be familiar with managing the risks and Iomervu's labeling will communicate the risks associated with intrathecal administration in the boxed warning as well as the risks described above in the *Warnings and Precautions* section of labeling. The proposed clinical settings are expected to be equipped with appropriate drugs, equipment, and healthcare providers who are available to diagnose, monitor, and manage these risks.

Due to the temporary importation discretion of iomeprol (as Iomeron) in 2022, this reviewer had concerns that differences in the SmPC (see section 3.2) and proposed US labeling regarding the risks associated with intrathecal use for Iomervu may lead to possible confusion and medication errors of intrathecal administration. Initially, the proposed name for Iomervu was (b) (4) and for reasons unrelated to this issue, the proposed name was changed to Iomervu in May 2024. Although Iomeron products containing the SmPC may still be in stock at facilities until (b) (4), remaining supplies are expected to be low and the differences in name of the imported stock and the US marketed stock upon Iomervu approval should help facilities distinguish the products and store them separately. Additionally, proposed Iomervu container labeling includes displayed warnings of "For intravenous or intra-atrial use only" and "Not For Intrathecal Use." This is sufficient in mitigating possible confusion of the risks of Iomervu and no additional risk mitigation is necessary. Additionally, the Applicant conducted an assessment of this issue and they did not identify any increased risk and stated that the boxed warning is a needed risk minimization measure. DIRM concurs that differences in labeling do not pose a major risk that would require additional risk management for Iomervu.

The safety profile of Iomervu is similar to other iodinated contrast agents, and known risks associated with the class which can be mitigated through appropriate labeling. This reviewer has determined that a REMS is not necessary to ensure the benefits of Iomervu outweigh the risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable for Iomervu. A REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with Iomervu use are similar to

other US approved contrast agents and healthcare providers who use this radiographic contrast agent for imaging should be familiar with the risks associated with Iomervu.

At the time of this review, evaluation of safety information and labeling was ongoing. Should DIRM have any concerns or questions or if new safety information becomes available, please send a consult to DRM; this recommendation can be reevaluated.

10. Appendices

Table 1. Listing of clinical studies of intravenous efficacy in adults

Study Identity	Study Design	Concentration/ Volume[1]/Flow Rate	Study Endpoints	No. of Patients[2]	Study Population	No. of Centers and Countries
CT head and body						
IOM-104E (48-848-007A, 48-848-007B, 48-848-008A, 48-848-008B)	Prospective, multi-center, double-blind, randomized	400 mgI/mL 112 mL 1-5 mL/sec 250 mgI/mL 145 mL 1-5 mL/sec	% adequate visualization on a 2-point scale and non-inferiority to comparator	59 59	Adult patients with a history or diagnosis necessitating head and/or body CT for diagnostic, preoperative, or postoperative evaluation	48-848-007A, 48-848-008A: 5 centers in US 48-848-007B, 48-848-008B: 5 centers in US
CT angiography (CTA)						
Peripheral angiography						
Albrecht et al. 2007	Prospective, single center	400 mgI/mL 100 mL 4 mL/sec	Image quality: % diagnostic arterial segments Diagnostic performance: Segment-level sensitivity and specificity for detection of >50% stenosis by DSA reference standard	50	Adult patients with peripheral arterial disease (chronic or acute ischemia)	1 center in Germany
Iezzi et al. 2008	Prospective, single center	Group A (n=20): 300 mgI/mL 120 mL Group B (n=20): 400 mgI/mL 90 mL 3 mL/sec	Image quality: % adequate visualization Diagnostic performance: Segment-level sensitivity and specificity for detection of >70% stenosis by DSA reference standard	40	Adult patients with peripheral arterial disease referred for DSA	1 center in Italy
Napoli et al. 2011	Prospective, single center	400 mgI/mL 130 mL 4 mL/sec	Segment- and region-level sensitivity and specificity for detection of ≥70% stenosis by DSA reference standard	212	Adult patients with symptomatic peripheral arterial disease referred for imaging after duplex ultrasound	1 center in Italy
Gruschwitz et al. 2023	Retrospective, single center	350 mgI/mL 110 mL 3 mL/sec	Segment-level sensitivity and specificity for detection of ≥75% stenosis by DSA reference standard	109	Adult patients with known or suspected peripheral arterial disease	1 center in Germany
Cerebral angiography						
Millon et al. 2012	Retrospective, single center	400 mgI/mL 25 mL 5 mL/sec	% adequate visualization	73	Adult patients with nontraumatic subarachnoid hemorrhage	1 center in France
Kim et al. 2020	Retrospective, single center	400 mgI/mL 80-100 mL 3-4 mL/sec	Image quality: % adequate visualization on a 3-point scale Diagnostic performance: Sensitivity and specificity for evaluation of residual/recurrent aneurysms, patency of parent artery, patency of adjacent branch by 3DRA reference standard	128	Adult patients with cerebral aneurysm who underwent postoperative CT angiography, DSA, and 3DRA	1 center in Korea
Visceral angiography						
Schaefer et al. 2013	Prospective, single center	350 mgI/mL NA	Image quality: Image quality on a 5-point scale	52	Adult patients with asymptomatic aortoiliac	1 center in Germany

		NA	Diagnostic performance: Sensitivity and specificity for detection of >50% stenosis by DSA reference standard		aneurysms or penetrating atherosclerotic ulcers	
Stueckle et al. 2004	Retrospective, single center	350 mgI/mL 100 mL 3 mL/sec	Sensitivity and specificity for detection of high-grade (≥85%) and low-grade (≥45%, <85%) stenosis by DSA reference standard	52	Adult patients with suspected aortic dissection, aortic aneurysm, or stenosis of the mesenteric or iliac arteries who underwent CT angiography and DSA of the abdominal vessels	1 center in Germany
Coronary CT angiography (CCTA)						
Andreini et al. 2017	Prospective, single center	400 mgI/mL 50 mL (BMI <24.9 kg/m^2), 60 mL (BMI >25 kg/m^2) 5 mL/sec	Image quality: % adequate visualization on a 4-point scale Diagnostic performance: Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	166	Adult patients without known coronary artery disease scheduled for ICA	1 center in Italy
Andreini et al. 2010	Prospective, single center	400 mgI/mL 80 mL 5 mL/sec	Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	210	Adult patients with suspected coronary artery disease scheduled for ICA	1 center in Italy
Brodoefel et al. 2008	Prospective, single center	400 mgI/mL 80 mL 5 mL/sec	Image quality: % adequate visualization on a 4-point scale Diagnostic performance: Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	125	Adult patients with suspected (or suspected progression of) coronary artery disease scheduled for ICA	1 center in Germany
Pontone et al. 2014	Prospective, single center	400 mgI/mL 90 mL 5 mL/sec	Image quality: % adequate visualization on a 4-point scale Diagnostic performance: Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	184	Adult patients with high risk for coronary artery disease scheduled for ICA	1 center in Italy
[redacted]						(b) (4)
CT urography						
Portnoy et al. 2011	Retrospective, single center	350 mgI/mL 90-120 mL 2.5 mL/sec (3-phase and split-bolus dual-phase)	% adequate visualization on a 3-point scale	150	Adult patients with hematuria and other urologic diseases	1 center in Israel
Bretlau et al. 2015	Retrospective, single center	400 mgI/mL 25-50 mL NA (split-bolus dual-phase)	Disease detection rate	771	Adult patients with hematuria	1 center in Denmark
Martingano et al. 2013	Retrospective, single center	350 mgI/mL 600 mgI/kg 2 mL/sec (split-bolus dual-phase)	Image quality: Visualization score on a 6-point scale Diagnostic performance:	35	Adult patients with hematuria who underwent both CT urography and MR urography	1 center in Italy

			Sensitivity and specificity for detection of urothelial malignancy			
Kahn et al. 2022	Retrospective, single center	300 mgI/mL 90-120 mL NA (4-phase)	Sensitivity and specificity for detection of hydronephrosis	15	Adult patients with and without hydronephrotic kidneys	1 center in Israel

Source: Sources of Clinical Data and Review Strategy Section of the Draft Unireview for Iomervu NDA 216016; NDA 216017

Abbreviations: 3DRA = three-dimensional rotational angiography, BMI = body mass index, CT = computed tomography, DSA = digital subtraction angiography, ICA = invasive coronary angiography, MR = magnetic resonance, n = number of patients, NA = not available

[1] Volumes not presented as a range are mean values.

[2] Patients who received Iomervu.

10.1. References

[1] Dear Healthcare Provider Letter for Iomeprol. July 6, 2023. https://www.fda.gov/media/159925/download

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[7] Conray (iothalamate meglumine) injection Prescribing Information. Guerbet. Raleigh, NC. Revised February 2023; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/013295s073lbl.pdf

[8] Isovue (iopamidol) injection Prescribing Information. Bracco Diagnostics. Monroe Township, NJ. Revised February 2023; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018735s070lbl.pdf

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