NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) Supplemental NDA
Application Number	NDA 018735/S-075
Priority or Standard	Standard
Submit Date	December 24, 2024
Received Date	December 26, 2024
PDUFA Goal Date	October 26, 2025
Division/Office	DIRM/OSM
Review Completion Date	October 10, 2025
Established/Proper Name	Iopamidol
Trade Name	ISOVUE
Pharmacologic Class	Radiographic contrast agent
Applicant	Bracco Diagnostics Inc.
Dosage form	Injection (diluted for oral use)
Applicant Proposed Dosing Regimen	6 mg Iodine/mL - 9 mg Iodine/mL dilution (b) (4)
Applicant Proposed Indication	ISOVUE is indicated for: • CT of the abdomen and pelvis to (b) (4) the gastrointestinal tract in adults and pediatric patients
Applicant Proposed SNOMED CT Indication Disease Term	169070004 | Computed tomography of abdomen (procedure)
Recommendation on Regulatory Action	Approval
Recommended Indication	ISOVUE is indicated for: • CT of the abdomen and pelvis to delineate the gastrointestinal tract in adults and pediatric patients
Recommended SNOMED CT Indication Disease Term	118948005 | Disorder of abdomen (disorder)
Recommended Dosing Regimen	6 mg Iodine/mL or 9 mg Iodine/mL dilution Adults and children ≥ 12 years – 500 mL to 1000 mL orally Children 6 years to 11 years – 360 mL to 500 mL orally Children 3 years to 5 years – 300 mL to 360 mL orally Children below the age of 3 years – 50 mL to 300 mL orally

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
RBPM=Regulatory Business Process Manager
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

ADME	absorption, distribution, metabolism, excretion
BLA	biologics license application
CFR	Code of Federal Regulations
DHOT	Division of Hematology Oncology Toxicology
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Isovue (iopamidol) injection is an iodinated radiographic contrast agent that attenuates x-ray photons and thereby opacifies body structures where it is present. It is currently approved for multiple indications after intravascular administration. This supplement proposes a new indication, for computed tomography (CT) of the abdomen and pelvis to (b) (4) the gastrointestinal (GI) tract in adults and pediatric patients, and a new route of administration, oral. The recommended patient population is adults and pediatric patients of all ages. Isovue injection is diluted to 6 mg iodine/mL (mg I/mL) or 9 mg I/mL prior to oral administration and the recommended volume ranges from 50 mL to 1000 mL depending on patient age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted substantial evidence of effectiveness for Isovue for delineation of the GI tract on abdominopelvic CT. Effectiveness is primarily supported by one adequate and well-controlled trial (IOP-121) and a published study that provided confirmatory evidence (Morgan et al. 2009).

In IOP-121, three blinded, independent readers scored delineation of bowel, divided into five segments from stomach to distal ileum inclusive, on CT scans obtained with orally administered Isovue in adult and pediatric patients. Adequate bowel delineation was defined as at least three of five segments having adequate opacification and differentiation from surrounding structures. At the lower bound of the 95% confidence interval, 71%, 75%, and 94% of patients, depending on reader, were considered to have adequate delineation.

In (Morgan et al. 2009), patients were randomized to iopamidol or one of two other orally administered contrast agents prior to clinically indicated CT. Three blinded readers scored opacification of bowel overall and by segment. At the lower bound of the 95% confidence interval, 71% of patients given iopamidol in the first stage of the study had satisfactory overall bowel opacification.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Computed tomography (CT) is a widely used imaging modality that relies on differential attenuation of x-rays to depict anatomy and pathology. Many normal structures, such as bowel, as well as many types of pathology have similar x-ray attenuation, which may make them difficult to distinguish. Administration of contrast agents can be used to differentiate various structures on CT.

Isovue (iopamidol) is a radiographic contrast agent that contains iodine and is capable of attenuating x-rays. When administered orally, iopamidol is largely retained in the bowel lumen and distributes with enteric contents to opacify the gastrointestinal tract. Through this mechanism, oral iopamidol is intended to improve delineation of bowel and allow it to be distinguished from adjacent structures.

Effectiveness of Isovue for delineation of bowel was evaluated in an adequate and well-controlled study (IOP-121) and a published study serving to provide confirmatory evidence (Morgan et al. 2009). In IOP-121, the proportion of patients with adequate delineation of bowel was 77%, 81%, and 97% depending on reader, with 95% confidence interval lower bounds of 71%, 75%, and 94%, respectively. In (Morgan et al. 2009), satisfactory overall bowel opacification was observed in 84% of 45 patients with 95% confidence interval lower bound of 71%.

Safety of orally administered Isovue was evaluated in 218 patients in IOP-121 as well as through postmarketing surveillance data obtained over the period from July 1, 1997, to August 31, 2024. The most commonly observed adverse reactions were vomiting, diarrhea, and nausea.

Overall, the benefit of Isovue for CT of the abdomen and pelvis to delineate the gastrointestinal tract in adults and pediatric patients outweighs the risks, and approval of this supplemental NDA is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CT is an anatomic imaging modality relying on attenuation of x-rays to create images that are widely used for assessment of many diseases. • X-ray attenuation of most soft tissues, including bowel, is similar on CT. • Many pathologic conditions have x-ray attenuation similar to normal soft tissues.	• It can be difficult to delineate bowel on CT and to distinguish bowel from pathology. • Contrast agents are often administered orally to improve delineation of bowel on CT.
Current Treatment Options	• Iodinated contrast agents with an indication for use on CT to opacify bowel include diatrizoate meglumine/diatrizoate sodium and iohexol. • Barium sulfate is a non-iodinated contrast agent also approved for this use.	• Multiple contrast agents are available to opacify the bowel on CT.
Benefit	• The Applicant conducted one adequate and well-controlled study, IOP-121, and submitted a published study (Morgan et al. 2009) that provided confirmatory evidence. • IOP-121 involved a prospective re-read by three blinded central readers of 218 retrospectively collected CT scans obtained with orally administered Isovue. Bowel delineation was rated for five bowel segments from stomach to distal ileum. Patents were assessed as having adequate delineation if at least three of five segments were adequately delineated. The study did not meet its predefined success criteria of at least 80% of patients with adequate delineation for at least two of three readers at the lower bounds of the 95% confidence intervals. Point estimates for the proportion of patients with adequate delineation were 77%, 81%, and 97%, with confidence interval lower bounds of 71%, 75%, and 94%, respectively. • (Morgan et al. 2009) was a prospective study in which patients were randomized to iopamidol or diatrizoate meglumine/diatrizoate	• Based on the totality of evidence, performance of Isovue for opacification of bowel at CT is sufficient. • While IOP-121 did not meet its predefined success criteria, the threshold of 80% was arbitrary and not based on minimal clinically useful performance. • Complete or near complete opacification of bowel is desirable, but partial opacification is still expected to provide benefit. • Structure delineation assessments are clinically meaningful endpoints that have been used in other studies demonstrating effectiveness of iodinated contrast agents.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sodium in the first stage and iopamidol or barium sulfate in the second. Three blinded readers evaluated bowel opacification overall and in five segments. In stage 1, satisfactory overall opacification was observed for iopamidol in 84% of 45 patients with 95% confidence interval lower bound of 71%.	
Risk and Risk Management	• The safety population consisted of the 218 patients in IOP-121, supplemented with surveillance data from postmarket use of oral iopamidol products outside the United States and from off label use of Isovue. • The most commonly reported adverse reactions were vomiting, diarrhea, and nausea. • Due to limited absorption of iopamidol from the gastrointestinal tract, the most common systemic adverse reaction was hypersensitivity.	• The safety profile of orally administered iopamidol is relatively benign. • No unexpected safety concerns were identified.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data were not submitted as part of this application and were not needed.**			

2 Therapeutic Context

2.1. Analysis of Condition

Radiography, fluoroscopy, and CT are anatomic imaging techniques that have a broad range of applications in the evaluation of various clinical conditions in adults and pediatric patients. These modalities rely on differential absorption of x-rays by body tissues to produce images. Tissues can be broadly categorized as having air, fat, water (most non-adipose soft tissues), or bone density, and there is little difference in x-ray attenuation among specific tissues within each category. Thus, imaging is often performed with contrast agents to further differentiate tissues and obtain additional diagnostic information.

One example of a situation in which it can be difficult to delineate tissues is evaluation of the gastrointestinal (GI) tract on abdominopelvic CT. The bowel is relatively homogenous in attenuation and individual loops can be indistinguishable from adjacent bowel, other organs, or pathology. This is particularly common in patients with lower body weight, where there is often little fat between bowel loops. One strategy that has long been used to mitigate this issue is to orally administer a contrast agent with limited GI absorption to create a difference in attenuation between the wall and lumen of the bowel. These are given sufficiently in advance of CT to allow distribution to the target bowel segments by physiologic motility.

Iodine can attenuate x-rays in the energy ranges typically used for CT and is employed in many contrast agents for this purpose. Iodine is not used directly, but instead is incorporated into organic molecules that influence pharmacokinetic properties and limit osmolarity of the drug. Isovue is an iodinated contrast agent containing iopamidol, which has a nonionic structure with three iodine atoms per molecule. It is approved and marketed for multiple indications with intravascular administration.

2.2. Analysis of Current Treatment Options

Among radiographic contrast agents with approved oral route indications, three are specifically approved for use with CT to opacify the bowel (Table 1). Because most other uses of radiographic contrast require higher attenuation and because over-opacification can cause artifact at CT, these drugs are typically diluted for this indication unless specifically formulated for it.

Table 1. Marketed Drugs Approved for Bowel Opacification for Computed Tomography

Established Name	Proprietary Name	Atom Providing X-ray Attenuation	Notes
iohexol	Omnipaque	iodine	Available as a ready to use oral solution (9 mg I/mL or 12 mg I/mL) or the injection formulation may be diluted
diatrizoate meglumine and diatrizoate sodium	Gastrografin, MD-Gastroview	iodine	Available as an oral solution but must be diluted for CT

Established Name	Proprietary Name	Atom Providing X-ray Attenuation	Notes
barium sulfate	Readi-Cat 2, Readi-Cat 2 Smoothie	barium	Contraindicated in patients at high risk of aspiration or gastrointestinal perforation

Source: Prescribing information for each drug

Other marketed iodinated contrast agents have been used off label for oral use with CT. In addition, it is possible to administer water to distend the bowel and provide "neutral" contrast. Because water is absorbed in the small intestine, solutions with osmotically active materials (i.e., sorbitol) are often used in place of water.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NDA 018735 for Isovue injection in single dose presentations was approved December 31, 1985. Isovue is also available in pharmacy bulk pack and imaging bulk pack presentations under NDA 020327, approved October 12, 1994. Currently approved indications are as follows:

1.1 Intra-arterial Procedures

ISOVUE is indicated for:

- Cerebral arteriography in adults
- Peripheral arteriography in adults
- Selective visceral arteriography and aortography in adults
- Coronary arteriography and cardiac ventriculography in adults
- Angiocardiography in pediatric patients

1.2 Intravenous Procedures

ISOVUE is indicated for:

- Excretory urography in adults and pediatric patients
- Computerized tomography (CT) of the head and body in adults and pediatric patients
- Peripheral venography in adults

This is the first efficacy supplement submitted for oral use with CT.

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of significant regulatory activity related to this supplemental NDA is presented in Table 2.

Table 2. Summary of Regulatory Activity for NDA 018735 S075

Date	Activity Type	Notes
12/17/2018	Type C meeting	Proposal for a supplement based on a retrospective study with prospectively designed blinded re-read and a review of published literature was generally acceptable. Semi-objective visualization scoring system and establishment of methods to minimize bias in patient selection recommended for IOP-121.
1/10/2020	Type C meeting	Agreement on visualization scoring system, definition of adequate visualization at patient-level, and patient selection criteria for IOP-121.
6/22/2023	Type B meeting	No objection to supplement submission. Request for justification of clinical utility of observed performance in IOP-121.
12/26/2024	Supplement submission	-

Source: FDA clinical reviewer

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No specific data quality issues were identified during review, and inspections were not necessary to reach a decision on this application.

4.2. Product Quality

This efficacy supplement adds a new indication. The environmental assessment has been provided and found acceptable.

Product Quality-related labeling changes have been proposed, including:

- A dilution table for dose preparation
- Diluent information

The dilution table was evaluated to confirm that the final product strengths (6 mg I/mL or 9 mg I/mL) are achieved after dilution. An information request (IR) was sent seeking clarification on the types of diluents and in-use time of the diluted products.

In response, the applicant proposed that:

- Water or clear liquids such as apple juice will be used as diluents
- The diluted drug product will not be stored but will be used immediately after dilution (consistent with the similarly approved drug product Omnipaque)

The applicant's response to the IR is acceptable. The supplement can be approved from a Product Quality review perspective.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Iopamidol is a radiographic contrast agent that is approved for diagnostic imaging procedures in adults and pediatric patients using intra-arterial (cerebral arteriography, peripheral arteriography, selective visceral arteriography and aortography, coronary arteriography and cardiac ventriculography in adults; angiocardiography in pediatric patients) and intravenous (excretory urography, CT of the head and body, peripheral venography in adults; excretory urography, CT of the head and body in pediatric patients) routes of administration at 0.20, 0.25, 0.30, and 0.37 g Iodine/mL concentrations. Initial approval of iopamidol was in 1985. The proposed new indication and new route of administration for this efficacy supplement are for CT of the abdomen and pelvis to (b) (4) the gastrointestinal tract in adults and pediatric patients by oral administration.

The Applicant submitted nonclinical pharmacology and toxicology studies of iopamidol that were conducted as part of the nonclinical development program that supported the NDA approval for iopamidol by intra-arterial and intravenous routes of administration. As part of the efficacy supplement, the Applicant submitted four non-GLP *in vivo* pharmacodynamic studies on the radiographic properties of iopamidol (Study No. 509, 361, 167, and 166 in rats, rabbits, and dogs), two non-GLP pharmacokinetic studies (absorption and excretion) of iopamidol following oral administration in rats (Study No. 370 and 371), two non-GLP single dose toxicity studies by oral (Study No. 169) and intraperitoneal routes (Study No. 3571), one non-GLP repeat dose oral toxicity study (Study No. 171), and one non-GLP mis-administration study (Study No. 12/1986). The nonclinical studies were supportive of the efficacy supplement and not pivotal because they were not GLP and were conducted prior to establishment of current guidelines for conduct of nonclinical pharmacology and toxicology studies intended to support safety. Iopamidol is poorly absorbed following oral administration and primarily eliminated in the feces. Therefore, the safety profile is expected to be more favorable as compared to iopamidol administration by other routes, e.g., intra-arterial and intravenous.

In summary, no significant drug-related toxicities are identified that preclude the approval of this efficacy supplement.

5.2. Referenced NDAs, BLAs, DMFs

NDA 018735 and NDA 020327 (Isovue Pharmacy Bulk Pack and Imaging Bulk Pack)

5.3. Pharmacology

The Applicant submitted four non-GLP *in vivo* pharmacology studies that evaluated the radiographic properties of iopamidol in the small and large intestine of rats and rabbits (Study No. 509), enteropooling in the rat (Study No. 361), imaging the esophagus of dogs and rabbits (Study No. 167), and general gastrographic properties in the dog (Study No. 166). The studies were reviewed briefly.

In Study No. 509, "*Contrasting properties in radiological examination of the small and large gut",* the radiographic properties of iopamidol and diatrizoate meglumine were evaluated in the small and large intestine of Sprague Dawley BR male rats (n=10 per group) and New Zealand male rabbits (n=4), respectively. For the small intestine, iopamidol (0.3 g iodine/mL) was administered directly to the stomach at a dose of 1.5 g iodine/kg body weight (bw) and imaged immediately following administration of contrast and at 5, 30, and 60 min, post-dose; diatrizoate meglumine (0.37 g iodine/mL) was administered as a reference compound at 1.5 g iodine/kg bw. Opacification of the stomach persisted with diatrizoate meglumine compared to iopamidol which was interpreted as resulting from precipitation of contrast agent based on gross macroscopic examination of tissues. According to the report, there was clear opacification of the jejunum and upper ileum at 30 min, followed by clear opacification of the small intestine from the jejunum to the ileum in rats administered iopamidol. For the large intestine, iopamidol (0.1 g iodine/mL) was administered as a dilute enema at a dose of 8, 12, 20, or 36 mL, ranging from 0.32 – 1.44 g iodine/kg bw, and imaged at 10, 20, 30, 60, and 120 min post-dose. Rectal administration of iopamidol enabled large intestine radiography which improved with increasing dose; 12 mL and 20 mL resulted in initial penetration of contrast into the colon and contracted rectum. At the high dose, there was complete filing of the large intestine with visualization of the proximal and distal segments.

In Study No. 361, "GASTROMIRO®: Enteropooling Effect and Influence on Blood Osmolality and Hematocrit Value After Oral Dosing the Rat. Comparative versus GASTROGRAFIN®", the enteropooling effect (accumulation of fluid in the small intestine) was evaluated in male Sprague Dawley rats after oral administration of iopamidol (0.3 g iodine/mL), diatrizoate meglumine (0.37 g iodine/mL), or water (10 mL/kg). Animals were euthanized 30, 60, or 90 min post-dose, the small intestine was ligated near the pylorus and at the ileocecal valve, and liquid content was collected and the volume was measured; blood was collected from the same animals to measure blood osmolality. For determination of hematocrit values, animals were euthanized 60 min post-dose with blood collected and processed.

Enteropooling was observed at 1.5 g iodine/kg bw and 3 g iodine/kg bw with little effect observed at 0.5 g iodine/kg bw; volume of liquid in the intestine was 10x and 20x greater compared to control, peaking between 30 min and 60 min for iopamidol. Administration of diatrizoate meglumine at 1.5 g iodine/kg bw and 3g iodine/kg bw also resulted in enteropooling that was up to 50% greater compared to iopamidol at the same dose. Liquid content in the GI tract was 3.5 ± 0.2 mL and 5.3 ± 0.3 mL at 60 min post-dose for iopamidol and diatrizoate meglumine, respectively, at 1.5 g iodine/kg bw. At 3 g iodine/kg bw, liquid content in the GI tract was 4.4 ± 0.6 mL and 6.5 ± 0.5 mL at 60 min post-dose for iopamidol and diatrizoate meglumine, respectively ($p < 0.05$ at all timepoints for 1.5 g iodine/kg and 60 min only at 3 g iodine/kg). Blood osmolality was modestly increased (up to +7 mOsm/kg) by iopamidol and diatrizoate meglumine at all dose levels. Osmolality for control was 300 ± 0.85 mOsm/kg and increased up to 304 ± 0.79 mOsm/kg, 307 ± 1.54 mOsm/kg, and 306 ± 0.65 mOsm/kg at 0.5, 1.5, and 3.0 g iodine/kg for iopamidol 60 min post-dose. For diatrizoate meglumine, osmolality increased up to 304 ± 0.82 mOsm/kg, 311 ± 1.25 mOsm/kg, and 311 ± 0.99 mOsm/kg at 0.5, 1.5, and 3.0 g iodine/kg at 60 min post-dose. Hematocrit was not affected by iopamidol (43.2 ±

0.33 volume %) or diatrizoate meglumine (43.2 ± 0.57 volume %) compared to water (42.8 ± 0.68 volume %).

In Study No. 167, "*Esophagographic Properties of Iopamidol*", contrast imaging of the esophagus was evaluated in male New Zealand rabbits (n=5) and a single male Beagle dog. In rabbits, iopamidol (0.3 g iodine/mL) was administered through a catheter in the cervical region of the esophagus at a dose of 1 mL/kg (3 separate doses). In the dog, contrast was administered at a dose of 0.75 mL/kg. According to the study report, there was good visualization of the region of interest, and of the internal surfaces of the esophagus and the contracted esophagogastric junction.

In Study No. 166, "*Gastrographic Properties of Iopamidol in the Dog*", contrast imaging of the stomach was evaluated in male Beagle dogs (n=2) where iopamidol (0.3 g iodine/mL) was administered orally via a catheter to the stomach at 0.225 g iodine/kg bw (0.75 mL/kg); gastric wall distention was achieved by administration of 100 mL air prior to iopamidol administration. Iopamidol permitted visualization of the mucosal plicae, medial and lateral walls, and the pyloric and duodenal areas. Based on the study report, optimal results were obtained at 15 min and 30 min post-dose with loss of visualization by 60 min.

5.4. ADME/PK

Table 3. ADME/PK Study Findings

Type of Study	Major Findings
Absorption	
Intestinal Absorption of GASTROMIRO® After Oral Dosing in the Rat: Comparative Versus GASTROGRAFIN® (Study 370)	Gastrointestinal absorption of iopamidol was estimated from fecal and renal excretion values after a single oral dose corresponding to 1.5 g iodine/kg bw in Sprague Dawley rats (n=12 males) and compared to diatrizoate meglumine (n=12 males). Iopamidol (0.3 g iodine/mL) was eliminated within 72 hr with 98.8 ± 7.1% in the feces and 1.8 ± 0.6% in the urine whereas the comparator diatrizoate meglumine (0.37 g iodine/mL) was 83.3 ± 9.2% in the feces and 2.1 ± 0.8% in the urine.
GASTROMIRO® blood levels and urinary and fecal excretion of product administered intraperitoneally to rats (Study No. 371)	Systemic absorption of iopamidol was evaluated in Sprague Dawley rats (n=3 males per time point for plasma kinetics and n=12 males for urinary and fecal elimination) after a single intraperitoneal administration. Iopamidol (0.3 g iodine/mL) at a dose of 1.5 g iodine/kg bw was eliminated within 24 hr post-dose with a $t_{1/2}$ of approximately 2.5 hr. Elimination was predominately by renal elimination with 89.5 ± 5.8% in the urine and 4.1 ± 1.9% in the feces. Cumulative elimination was 93.6 ± 5.7% at 24 hr. Iopamidol was present in plasma following intraperitoneal administration, reaching peak plasma levels by 15 min post-dose.

Type of Study	Major Findings
Distribution	
N/A (reviewed in initial NDA submission)	
Metabolism	
N/A (reviewed in initial NDA submission)	
Excretion	
N/A (reviewed in initial NDA submission)	
TK data from general toxicology studies	
N/A (reviewed in initial NDA submission)	
TK data from reproductive toxicology studies	
N/A (reviewed in initial NDA submission)	

Source: Reviewer's table
Note: Values presented as mean ± standard deviation
Abbreviations: ADME, absorption, distribution, metabolism, excretion; bw = body weight; N/A = not applicable; PK, pharmacokinetics; $t_{1/2}$ = half-life; TK, toxicokinetics

5.5. Toxicology

5.5.1. General Toxicology

The Applicant submitted two single dose toxicity studies (Study No. 169 in Sprague Dawley rats by oral route and Study No. 357 by intraperitoneal route in BR rats), and one repeat dose toxicity study (Study No. 171 by oral route in BR rats) to support the oral route of administration. However, the two single dose toxicity studies were not considered adequately designed and conducted because they were not performed according to current guidance and included only clinical observations, mortality, and LD50 determination. The repeat dose oral toxicity study was considered adequate in demonstrating safety for iopamidol by oral route and a no observed adverse effect level (NOAEL) could be determined despite conduct prior to establishment of current guidance documents for conduct of nonclinical toxicology studies. The submitted oral (and intraperitoneal) toxicity studies were conducted in 1984 – 1986 and were not considered pivotal studies.

In Study No. 169, rats (n=5/sex/group) were administered iopamidol (0.3 g iodine/mL) or diatrizoate meglumine (0.37 g iodine/mL) by oral route at 9.0 g iodine/kg bw and monitored for clinical signs or mortality; the LD50s for iopamidol and diatrizoate meglumine were > 9.0 g iodine/kg bw.

In Study No. 357, rats (n=5/sex/group) were administered iopamidol (0.3 g iodine/mL) by intraperitoneal route at 8.0 to 16.0 g iodine/kg bw (8.0, 10.0, 11.5, 13.5, 16.0 g iodine/kg bw) or diatrizoate meglumine (0.37 g iodine/mL) at 6.6 to 9.6 g iodine/kg bw (6.6, 7.4, 8.4, 9.0, 9.6 g iodine/kg bw. The LD50s for iopamidol and diatrizoate meglumine were 12.0 and 9.2 g iodine/kg bw, respectively. With iopamidol, all deaths occurred by 4 days and most within 24 hours, preceded by prostration with muscular hypotonia, severe dyspnea, and horripilation. With diatrizoate meglumine, all deaths occurred within 1 to 3 hours of dosing, preceded by tonoclonic convulsions, opisthotonos, Straub tail, and vocalization.

In study No. 171, rats (n=13/sex/group) were administered iopamidol (0.3 g iodine/mL) by oral route daily for 4 weeks at 0 (vehicle control), 0.9, 3.0, and 9.0 g iodine/kg bw for the main study group with a subset of treated rats (n=3/sex/group) in the 2-week recovery group. No mortality

was observed up to the maximum feasible oral dose and there were no significant findings by body weights, food consumption, urinalysis, hematology, coagulation, and histologic examinations. Diarrhea was reported in animals administered 9 g iodine/kg bw starting at 5 days and at 3 g iodine/kg bw at 15 days, and there was a significant increase in blood urea nitrogen in males administered iopamidol at 9 g iodine/kg bw that was not reversible following a 2-week recovery period. Based on the findings reported at the high dose, the NOAEL for iopamidol would be 3.0 g iodine/kg bw, corresponding to a dose margin of 3.2-fold by body surface area (BSA) scaling for a maximum 1000 mL oral dose of 9 mg iodine per mL of diluted iopamidol solution.

Other General Toxicology Studies

None.

5.5.2. Genetic Toxicology

Nonclinical genotoxicity data were submitted and reviewed as part of the initial NDA submission. Iopamidol was negative for mutagenicity in genotoxicity studies (Ames test, *Saccharomyces cerevisiae* and *Saccharomyces pombe* gene mutation assay, and *in vivo* mouse host-mediated assay with intraperitoneal *Saccharomyces pombe*). No new studies were submitted as part of this NDA submission.

Other Genetic Toxicity Studies

None.

5.5.3. Carcinogenicity

Carcinogenicity studies of iopamidol were not conducted and are not recommended for a single or infrequent use radiographic contrast agent.

5.5.4. Reproductive and Developmental Toxicology

Developmental and reproductive toxicology data were submitted and reviewed as part of the initial NDA submission. Iopamidol did not affect embryofetal development and did not induce teratogenic changes in the offspring of rats at up to 4.0 g iodine/kg, administered intravenously once a day from days 6 through 15 of pregnancy. Iopamidol did not affect embryofetal development and did not induce teratogenic changes in the offspring of New Zealand white rabbits at up to 2.0 g iodine/kg, administered intravenously once a day from days 6 through 18 of pregnancy. In animal reproduction studies performed in rats, intravenously administered iopamidol did not induce any adverse effects on fertility or general reproductive performance. No new developmental and reproductive studies of iopamidol by oral route were submitted as part of this NDA submission.

5.5.5. Other Toxicology Studies

The Applicant submitted a pulmonary tolerability (misadministration) toxicity study (Study No. 12/1986) in male BR rats (n=5/group) administered a single tracheal insufflation of iopamidol (0.3 g iodine/mL) or diatrizoate meglumine (0.37 g iodine/mL) at 0.24, 0.30, and 0.37 g iodine/kg bw. No mortality was reported for iopamidol at all dose levels whereas 2 and 4 deaths were reported at 0.30 and 0.37 g iodine/kg bw, respectively, for diatrizoate meglumine. Trachea and lungs from control (0.9% NaCl), vehicle control (orange flavor, sodium cyclamate, red curacao flavor, disodium edetate, saccharin, sodium hydroxide, water for injection) and treated animals underwent histopathologic examination after sacrifice at 30 min, 3 and 24 hr, and 7 and 14 d. Histopathologic findings included increased frequency of alveolar histiocytes in animals treated with diatrizoate meglumine (30 min and 3 hr) or iopamidol (1 animal at 14 d), slight or moderate inflammation in control (0.9% NaCl) and vehicle control animals (3 hr), moderate pneumonia in the 0.37 g iodine/kg bw diatrizoate meglumine animals (3 of 5 animals at 24 hr), pneumonia in the 0.30 and 0.37 g iodine/kg bw diatrizoate meglumine animals (1 animal for each dose at 7 d), and mild focus of subacute pneumonia with 0.37 g iodine/kg bw diatrizoate meglumine (1 animal at 14 d).

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant proposes to use Isovue for oral administration to [redacted] (b) (4) the GI tract during CT examinations of the abdomen and pelvis in adult and pediatric patients. Since the product proposed for oral administration is a dilution of Isovue approved under NDA 018735 for intra-arterial and intravenous procedures, it is quantitatively and qualitatively identical in composition to already approved product. For the proposed indication, Isovue will be administered as a dilute oral solution (6 or 9 mg I/mL) at the following doses approximately 60 minutes before beginning the CT procedure:

- Adults and pediatric patients 12 years of age or older: 500 to 1000 mL
- Pediatric patients below 12 years of age:
  - Less than 3 years of age: 50 mL to 300 mL
  - 3 to 5 years of age: 300 mL to 360 mL
  - 6 to 11 years of age: 360 mL to 500 mL

The primary efficacy endpoint, adequate anatomic delineation of the GI tract at the patient-level, from the pivotal study IOP-121 in adult and pediatric patients greater than 3 years of age was deemed acceptable. The efficacy and safety in pediatric patients less than 3 years of age were extrapolated from older patients based on oral contrast volumes reported in the literature and the gastric capacity of this age group.

The proposed dosages for adult and pediatric patients and the proposed imaging initiation time are deemed acceptable.

No dosage modification is recommended based on body weight or organ function.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 018735 S075 and the cited literature and concurs that an approval is warranted due to acceptable efficacy and safety profiles.

6.1.2. Postmarketing Requirements and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Isovue is an approved non-radioactive radio-opaque injectable solution of iopamidol (the active ingredient). Each molecule of iopamidol contains three iodine atoms, which have a much higher atomic number than those of atoms in soft tissues. The higher atomic number of iodine is

associated with an increased ability to attenuate x-rays at the energies used for CT. Thus, Isovue opacifies any structure of the body to which it is distributed by increasing x-ray attenuation.

Following oral administration, iopamidol is minimally absorbed from the gastrointestinal tract. Less than 1% of the administered dose is recovered in urine within 12 hours post-dose. The pharmacokinetics (PK) of iopamidol have been characterized in the previous submission for intravascular administration. Please refer to the Isovue Prescribing Information for the PK of iopamidol.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed Isovue dose for oral administration in adults and pediatric patients 12 years of age or older (6 or 9 mg I/mL, 500 to 1000 mL) is acceptable (refer to Section 6.3.2.2 for details).

The proposed Isovue doses for oral administration in pediatric patients less than 3 years of age (6 or 9 mg I/mL, 50 to 300 mL), 3 to 5 years of age (6 or 9 mg I/mL, 300 to 360 mL), and 6 to 11 years of age (6 or 9 mg I/mL, 360 to 500 mL) are acceptable (refer to Section 6.3.2.2 for details).

The proposed imaging initiation time at approximately 60 minutes post administration is acceptable (refer to Section 6.3.2.2 for details).

Therapeutic Individualization

No dosage modification is recommended based on body weight or organ function (refer to Section 6.3.2.3 for details).

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The absorption of orally administered iopamidol in humans was derived from two studies using Gastromiro (flavored iopamidol 300 mg I/mL for enteral administration), one conducted by the Applicant in adult patients (Rinetti et al. 1987) and the other from a study in pediatric patients (Langer and Kaufmann 1989). The doses and concentrations used in these two studies are summarized in Table 4 below. The major formulation differences between Gastromiro and Isovue are the addition of (b) (4) flavorings in Gastromiro (b) (4) (disodium edetate in Gastromiro and edetate calcium disodium in Isovue), and (b) (4) (citric acid in Gastromiro and tromethamine in Isouve). These differences are not expected to affect bioavailability following oral administration. Therefore, the pharmacokinetic characteristics of orally administered Isovue can be extrapolated from the Gastromiro data.

Table 4. Doses and Concentrations of Iopamidol Used in Human Pharmacokinetic Studies

Study	Iopamidol Concentration, Route of Administration	Volume	Dose Level
Rinetti et al. 1987	300 mg I/mL undiluted, Oral	100 mL	30 g I
Langer and Kaufman 1989	300 mg I/mL diluted by 50%, Oral	5 mL/kg bw	0.75 g I/kg bw

Source: Table A in Section 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: mg I/mL, milligrams of iodine per milliliter; g I, grams of iodine; bw, body weight

Bracco Study in Adult Patients (Rinetti et al. 1987)

Ten adult patients (mean age 61.3±11.9 years; range 46-75 years) received an oral dose of 100 mL of undiluted Gastromiro. Blood samples were collected at baseline and at 30 minutes, 1, 2, 4, 6, 8, and 12 hours post exposure. Urine samples were obtained at baseline and between 0 to 4, 4 to 8, and 8 to 12 hours after exposure.

Peak plasma values occurred at 1 to 2 hours after Gastromiro administration. The total urinary excretion at 12 hours was 0.37% ± 0.32% of the administered dose, indicating very low systemic absorption following oral administration of undiluted Gastromiro. Of note, iopamidol excretion is primarily through kidneys (80-90%) after IV administration.

Pediatric Patients (Langer and Kaufmann 1989)

Three hundred and eighteen pediatric patients received iopamidol 300 and iohexol 300 (a non-ionic iodinated contrast agent approved for oral administration in the United States) at 1:1 dilution resulting in an iodine concentration of 150 mg I/mL. The urine of 8 patients was collected for 24 hours after oral administration of the agent. The urinary iodine concentration ranged from 0.075% to 0.527% of the applied dose in seven patients and was 1.458% for the remaining patient.

Overall, average systemic absorption of orally administered iopamidol was limited in both adult and pediatric patients (<1%).

Food did not interfere with the efficacy or safety of orally administered iopamidol. Refer to details in Section 6.3.2.4.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Substantial evidence of effectiveness has been demonstrated. See details in Sections 7.2 and 8.

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The proposed Isovue concentration for oral administration (6 or 9 mg I/mL) was based on previous experience in published literature (Gore 2008). The proposed Isovue doses for oral

administration in adults and pediatric patients 12 years of age or older (6 or 9 mg I/mL, 500 to 1000 mL) and in pediatric patients less than 3 years of age (6 or 9 mg I/mL, 50 to 300 mL), 3 to 5 years of age (6 or 9 mgI/mL, 300 to 360 mL), and 6 to 11 years of age (6 or 9 mg I/mL, 360 to 500 mL) were supported by the pivotal study IOP-121. There were no adverse reactions attributable to oral use of Isovue in adult and pediatric patients in IOP-121.

The proposed imaging initiating time is 60 minutes post administration and was supported by the pivotal study IOP-121.

Doses in Adult Patients

No formal dose-finding study was performed to determine the adult dose. IOP-121 evaluated the Isovue dose of 9.7 mg I/mL and 930 mL (9 g I) in 152 adult patients. Clinical studies were conducted by the Applicant and published in the scientific literature with orally administered Gastromiro diluted between 2% to 20% in volumes up to 1000 mL (refer to Section 7.1). As discussed in Section 8.1, study IOP-121 provided primary evidence of effectiveness, and the legacy clinical studies and published literature provided confirmatory and supportive evidence of effectiveness. The safety profile from IOP-121 and postmarketing surveillance data of orally administered Isovue (off label use) are acceptable (refer to Section 8.2). Based on these effectiveness and safety findings, the proposed dose for adult patients (6 or 9 mg I/mL, 500 to 1000 mL) is deemed acceptable.

Doses in Pediatric Patients

No formal dose-finding study was performed to determine the pediatric doses. The proposed Isovue dose for pediatric patients 12 years of age or older is identical to the proposed adult dose (6 or 9 mg I/mL, 500 to 1000 mL). In the pivotal study IOP-121, the pediatric patients aged 12 to 17 years (n=6) received the same dose as adult patients (9.7 mg I/mL, 930 mL). For younger pediatric patients in IOP-121 (aged 3 to 11 years, n=60), Isovue doses ranged from 241 to 490 mL with concentrations of 5.7 to 8.9 mg I/mL. The volume administered in pediatric patients aged 3 to 5 years (n=13) ranged from 301 to 368 mL, while patients aged 6 to 11 years (n=47) received volumes ranging from 241 to 490 mL. The proportion of pediatric patients with adequate bowel delineation on CT was numerically lower than that observed in adult patients under 65 years of age for two of the three readers. However, the effect size was considered adequate in pediatric patients (refer to Section 8.1.1.1 for details). The proposed doses for pediatric patients 3 years of age or older are deemed acceptable because of the acceptable efficacy and safety profile (refer to Section 8).

IOP-121 did not evaluate Isovue in patients younger than 3 years of age. The proposed volume of 50 to 300 mL for pediatric patients less than 3 years of age is based on considerations including oral contrast guidelines at sites in study IOP-121, evidence in the literature, and gastric capacity.

Gastric capacity ranges from 10 to 100 mL in neonates, 90 to 500 mL in infants and toddlers, 750 to 960 mL in older children, and 1500 mL in adolescents (Bai et al. 2016). Per FDA definition of pediatric subpopulations for drugs and biologics, the age ranges are birth through 27 days for

neonates, 28 days to 23 months for infants, 2 years to 11 years for children, and 12 years to less than 17 years for adolescents. The oral contrast volumes for abdominal and pelvic CT in pediatric patients can vary within clinical practice, but an example of a published dosing regimen up to 12 years of age is shown in Table 5 (Frush 2008).

Table 5. Oral Contrast Volume for Abdominal and Pelvic CT in Infants and Children

Age	Amount (1.5-3.0% solution)
1–6 months	60–120 ml (2–4 oz)
6–12 months	120–180 ml (4–6 oz)
1–4 years	180–270 ml (6–9 oz)
4–8 years	270–360 ml (9–12 oz)
8–12 years	360–480 ml (12–16 oz)
12–16 years	480–600 ml (16–20 oz)

Source: Responses to Clinical Pharmacology Information Request issued on July 18, 2025.

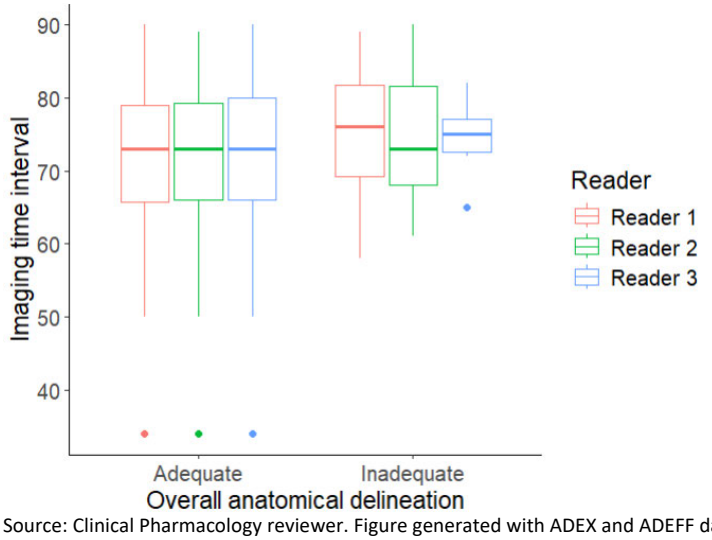
The proposed volume of 50 to 300 mL for pediatric patients less than 3 years of age aligns with oral contrast volumes reported in the literature and the gastric capacity of this age group, and therefore, is considered reasonable for efficacy.

In addition, the systemic exposure of iopamidol at the proposed oral dose is expected to be much lower than that of intra-arterial or intravenous administration (e.g., maximum intra-arterial dose for angiocardiography in pediatrics less than 2 years of age: 40 mL at concentration of 370 mg I/mL; maximum intravenous dose for CT of head and body: 100 mL at concentration of 300 mg I/mL) due to less than 1% oral absorption.

Imaging Initiation Time

In IOP-121, the CT scans were initiated at 34 to 90 minutes following Isovue administration. No differences in bowel delineation were observed across the imaging window times (Figure 1). The proposed imaging initiation time of 60 minutes following Isovue administration falls within the time interval range evaluated in the study IOP-121 and is considered acceptable based on the observed lack of effect of time interval on bowel delineation from 34 to 90 minutes.

Figure 1. Imaging Time Interval in Cases with Adequate and Inadequate Bowel Delineation



Source: Clinical Pharmacology reviewer. Figure generated with ADEX and ADEFF datasets submitted in the original submission.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

The data do not support a need for dosage adjustment based on body weight. Subgroup analysis of efficacy data from IOP-121 demonstrated comparable bowel delineation across different body weight groups in patients <12 years of age and ≥12 years of age (Table 6 and Table 7). Hepatic and renal dysfunction are not expected to impact Isovue due to limited systemic absorption following oral administration.

Table 6. Bowel Delineation in Patients <12 years of Age by Body Weight Quartile (Study IOP-121, Off-Site Assessment, Patient-Level)

	Off-Site Readers		
	Reader 1 n (%) [95% CI]	**Reader 2 n (%) [95% CI]**	**Reader 3 n (%) [95% CI]**
Weight Group 1: ≤23.35 kg			
Anatomic Delineation	15[a]	15[a]	15[a]
Adequate	12 (80.0) [54.8, 93.0]	13 (86.7) [62.1, 96.3]	14 (93.3) [70.2, 98.8]
Inadequate	3 (20.0) [7.0, 45.2]	2 (13.3) [3.7, 37.9]	1 (6.7) [1.2, 29.8]
Weight Group 2: >23.35, ≤27.85kg			
Anatomic Delineation	15[a]	15[a]	15[a]
Adequate	8 (53.3) [30.1, 75.2]	11 (73.3) [48.0, 89.1]	15 (100.0) [79.6, 100.0]
Inadequate	7 (46.7) [24.8, 69.9]	4 (26.7) [10.9, 52.0]	0 (0.0) [0.0, 20.4]
Weight Group 3: >27.85, ≤36.85 kg			
Anatomic Delineation	15[a]	15[a]	15[a]
Adequate	8 (53.3) [30.1, 75.2]	8 (53.3) [30.1, 75.2]	14 (93.3) [70.2, 98.8]
Inadequate	7 (46.7) [24.8, 69.9]	7 (46.7) [24.8, 69.9]	1 (6.7) [1.2, 29.8]
Weight Group 4: >36.85 kg			
Anatomic Delineation	15[a]	15[a]	15[a]
Adequate	13 (86.7) [62.1, 96.3]	12 (80.0) [54.8, 93.0]	15 (100.0) [79.6, 100.0]
Inadequate	2 (13.3) [3.7, 37.9]	3 (20.0) [7.0, 45.2]	0 (0.0) [0.0, 20.4]

Source: Table C in the responses to Clinical Pharmacology Information Request issued on June 5, 2025.

Table 7. Bowel Delineation in Patients ≥12 years of Age by Body Weight Quartile (Study IOP-121, Off-Site Assessment, Patient-Level)

	Off-Site Readers		
	Reader 1 n (%) [95% CI]	**Reader 2 n (%) [95% CI]**	**Reader 3 n (%) [95% CI]**
Weight Group 1: ≤63.5 kg			
Anatomic Delineation	42[a]	42[a]	42[a]
Adequate	33 (78.6) [64.1, 88.3]	35 (83.3) [69.4, 91.7]	41 (97.6) [87.7, 99.6]
Inadequate	9 (21.4) [11.7, 35.9]	7 (16.7) [8.3, 30.6]	1 (2.4) [0.4, 12.3]
Weight Group 2: >63.5, ≤77.1 kg			
Anatomic Delineation	39[a]	39[a]	39[a]
Adequate	31 (79.5) [64.5, 89.2]	32 (82.1) [67.3, 91.0]	37 (94.9) [83.1, 98.6]
Inadequate	8 (20.5) [10.8, 35.5]	7 (17.9) [9.0, 32.7]	2 (5.1) [1.4, 16.9]
Weight Group 3: >77.1, ≤91.1 kg			
Anatomic Delineation	38[a]	38[a]	38[a]
Adequate	30 (78.9) [63.7, 88.9]	31 (81.6) [66.6, 90.8]	37 (97.4) [86.5, 99.5]
Inadequate	8 (21.1) [11.1, 36.3]	7 (18.4) [9.2, 33.4]	1 (2.6) [0.5, 13.5]
Weight Group 4: >91.1 kg			
Anatomic Delineation	39[a]	39[a]	39[a]
Adequate	33 (84.6) [70.3, 92.8]	34 (87.2) [73.3, 94.4]	38 (97.4) [86.8, 99.5]
Inadequate	6 (15.4) [7.2, 29.7]	5 (12.8) [5.6, 26.7]	1 (2.6) [0.5, 13.2]

Source: Table D in the responses to Clinical Pharmacology Information Request issued on June 5, 2025.

6.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food-drug interactions have not been fully characterized for orally administered iopamidol, but a published study randomized patients undergoing CT exams with oral contrast to fasted (at least 4 hours) or non-fasted (unrestricted consumption of liquids and solid food) groups (Neeman et al. 2021). The study included 691 patients in the fasted group and 566 patients in the non-fasted group who received oral 1 L administration of meglumine ioxitalamate approximately 90 minutes prior to CT scanning. None of the patients in the nonfasted group was referred for a repeat CT scan, suggesting that food did not interfere with the interpretation of the gastrointestinal imaging with meglumine ioxitalamate. Both meglumine ioxitalamate and Isovue share the same mechanism of action, therefore food is not expected to affect CT examination of gastrointestinal tract with Isovue. Of note, the rates of adverse gastrointestinal symptoms were not significantly different between the non-fasted and the fasted groups (nausea: 7.9% versus 6.8%, p = 0.42; vomiting: 3.5% versus 2.6%, p = 0.3; abdominal pain: 1.6% versus 1.7%, p = 0.89).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 8. Table of Clinical Studies

Trial Identity	Trial Design	Regimen/Schedule/Route	Key Endpoints	Sample Size	Study Population	Number of Centers and Countries
IOP-121 (NCT 04453059)	Retrospective, single-arm, cohort	Age ≥12 years: 500-1000 mL 2-3% Isovue 300, po Age <12 years: 50-500 mL 2-3% Isovue 300, po	Bowel delineation by segment	218	Adult and pediatric patients who had abdominal/pelvic CT as standard of care and had received oral Isovue-300	2 centers (United States)
Macarini	Randomized, double blind, active comparator controlled	Gastromiro 8-20 mL diluted to 6-20%, po or pr Gastrografin 10-20 mL diluted to 6-20%, po or pr	Diagnostic value/contrast quality	Gastromiro 25 Gastrografin 25	Adults with suspected GI disease indicated for abdominal CT	1 center (Italy)
Lanza	Randomized, double blind, active comparator controlled	Gastromiro 3-20 mL diluted to 2-3%, po or pr Gastrografin 8-32 mL diluted to 2-3%, po or pr	Diagnostic value/contrast quality	Gastromiro 25 Gastrografin 25	Adults with suspected GI disease indicated for abdominal CT	1 center (Italy)
(Doyle et al. 1993)	Randomized, double blind, active comparator controlled	Gastromiro 3%, 400-700 mL, po Urografin 2.4%, 400-700 mL, po E-Z CAT 1.4%, 400-700 mL, po	Bowel opacification by segment	Gastromiro 52 Urografin 48 E-Z CAT 50	Patients referred for abdominal or abdominal/pelvic CT	1 center (United Kingdom)
(Morgan et al. 2009)	Reader blind, active comparator controlled	Gastromiro 2.5%, 1 L, po Gastrografin 2%, 1 L, po E-Z CAT 1.1%, 1 L, po	Bowel opacification by segment and overall	Gastromiro 79 Gastrografin 54 E-Z CAT 34	Patients scheduled for abdominal/pelvic CT	1 center (United Kingdom)

Source: Adapted from Summary of Clinical Efficacy section 2.7.3.2.1, Table J, and Table M
Abbreviations: CT = computed tomography, GI = gastrointestinal, po = by mouth, pr = by rectum

7.2. Review Strategy

Primary evidence of effectiveness was study IOP-121, which is reviewed in detail in the next section. The Applicant also submitted two published studies and two "legacy" studies (Macarini and Lanza) as supportive evidence. The legacy studies were conducted for the Applicant as part of the evidence of effectiveness of Gastromiro, an oral formulation of iopamidol 300 mg iodine/mL marketed outside the United States. One of the published studies, (Morgan et al. 2009), was reviewed as confirmatory evidence. The other three studies used different dosing and administration than proposed for labeling and were only briefly reviewed.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. IOP-121

Trial Design

IOP-121 was a retrospective, single-arm, cohort study intended to evaluate effectiveness of Isovue to opacify and delineate the GI tract on abdominal and pelvic CT. It incorporated blinded re-evaluation of CT images using a prospectively designed reading paradigm.

The study enrolled adult and pediatric patients who had abdominal and pelvic CT with oral administration of Isovue. Key patient selection criteria included documented administration of 500 mL to 1000 mL (for patients ≥12 years old) or 50 mL to 500 mL (for patients <12 years old) of Isovue 300 diluted to 2% - 3% (±10%; equivalent to 6 mg iodine/mL to 9 mg iodine/mL) and CT scan initiation 30 to 90 minutes after administration. Intravenous contrast was allowed as long as it was also Isovue. CT images, demographic data, and safety data were required to be available. Notable exclusions were patients who did not actively drink the contrast, patients who had any abdominal or pelvic surgery that resulted in alteration of bowel transit time, and CT performed for known or suspected bowel obstruction. Patient selection was to start from the date of IRB approval of the protocol and proceed backward in time until a sufficient number of consecutively enrolled patients who met the selection criteria were obtained.

CT images were evaluated in randomized order by three independent radiologists who were blinded to all patient information, including administration scheme of the oral Isovue. The initial assessment was for technical adequacy of the images on a 4-point scale:

- 1 = Presence of artifacts unrelated to the oral contrast agent (such as respiratory or motion artifacts) totally compromising image quality and interpretability
- 2 = GI tract segments, including stomach, duodenum, jejunum, and proximal/distal ileum are not adequately/completely covered anatomically in the field of view of the CT scan so that only partial evaluation of the GI segments would be possible

- 3 = Presence of artifacts unrelated to the oral contrast agent (such as respiratory or motion artifacts) partially compromising image quality but evaluation of the GI segments is still possible
- 4 = Absence of artifacts unrelated to the oral contrast agent (such as respiratory or motion artifacts), GI tract clearly visualized and completely covered in the CT scan.
    - Source: IOP-121 protocol section 6.6.1

Afterward, readers evaluated anatomic delineation of the GI tract. The GI tract was divided into five segments, stomach, duodenum, jejunum, proximal ileum, and distal ileum. No definition of segmental boundaries was provided. The esophagus, colon, and rectum were not evaluated. The most distal segment where oral contrast could be seen was recorded. Anatomic delineation and opacification of each segment was scored on a 3-point scale:

- 1 (poor) = Opacification is absent or insufficient to differentiate the segment from the surrounding fat tissue and/or from adjacent organs and/or from adjacent pathologic abnormalities (if present) such as masses, lymph nodes, abscesses, fluid collections; OR major streak artifacts caused by the oral contrast agent are present, impairing image assessment and anatomic delineation of the segment
- 2 (sufficient) = Opacification is incomplete but enough to differentiate the segment from the surrounding fat tissue and/or from adjacent organs and/or from adjacent pathologic abnormalities (if present) such as masses, lymph nodes, abscesses, fluid collections; AND streak artifacts caused by the oral contrast agent are absent or minimal, not impairing image assessment and anatomic delineation of the segment
- 3 (good) = Opacification is complete and the segment can be easily differentiated from the surrounding fat tissue and/or from adjacent organs and/or from adjacent pathologic abnormalities (if present) such as masses, lymph nodes, abscesses, fluid collections; AND streak artifacts caused by the oral contrast agent are absent or minimal, not impairing image assessment and anatomic delineation of the segment.
    - Source: Adapted from IOP-121 protocol section 6.6.2

Study Endpoints

The primary endpoint for IOP-121 was the proportion of patients who had adequate anatomic delineation of the GI tract. This was defined as adequate delineation of at least three of the five segments. In turn, a segment was considered to have adequate anatomic delineation if it was scored 2 (sufficient) or 3 (good).

Other predefined endpoints relevant to this review included proportion of patients with adequate anatomic delineation on a per segment basis, technical adequacy of the CT images, and inter-reader agreement for the primary endpoint.

Statistical Analysis Plan

Three analysis populations were predefined for IOP-121.

- Safety: all enrolled patients who received oral administration of Isovue-300
- Intent to diagnose (ITD): all patients who underwent CT examination of the abdomen and pelvis after oral administration of Isovue-300 and had off-site data available based on the blinded review of CT images
- Per protocol (PP): all patients in the ITD analysis population who had technically adequate images per off-site blinded review, and did not have major protocol deviations

The primary efficacy analysis was performed in the PP population.

Study success was defined as the proportion of patients with adequate anatomic delineation of at least 80% at the lower bound of the 95% Wilson confidence interval for at least two of three readers.

Protocol Amendments

The IOP-121 protocol was amended three times, however two of the amendments were made prior to initiation of the study and are not detailed here. Amendment 3 changed the allowable time range between completing oral contrast administration and CT scanning from 60 – 90 minutes to 30 – 90 minutes. A total of 46 (21%) patients were enrolled under Amendment 2 and the remainder under Amendment 3.

8.1.1.1. IOP-121 Results

Compliance With Good Clinical Practices

The Applicant declared that IOP-121 was conducted in compliance with Title 21, CFR Part 50, CFR Part 56, and CFR Part 312, and with the ethical principles of Good Clinical Practices (GCP) as outlined in ICH E6 (November 2016).

Financial Disclosure

The Applicant certified that they have not entered into any financial arrangement with the clinical investigators of IOP-121.

Patient Disposition and Protocol Violations/Deviations

All screened patients were enrolled into the study. All enrolled patients received Isovue orally, underwent CT of the abdomen and pelvis, and had images available. No protocol deviations were reported. Therefore, the safety population, ITD population, and PP population were identical.

Table of Demographic Characteristics

The anticipated patient population for oral Isovue is broad, encompassing many different disease conditions in both sexes, all ages, and all races. The enrolled population in IOP-121 appears reasonably representative (Table 9). Ethnicity data were not reported in the study.

Table 9. Patient Demographics in IOP-121

	Safety Population		
Characteristic	**Age ≤16 Years (n=66)**	**Age >16 Years (n=152)**	**All Ages (n=218)**
Sex, n (%)			
Male	35 (53)	63 (41)	98 (45)
Female	31 (47)	89 (59)	120 (55)
Age, years			
Mean (standard deviation)	8.6 (2.8)	51.7 (18.1)	38.6 (25)
Median (range)	9 (3, 16)	51 (18, 97)	38.5 (3, 97)
Age group, n (%)			
≤16 years	66 (100)	0	66 (30)
≥ 65 years	0	40 (26)	40 (18)
≥ 75 years	0	18 (12)	18 (8)
Race, n (%)			
White	48 (73)	116 (76)	164 (75)
Black or African American	6 (9)	13 (9)	19 (9)
Asian	3 (5)	5 (3)	8 (4)
Native Hawaiian or Other Pacific Islander	1 (1)	0	1 (<1)
Not reported or unknown	8 (12)	18 (12)	26 (12)

Source: IOP-121 Clinical Study Report, Table C and FDA clinical reviewer

Other Baseline Characteristics

The most common indication for CT in IOP-121 was pain (Table 10). Nearly all patients also received intravenous iodinated contrast. This is expected, as abdominopelvic CT for most indications is performed with intravenous contrast, and indications that do not generally use intravenous contrast, such as kidney stones, tend to also not use enteric contrast. CT tube potential is noted as it can affect visibility of iodinated contrast, with lower values over the typically used range increasing iodine conspicuity. In this study, most adult patients were scanned at 120 kVp and most children at 80 kVp or 100 kVp, which are typical values in routine clinical practice.

Table 10. Patient Baseline Characteristics in IOP-121

	Safety Population		
Characteristic	**Age ≤16 Years (n=66)**	**Age >16 Years (n=152)**	**All Ages (n=218)**
Weight, kg			
Mean (standard deviation)	33.6 (13.5)	81.4 (23.8)	66.9 (30.6)
Median (range)	29.9 (14.8, 73)	77.3 (44.8, 208.3)	67.1 (14.8, 208.3)

	Safety Population		
Characteristic	Age ≤16 Years (n=66)	Age >16 Years (n=152)	All Ages (n=218)
CT Indication, n (%)*			
Pain	63 (95)	121 (80)	184 (84)
Vomiting	3 (5)	7 (5)	10 (5)
Mass or cancer	3 (5)	12 (8)	15 (7)
Intravenous contrast, n (%)			
Yes	66 (100)	147 (97)	213 (98)
No	0	5 (3)	5 (2)
CT tube potential, n (%)			
80 kVp	13 (20)	0	13 (6)
100 kVp	50 (76)	20 (13)	70 (32)
120 kVp	3 (4)	129 (85)	132 (61)
140 kVp	0	3 (2)	3 (1)

Source: IOP-121 Clinical Study Report, Table C and section 11.1, and FDA clinical reviewer
Abbreviations: CT = computed tomography, kVp = kilovolt peak
* Not all indications are listed and indications are not mutually exclusive. Percentages are not expected to sum to 100%.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites, with administered dose recorded by study staff. Therefore, compliance was not an issue.

Efficacy Results–Primary Endpoint

As shown in Table 11, the proportion of patients who had adequate delineation of the gastrointestinal tract, defined as sufficient or good delineation of at least three segments of bowel, ranged from 77% to 97% depending on reader. The lower bounds of the 95% confidence intervals for the three readers were 71%, 75%, and 94%. Thus, one of the three readers exceeded the predefined threshold of 80% and the study did not meet its success criteria of at least two readers exceeding 80%.

Table 11. Patient-Level Adequacy of Gastrointestinal Tract Anatomic Delineation in IOP-121

	Per Protocol Population (n=218)	
Reader	Adequate Anatomic Delineation % (95% CI)	Inadequate Anatomic Delineation % (95% CI)
Reader 1	77 (71, 82)	23 (18, 29)
Reader 2	81 (75, 85)	19 (15, 25)
Reader 3	97 (94, 98)	3 (2, 6)

Source: IOP-121 Clinical Study Report, Table H
Abbreviation: CI = confidence interval

No substantial difference was identified by sex for adequacy of bowel delineation (Table 12).

Table 12. Patient-Level Adequacy of Gastrointestinal Tract Anatomic Delineation by Sex in IOP-121

	Adequate Anatomic Delineation Per Protocol Population (n=218) % (95% CI)	
Reader	**Male (n=98)**	**Female (n=120)**
Reader 1	76 (66, 83)	78 (70, 85)
Reader 2	80 (71, 86)	82 (74, 88)
Reader 3	97 (91, 99)	97 (92, 99)

Source: IOP-121 Clinical Study Report, Section 11.3.4.3
Abbreviation: CI = confidence interval

The proportion of pediatric patients with adequate delineation trended lower than for patients aged >16 to <65 years for Reader 1 and Reader 2 (Table 13). Similarly, the proportion of adults aged at least 65 years with adequate delineation trended lower for all readers. However, the effect size in the younger and older patients appears sufficient. Subgroup analysis by CT tube potential is not shown, as tube potential was closely coupled to age.

Table 13. Patient-Level Adequacy of Gastrointestinal Tract Anatomic Delineation by Age in IOP-121

	Adequate Anatomic Delineation Per Protocol Population (n=218) % (95% CI)		
Reader	**Age ≤ 16 (n=66)**	**Age >16 - <65 (n=112)**	**Age ≥65 (n=40)**
Reader 1	68 (56, 78)	84 (76, 90)	73 (57, 84)
Reader 2	74 (63, 83)	88 (80, 92)	73 (57, 84)
Reader 3	97 (90, 99)	98 (94, 100)	93 (80, 97)

Source: IOP-121 Clinical Study Report, Table J and FDA clinical reviewer
Abbreviation: CI = confidence interval

The proportion of patients Reader 1 scored with adequate bowel delineation trended lower for race other than White compared to White patients (Table 14). Because of the smaller differences for Readers 2 and 3 and the limited number of patients with race other than White, the significance of this finding is uncertain. Subgroup analysis by ethnicity cannot be performed as ethnicity data were not reported.

Table 14. Patient-Level Adequacy of Gastrointestinal Tract Anatomic Delineation by Race in IOP-121

	Adequate Anatomic Delineation Per Protocol Population (n=218) % (95% CI)		
Reader	**White (n=164)**	**Other Than White (n=28)**	**Not Reported (n=26)**
Reader 1	81 (74, 86)	54 (36, 70)	77 (58, 89)
Reader 2	82 (76, 87)	75 (57, 87)	77 (58, 89)
Reader 3	97 (93, 99)	96 (82, 99)	96 (81, 99)

Source: IOP-121 Clinical Study Report, Section 11.3.4.3 and FDA clinical reviewer
Abbreviation: CI = confidence interval

It is not meaningful to perform a subgroup analysis by whether patients received intravenous contrast as very few patients did not. Based on differences in localization of enteric and vascular contrast (intraluminal versus intramural) and long-standing clinical experience with

enteric iodinated contrast for CT, oral Isovue is not expected to perform differently in patients who do or do not receive intravenous contrast.

Data Quality and Integrity

FDA Office of Scientific Investigations audits were not requested for this retrospective study. IOP-121 recruited patients from two sites in the same United States hospital system. The results from the two sites appear similar (Table 15).

Table 15. Patient-Level Adequacy of Gastrointestinal Tract Anatomic Delineation by Study Site in IOP-121

	Adequate Anatomic Delineation Per Protocol Population (n=218) % (95% CI)	
Reader	**Site 02 (n=109)**	**Site 03 (n=109)**
Reader 1	79 (70, 86)	75 (66, 82)
Reader 2	83 (74, 89)	79 (70, 86)
Reader 3	97 (92, 99)	96 (91, 99)

Source: FDA clinical reviewer
Abbreviation: CI = confidence interval

Efficacy Results – Other Relevant Endpoints

Readers 1 and 3 scored all patient images as 4 for image quality, indicating absence of artifact unrelated to oral Isovue and complete anatomic coverage of the bowel to be evaluated. Reader 2 scored 97% of patient images as 4 and the remaining 3% as 3 (artifact unrelated to oral Isovue that did not prevent evaluation of the bowel).

Because the primary endpoint does not distinguish between scores of 2 (sufficient) and 3 (good), the total score for the five bowel segments, ranging from 5 to 15, was examined. The mean total score was 10.9, 11.4, and 11.6 for Readers 1, 2, and 3, respectively. These values indicate that the higher proportion of patients with adequate delineation for Reader 3 was driven by relatively small differences in overall scoring.

Per segment analyses of proportion of patients with adequate delineation and delineation score (range 1 to 3) are presented in Table 16 and Table 17. The proportion of patients with adequate delineation was more than 80% at the lower bound of the 95% confidence interval for the proximal ileum and distal ileum for all readers and in the stomach for Reader 3. The lowest proportions were the duodenum and stomach for Readers 1 and 2, and jejunum for Reader 3. The per segment delineation scores follow the same trends as the proportion of patients with adequate delineation except for the stomach for Reader 3, where the proportion is second highest but the score is third highest. This reflects the larger number of patients scored 2 (sufficient) instead of 3 (good) for the stomach than the distal ileum. The mean number of bowel segments per patient scored as adequately delineated was 3.6, 3.7, and 4.3 for Readers 1, 2, and 3, respectively. One patient had no segments scored as adequate by Reader 2. Three, six, and one patient, depending on reader, had one segment scored as adequate.

Table 16. Per Segment Adequacy of Gastrointestinal Tract Anatomic Delineation in IOP-121

	Adequate Anatomic Delineation Per Protocol Population (n=218) % (95% CI)		
Segment	**Reader 1**	**Reader 2**	**Reader 3**
Stomach	52 (46, 59)	58 (52, 65)	95 (91, 97)
Duodenum	50 (43, 57)	53 (46, 59)	78 (73, 83)
Jejunum	76 (70, 81)	80 (75, 85)	65 (59, 71)
Proximal ileum	95 (92, 98)	93 (89, 96)	100 (97, 100)
Distal ileum	86 (81, 90)	87 (82, 91)	88 (83, 91)

Source: IOP-121 Clinical Study Report, Table I
Abbreviation: CI = confidence interval

Table 17. Per Segment Anatomic Delineation Scores in IOP-121

	Anatomic Delineation Score Per Protocol Population (n=218) Mean (Standard Deviation)		
Segment	**Reader 1**	**Reader 2**	**Reader 3**
Stomach	1.72 (0.77)	1.85 (0.81)	2.32 (0.57)
Duodenum	1.61 (0.68)	1.74 (0.79)	2.05 (0.69)
Jejunum	2.09 (0.75)	2.34 (0.79)	1.88 (0.75)
Proximal ileum	2.76 (0.52)	2.79 (0.55)	2.72 (0.46)
Distal ileum	2.68 (0.7)	2.69 (0.69)	2.59 (0.7)

Source: FDA clinical reviewer

Both the per patient and per segment analyses show greater agreement between Reader 1 and Reader 2 than either with Reader 3. All three readers agreed on the per patient assessment of adequacy of gastrointestinal tract delineation in 72% of cases, with a generalized kappa of 0.27. At the segment-level, the three readers appeared to agree more in the jejunum, proximal ileum, and distal ileum than in the stomach and duodenum.

Dose/Dose Response

The dose and dose to scan time of Isovue in IOP-121 are summarized in Table 18. The dilution and volume of drug administered were identical in all adult patients, precluding dose-response analyses on a per mg I or per mL basis. No clear correlation between total segment score and dose on a mL/kg basis was found for adults or pediatrics (analysis not shown). In the pediatric subgroup, no clear correlation was identified between total volume of contrast and total segment score.

Table 18. Dosing of Oral Isovue in IOP-121

	Safety Population		
Parameter	**Age ≤16 Years (n=66)**	**Age >16 Years (n=152)**	**All Ages (n=218)**
Isovue dilution, mg Iodine/mL			
Mean (standard deviation)	6.7 (1.1)	9.7 (0)	8.8 (1.5)
Median (range)	6.2 (5.7, 9.7)	9.7 (9.7, 9.7)	9.7 (5.7, 9.7)
Oral Isovue volume administered, mL			
Mean (standard deviation)	467 (160)	930 (0)	790 (231)
Median (range)	460 (241, 930)	930 (930, 930)	930 (241, 930)

Parameter	Safety Population Age ≤16 Years (n=66)	Age >16 Years (n=152)	All Ages (n=218)
Time between end of oral Isovue and CT, minutes			
Mean (standard deviation)	74 (10)	72 (9)	73 (9)
Median (range)	75 (34, 89)	72 (50, 90)	73 (34, 90)

Source: IOP-121 Clinical Study Report, Table E and FDA clinical reviewer
Abbreviation: CT = computed tomography

8.1.2. (Morgan et al. 2009)

Trial Design

(Morgan et al. 2009) was a prospective study evaluating bowel opacification on CT after administration of Gastromiro (iopamidol oral solution, not marketed in U.S.), Gastrografin (diatrizoate meglumine/diatrizoate sodium, NDA 011245), and E-Z-Cat (barium sulfate, NDA 208036). Patients scheduled for clinically indicated CT of the abdomen and pelvis were instructed to avoid eating for three hours prior to their appointment. At the appointment, each patient received 1000 mL of one of the contrast agents, to be consumed orally over one hour. Each contrast agent was diluted in water prior to administration resulting in concentrations of 7.5 mg I/mL for Gastromiro, 7.4 mg I/mL for Gastrografin, and 1.1% w/v for E-Z-Cat. The method of assignment of the agents was not described. If the CT scan was delayed, they were given an additional 250 mL and instructed to slowly drink until the scan was performed. Patients were asked to rate palatability using a visual analog scale. Contrast consumption was rated by a radiographer or assistant, blinded to identity of the contrast, on a four point scale (1 very poor, 2 poor, 3 OK, and 4 ideal) based on the amount of contrast remaining at 1 hour, with 4 defined as none remaining, 3 as more than 0 to <25% remaining, 2 as 25% to <50% remaining, and 1 as 50% or more remaining.

Three radiologists, blinded to identity of the contrast agent, scored the CT images for bowel opacification using a 4-point scale:

- 1 very poor - large areas of unopacified bowel
- 2 poor - some areas of bowel were unopacified, and could possibly be misconstrued as another cause of soft tissue opacity
- 3 OK - some areas were poorly opacified, but all the small bowel was clearly identifiable by contrast
- 4 ideal - complete bowel opacification

Scoring was for the overall bowel and by segment, with segments including stomach, duodenum, jejunum, proximal ileum, and distal ileum. Segment boundaries for the study were not stated. There was no discussion of whether the readers evaluated in consensus or independently.

The study was conducted in two stages. In the first, patients received either Gastromiro or Gastrografin. In the second, patients received either Gastomiro or E-Z-Cat.

Patient Disposition

In stage 1 of the study, using Gastromiro and Gastrografin, 11 patients did not fully complete the palatability questionnaire. Six patients were not scored for bowel opacification because their identification code was not recorded. In stage 2, using Gastromiro and E-Z-Cat, all patients were evaluable.

Demographic Characteristics

In stage 1 of the study, 50/101 (50%) patients were males. The mean patient age was 57 years with a range of 17 to 88 years. In stage 2, 31/66 (47%) patients were male. The mean patient age was 59 years with a range of 18 to 88 years.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The authors defined satisfactory compliance with the contrast administration protocol as scoring 3 or 4 on the four-point scale, in other words less than 25% of the dose remaining at 1 hour. In stage 1, 40 of 47 (85%) patients in the Gastromiro group and 31 of 54 (57%) patients in the Gastrografin group had satisfactory compliance. Thirteen patients received extra contrast due to a delay in their CT scan, four in the Gastromiro group and nine in the Gastrografin group.

Analogous results were not reported for study stage 2, though compliance was stated as similar between Gastromiro and E-Z-Cat.

Results

The results of bowel opacification scoring are shown in Table 19. Because of the inherently subjective and nonlinear nature of these scores, the absolute values are difficult to interpret. This is further complicated by the apparent variability of scoring for Gastromiro between the two stages of the study. However, the mean ratings indicate “OK” (score 3) opacification by iopamidol for the jejunum and ileum. The pattern of scores generally indicates better opacification of the ileum and to a lesser extent jejunum than stomach or duodenum for all tested agents. This matches the pattern seen in IOP-121, which shared similar volume, concentration, and timing of iopamidol administration.

The authors defined satisfactory bowel opacification as score 3 or 4 for the overall bowel rating. In stage 1 of the study, 38/45 (84%; 95% confidence interval 71%, 92%) patients had satisfactory opacification with Gastromiro compared to 32/48 (67%; 95% confidence interval 53%, 78%) patients with Gastrografin. Analogous results are not reported for stage 2.

Table 19. Bowel Opacification Scores in (Morgan et al. 2009)

	Mean Bowel Opacification Score Range 1 (very poor) to 4 (ideal)			
	First Stage		Second Stage	
Segment	Gastromiro n=45	Gastrografin n=48	Gastromiro n=32	E-Z-Cat n=34
Overall bowel	3.1	2.6	2.8	3.4
Stomach	3.3	2.8	2.5	2.8
Duodenum	3	2.5	2.6	2.8
Jejunum	3.2	2.6	2.9	3.2
Proximal ileum	3.6	3	3.1	3.4
Distal ileum	3.3	3.4	3.3	3.5

Source:(Morgan et al. 2009), Tables 1 and 2

8.1.3. (Doyle et al. 1993)

(Doyle et al. 1993) was a prospective study evaluating bowel opacification on CT after administration of Gastromiro (iopamidol oral solution), Urografin (diatrizoate meglumine/diatrizoate sodium), and E-Z-Cat (barium sulfate). Patients scheduled for clinically indicated CT of the abdomen or of the abdomen and pelvis received either 400 mL (abdomen) or 700 mL (abdomen and pelvis) of a randomly selected contrast agent, to be consumed orally over 20 minutes (abdomen) or 40 minutes (abdomen and pelvis), with 100 mL of the total to be ingested immediately prior to scanning. Each contrast agent was diluted in water prior to administration resulting in concentrations of 9 mg I/mL for Gastromiro, 8.9 mg I/mL for Urografin, and 1.4% w/v for E-Z-Cat.

Two radiologists, blinded to identity of the contrast agent, independently scored the CT images for bowel opacification using a 2-point scale:

- 0 – no or poor opacification
- 1 – good opacification

The readers also evaluated the presence of artifact on a binary scale. All scoring was by segment, with segments including stomach, duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, and rectum. Segments excluded from view were excluded, and the rectum was excluded in patients co-administered rectal contrast. Segment boundaries for the study were not stated.

As with the studies previously considered in this review, the jejunum and ileum tended to have the highest proportion of patients with “good” opacification for all tested agents (Table 20). Here, the jejunum was numerically more likely to be opacified than the ileum, which might reflect the lower volume of contrast administered and shorter time between start of administration and scanning. These factors are also expected to have contributed to limited opacification of the colon and rectum in this study.

Table 20. Bowel Opacification Scores in (Doyle et al. 1993)

	Bowel Opacification Score (% of patients with indicated score)											
		Gastromiro (n=52)			Urografin (n=48)				E-Z-Cat (n=50)			
Segment	n	Good	Poor	Disc	n	Good	Poor	Disc	n	Good	Poor	Disc
Stomach	50	74	20	6	42	71	14	14	47	81	13	6
Duodenum	50	66	26	8	46	70	22	9	49	67	18	14
Jejunum	50	92	4	4	48	81	2	17	50	86	2	12
Ileum	38	84	5	11	36	67	14	19	31	84	10	6
Ascending colon	41	17	80	2	43	19	74	7	34	41	50	9
Transverse colon	49	4	90	6	46	9	83	9	49	14	73	12
Descending colon	41	7	90	2	42	12	83	5	34	21	68	12
Rectum	26	15	80	0	26	4	96	0	22	14	82	5

Source: (Doyle et al. 1993), Table III
Abbreviation: Disc = discrepant
Note: Scores of Good or Poor indicate agreement of the two independent readers. Discrepant indicates one reader scored Good and the other Poor.

The authors state that contrast-related artifact was frequent with all agents, but that no significant difference was observed between them. These data are not presented in the article. It is likely that incidence of contrast-related artifact would be lower if modern CT image processing algorithms were used.

8.1.4. Macarini

“Iopmidol (Iopamiro (R)) "300" for gastrography in Computezed Axial Tomography of the digestive tract: a double-blind study versus sodium-meglumine diatrizoate”, referred to by author name Macarini in this review, was a prospective study conducted from August 1984 to February 1985 evaluating bowel opacification on CT after administration of Gastromiro (iopamidol oral solution; Gastromiro was used despite study title) and Gastrografin (diatrizoate meglumine/diatrizoate sodium). Patients with suspected GI disease and a clinical indication for abdominal CT were randomized to receive either Gastromiro or Gastrografin. Each contrast agent was diluted in water prior to administration resulting in concentrations of 18 to 60 mg I/mL for Gastromiro and 22.2 to 74 mg I/mL for Gastrografin. For the oral route, patients received 100 to 160 mL for Gastromiro and 110 to 120 mL for Gastrografin. Timing between administration and CT scan was not stated. Patients with need for rectal contast were also enrolled in the study.

One reader, blinded to identity of the contrast agent, assessed the images for contrast quality on a 4-point scale of excellent, good, fair, or poor. The reader also evaluated the presence of artifact on a binary scale.

A total of 50 patients were enrolled, including 12 who received rectal contrast. Among the remaining patients, 18 received oral Gastromiro with contrast quality rated excellent for 22%, good for 44%, fair for 28%, and poor for 6%. The 20 patients in the oral Gastrografin group were

scored excellent for 15%, good for 30%, fair for 45%, and poor for 10%. Artifact was observed in 4 (22%) patients for oral Gastromiro and 4 (20%) for oral Gastrografin.

8.1.5. Lanza

"Clinical trial of Iopamidol (Iopamiro (R)) 300 for gastrography in abdominal CAT scanning: a blind study versus sodium-meglumine diatrizoate", referred to by author name Lanza in this review, was a prospective study conducted from October 1984 to February 1985 evaluating bowel opacification at CT after administration of Gastromiro (iopamidol oral solution; Gastromiro was used despite study title) and Gastrografin (diatrizoate meglumine/diatrizoate sodium). Patients with suspected GI disease and a clinical indication for abdominal CT were randomized to receive either Gastromiro or Gastrografin. Each contrast agent was diluted in water prior to administration resulting in concentrations of 6 to 9 mg I/mL for Gastromiro and 7.4 to 11.1 mg I/mL for Gastrografin. For the oral route, patients received 400 to 600 mL. Timing between administration and CT scan was not stated. Patients with need for rectal contast were also enrolled in the study.

One reader, blinded to identity of the contrast agent, assessed the images for contrast quality on a 4-point scale of excellent, good, fair, or poor. The reader also evaluated the presence of artifact.

A total of 50 patients were enrolled, including 20 who received rectal contrast. Among the remaining patients, 15 received oral Gastromiro with contrast quality rated excellent for 80%, good for 7%, fair for 13%, and poor for 0%. The 15 patients in the oral Gastrografin group were scored excellent for 80%, good for 13%, fair for 7%, and poor for 0%. Artifact was observed in 2 (13%) patients for oral Gastromiro and 1 (7%) for oral Gastrografin.

8.1.6. Integrated Assessment of Effectiveness

The Applicant has provided substantial evidence of effectiveness for the use of orally administered Isovue for CT of the abdomen and pelvis to delineate the gastrointestinal tract in adults and pediatric patients. While it did not meet predefined criteria for success, we consider IOP-121 to be adequate and well controlled as discussed below. (Morgan et al. 2009) provided confirmatory evidence of effectiveness.

IOP-121 evaluated anatomic delineation and opacification of the bowel at CT after oral administration of Isovue using scores from multiple independent readers on a predetermined scale. This general study design has been used to provide evidence of effectiveness for other visualization indications for CT contrast agents. A weakness of the IOP-121 study design was its retrospective nature, enrolling patients who received Isovue as part of their routine care rather than as part of a predefined study protocol. The risk of biased enrollment was mitigated through the requirement for inclusion of consecutive patients that met enrollment criteria. Further, image quality or other factors that might be affected by contrast effectiveness were not used for patient selection.

Another weakness of the IOP-121 design was lack of comparison of bowel delineation on CT with oral Isovue to that of CT without oral Isovue, either within the same patients or in separate

control patients who did not receive oral Isovue. Thus, it was not possible to determine how much of the rated anatomic delineation was due to enteric contrast versus inherent ability to visualize the bowel on noncontrast CT, for example in patients with substantial intra-abdominal fat. This weakness was partially offset by the requirement for bowel opacification by contrast as part of delineation scores 2 and 3. Because the benefit of enteric contrast for bowel delineation is derived from luminal opacification, opacification is inherently expected to be associated with improvement in bowel delineation relative to non-opacified bowel.

IOP-121 did not meet its predefined success criterion of 80% of patients with adequate anatomic delineation for at least two of three readers at the lower bound of the 95% confidence interval. However, the 80% threshold appears to be arbitrary rather than representing the minimum value necessary for clinical utility. The observed lower bounds were 71%, 75%, and 94%, and it is doubtful that the clinical value of the drug is meaningfully impacted by the magnitude of difference from 80% for readers 1 and 2.

Adequate anatomic delineation in IOP-121 was defined as at least three of five bowel segments adequately delineated. While the goal of oral contrast is to opacify bowel completely to maximize delineation, it is not necessary for this to be achieved to have benefit. Segments of bowel that are opacified and adequately delineated will provide benefit even if other segments are not opacified. In other words, success for oral contrast need not be considered in a binary manner. The mean number of segments scored as adequate ranged from 3.6 to 4.3 across the three readers, and only a single patient for one reader had no segments scored adequate.

Inter-reader agreement in IOP-121 was low, with kappa for patient-level adequacy of anatomic delineation of 0.27. However, it appears that readers were much more likely to agree for the proximal ileum and distal ileum than the stomach and duodenum. For the stomach, this might reflect differences in reader opinion on what is considered complete or sufficient opacification given the wide variation in gastric distension on routine CT. We believe that enteric contrast is more likely to provide meaningful benefit in the jejunum and ileum than stomach and duodenum because the former are more variable in position and typically more difficult to delineate. It is also notable that the jejunum, proximal ileum, and distal ileum are much longer segments than stomach and duodenum, representing a much larger portion of the bowel.

The major weaknesses of (Morgan et al. 2009) were use of a rating scale based solely on bowel opacification, lack of per reader results, absence of source data, and use of the Gastromiro formulation of iopamidol. In regard to the rating scale, as previously noted, presence of luminal opacification is expected to be associated with improvement in bowel delineation. Additionally, results suggested similar opacification ratings among iopamidol and two other oral contrasts approved to visualize bowel on CT. In regard to formulation differences, Gastromiro contains flavoring agents and an antioxidant that are not present in Isovue. The difference in flavoring agents raises the possibility of differences in effectiveness between Gastromiro and Isovue as contrast palatability can affect compliance, and bowel opacification is dependent on volume and timing of contrast ingested. However, at the dilution used for the study, it is unlikely that the flavoring agents significantly affected palatability.

(Doyle et al. 1993), Macarini, and Lanza shared several issues that affected their applicability to this NDA supplement. None of the three studies used image rating scales that directly assessed

bowel delineation, instead focusing on bowel opacification or contrast quality. Each study differed substantially in concentration of iopamidol, volume of contrast, and/or timing between contrast administration and imaging compared to the dosing regimen proposed by the Applicant. There was also variability in anatomic coverage of the CTs, with abdomen only scans included, which excluded substantial portions of bowel from evaluation. In addition, Macarini and Lanza each enrolled very few patients and had a single image evaluator. These studies have limited ability to demonstrate effectiveness of oral Isovue, but are generally supportive.

Contrast-related artifact on CT performed with oral iopamidol was noted "frequently" in (Doyle et al. 1993), in 22% of patients in Macarini, and in 13% of patients in Lanza. Such artifact could impact not only bowel, but also adjacent structures. IOP-121 included contrast-induced artifact in the anatomic delineation rating, so it is not possible to determine the frequency of such artifact in the study. It is likely that the frequency and severity of contrast-induced artifact is lower when using modern CT equipment and image reconstruction algorithms. We also note that Omnipaque is approved for oral use to visualize bowel on CT at a similar concentration of iodine, and there has been long-standing off label use of Isovue and approved use of Gastromiro abroad for this indication, suggesting that the incidence of contrast-induced artifact does not significantly limit clinical utility.

8.2. Review of Safety

8.2.1. Safety Review Approach

Study IOP-121, which was evaluated for effectiveness, was also considered for safety. Additionally, postmarketing experience with orally administered Isovue (off label) and Gastromiro (outside United States) was reviewed. To address potential safety issues unique to the oral route of administration, additional published studies of iopamidol for fluoroscopic procedures were examined. Because the data sources are heterogenous and electronic records were not available other than for IOP-121, no pooling was attempted.

(Morgan et al. 2009) was not reviewed for safety because the publication did not report adverse events or other safety results. (Doyle et al. 1993), Macarini and Lanza also were not included in the safety review. These studies differed in dosing and administration from proposed labeling. Note that the safety results from these studies did not reveal adverse events beyond those described in postmarketing data.

Safety data was interpreted in the context of adverse reactions documented in the Isovue prescribing information for intravascular indications and the expected low systemic absorption of iopamidol when administered orally. Assuming 1% of orally administered iopamidol is absorbed, which is likely an overestimate (refer to Section 6), about 184 mg iopamidol will reach the systemic circulation at the maximum recommended adult dose. Recommended intravascular doses vary widely by indication but reach as high as 153 grams of iopamidol.

8.2.2. Review of the Safety Database

Overall Exposure

Demographics in IOP-121 are described in Table 9 and dosing in Table 18. These parameters are compatible with the population of intended use and dosing information proposed in the prescribing information.

The Applicant provided postmarketing surveillance data from their database covering July 1, 1997, to August 31, 2024. Based on product distribution, the estimated exposure over this period for Gastromiro is (b) (4) patients and for Isovue is (b) (4) patients. Note that in some countries Gastromiro is approved both for fluoroscopic procedures and for CT. The product can be used undiluted for fluoroscopy, raising potential for different adverse event profiles from the diluted product used for CT. It is not possible to accurately estimate the frequency of oral Isovue administration, though the product is very likely used much more often for intravascular indications.

Adequacy of the Safety Database

The safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No major issues regarding data integrity or submission quality were identified.

Categorization of Adverse Events

In IOP-121, any untoward medical occurrence identified in the medical record with onset within 72 hours after the CT examination and considered associated with administration of Isovue (regardless of causality assessment) was to be recorded as an adverse event.

For the Applicant's postmarketing surveillance data, the Applicant reviewed all spontaneously reported adverse events and coded them using MedDRA version 27.0. Only events occurring after oral or rectal administration were included. Events considered unrelated to iopamidol by the reporter and Applicant were not submitted.

Routine Clinical Tests

No vital sign, safety laboratory, or electrocardiogram data were submitted. The absence of these tests is acceptable due to the high likelihood that systemically absorbed iopamidol mediates potential effects on them, combined with the history of approved intravascular use at much higher systemic doses with associated investigational and postmarketing safety experience.

8.2.4. Safety Results

Deaths

In postmarketing surveillance, two cases of treatment emergent death where relationship to Gastromiro could not be ruled out by the Applicant or reporter were submitted.

A female patient with colon cancer, bowel obstruction, heart failure, chronic obstructive pulmonary disease, and pneumonia was hospitalized for progressive weakness and feeding difficulty. An unstated dose of Gastromiro was attempted prior to CT scan, but the patient vomited and the administration was stopped. She also received 50 mL of Iomeron 300 (iomeprol) intravenously with the CT. The patient became cyanotic and died at an unstated time. The Applicant did not rule out a causal relationship to Gastromiro due to the close temporal association. We agree with this point but consider the patient's medical conditions or potentially iomeprol as more likely causes.

A 72-year-old female patient with metastatic breast cancer underwent a routine follow up CT examination with Gastromiro and intravenous Iomeron at unstated doses. Approximately two minutes after the CT, she reported malaise and experienced atrial fibrillation. Interventions included intubation, defibrillation, saline, betamethasone, and transfer to intensive care. She died later the same day. No information on cause of death or intensive care unit course is available. This report is again confounded by the concomitant use of intravenous Iomeron.

Serious Adverse Events

Serious adverse events are included in treatment emergent adverse events and adverse reactions below.

Dropouts and/or Discontinuations Due to Adverse Effects

Not applicable to the available data sources.

Treatment Emergent Adverse Events and Adverse Reactions

Two treatment emergent adverse events, atrial fibrillation and urticaria, in two adult patients were reported in IOP-121. Both patients had co-administration of Isovue intravenously with their CT. The investigator and the Applicant considered these events as unrelated to oral Isovue. We agree that if the adverse events were due to iopamidol, the intravenous Isovue was more likely to be the cause than oral Isovue.

For the postmarketing surveillance data, the Applicant did not submit events they considered unrelated, and thus they characterized all submitted adverse events as adverse reactions (Table 21). Data regarding co-administration of intravenous iodinated contrast and what fraction of the events were from use for CT as opposed to fluoroscopy are not available. However, it is likely that many reports are confounded by the presence of intravenous iopamidol or other iodinated contrast agent. This is mitigated to some extent by the presence of many of these events (or closely related terms) in Section 6 of the current Isovue prescribing information.

Rectal perforation, aspiration pneumonia, and aspiration are considered related to the manner of drug administration itself rather than Isovue specifically. See Section 8.2.5 for related discussion regarding aspiration. Adverse event, application site reaction, and death are not sufficiently detailed to be useful for labeling. Among the remaining events, asthenopia, eyelid edema, diarrhea/frequent bowel movements, oral hypoesthesia/paresthesia, lip swelling, esophageal pain, asthenia, dizziness, depression, emotional distress, stress, acute kidney injury, anuria, hematuria, and hypertensive crisis are not listed as adverse reactions in the current Isovue prescribing information. Due to the limited absorption of iopamidol when Isovue is administered orally, we consider events that are not attributable to the gastrointestinal system or to hypersensitivity as unlikely to be related. Additionally, nausea, vomiting, and urticaria are listed in the current Isovue prescribing information as adverse reactions from intra-arterial or intravenous use because they were identified in clinical trials of intravascularly administered Isovue. Thus, nausea, vomiting, diarrhea, esophageal pain, oral paresthesia, lip swelling, eyelid edema, and urticaria will be added to section 6.2 Postmarketing Experience of the prescribing information as adverse reactions.

Table 21. Postmarketing Adverse Reactions for Gastromiro and Enteric Isovue as Assessed by Applicant

MedDRA System Organ Class	Gastromiro		Isovue		
Preferred Term	Serious	Nonserious	Serious	Nonserious	Total
Cardiac disorders	2	0	0	0	2
Atrial fibrillation	1	0	0	0	1
Tachycardia	1	0	0	0	1
Eye disorders	2	1	0	6	9
Asthenopia	0	0	0	1	1
Blindness transient	1	0	0	0	1
Eye pruritus	0	0	0	2	2
Eyelid edema	1	1	0	0	2
Lacrimation increased	0	0	0	1	1
Vision blurred	0	0	0	2	2
Gastrointestinal disorders	4	3	3	17	27
Abdominal pain	0	0	0	1	1
Diarrhea	2	1	0	3	6
Frequent bowel movements	0	0	0	1	1
Hypoesthesia oral	0	0	0	1	1
Lip swelling	0	0	0	1	1
Nausea	1	0	1	3	5
Esophageal pain	0	1	0	0	1
Paraesthesia oral	1	0	0	0	1
Rectal perforation	0	0	1	0	1
Vomiting	0	1	1	7	9

MedDRA System Organ Class	Gastromiro		Isovue		
Preferred Term	Serious	Nonserious	Serious	Nonserious	Total
General disorders and administration site conditions	5	1	0	5	11
Adverse event	0	0	0	1	1
Application site reaction	1	0	0	0	1
Asthenia	0	0	0	1	1
Chest discomfort	1	0	0	0	1
Death	1	0	0	0	1
Face edema	0	1	0	0	1
Feeling abnormal	0	0	0	1	1
Malaise	2	0	0	2	4
Immune system disorders	1	0	2	2	5
Anaphylactic reaction	1	0	1	0	2
Anaphylactoid reaction	0	0	1	0	1
Hypersensitivity	0	0	0	2	2
Infections and infestations	1	0	0	0	1
Pneumonia aspiration	1	0	0	0	1
Musculoskeletal and connective tissue disorders	0	0	0	1	1
Back pain	0	0	0	1	1
Nervous system disorders	2	0	0	6	8
Dizziness	0	0	0	4	4
Headache	0	0	0	1	1
Syncope	1	0	0	0	1
Tremor	1	0	0	1	2
Psychiatric disorders	0	1	0	2	3
Depression	0	0	0	1	1
Emotional distress	0	1	0	0	1
Stress	0	0	0	1	1
Renal and urinary disorders	1	0	2	0	3
Acute kidney injury	0	0	1	0	1
Anuria	0	0	1	0	1
Hematuria	1	0	0	0	1
Respiratory, thoracic and mediastinal disorders	4	1	1	8	14
Aspiration	1	0	0	1	2
Bronchospasm	0	0	0	1	1
Cough	0	0	0	1	1
Dyspnoea	1	1	1	2	5
Laryngeal edema	1	0	0	0	1
Nasal pruritis	0	0	0	1	1
Respiratory failure	1	0	0	0	1
Sneezing	0	0	0	2	2
Skin and subcutaneous tissue disorders	3	8	0	18	29
Erythema	0	1	0	0	1
Pruritus	0	2	0	7	9
Rash	1	2	0	4	7
Urticaria	2	3	0	7	12

MedDRA System Organ Class Preferred Term	Gastromiro		Isovue		Total
	Serious	Nonserious	Serious	Nonserious	
Vascular disorders	1	0	1	2	4
Blood pressure decreased	0	0	0	1	1
Hypertension	1	0	0	0	1
Hypertensive crisis	0	0	1	0	1
Hypotension	0	0	0	1	1

Source: Adapted from Summary of Clinical Safety, Tables W, Y, and Z
Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities

8.2.5. Analysis of Submission-Specific Safety Issues

Aspiration

While iopamidol is not expected to cause aspiration, the oral route of administration raises the issue of safety of Isovue if it were to be aspirated. Ionic monomer/high-osmolar iodinated contrast agents are associated with pulmonary adverse effects if aspirated. For example, the Gastrografin prescribing information contains a warning that aspiration of the drug may result in pulmonary edema, pneumonitis, or death. This effect is thought to be mediated at least in part by the osmolality of the drug, which is much lower for oral Isovue at the recommended dilution (approximately 12 to 18 mOsm/kg versus approximately 2150 mOsm/kg for undiluted Gastrografin).

The Applicant submitted three published studies that reported aspiration of iopamidol products during fluoroscopy, all using higher concentrations (150 to 370 mg I/mL) than intended for bowel opacification at CT.

- (Auffermann et al. 1987) reported 23 patients who had aspiration of iopamidol during esophagram using Solutrast Gastro (equivalent to Gastromiro) among 161 adults with increased risk for aspiration or leakage. No symptoms were identified in any of the patients over 48 hours of observation.
- (Bell et al. 1987) reported five patients with aspiration among 40 patients with suspected upper gastrointestinal perforation who underwent fluoroscopy using iopamidol. No respiratory sequelae were reported other than cough. Duration of follow up was not stated. This study also described two patients with tracheo-esophageal fistula demonstrated by iopamidol fluoroscopy, one of whom died after surgical treatment of the fistula.
- (Zieger et al. 1988) reported five patients with aspiration of Solutrast Gastro among 139 pediatric patients with a variety of clinical indications for fluoroscopy. No serious complications were reported.

Aspiration of any material in sufficient quantity is expected to lead to serious adverse consequences. The available data do not suggest a substantial increased risk above this baseline for iopamidol at the intended dilution, and no warning is considered necessary in the prescribing information. This approach is compatible with the labeling for another orally administered iodinated contrast agent indicated for abdominal CT, Omnipaque (iohexol).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing

Safety/Tolerability

COA analyses were not performed and were not needed for this application.

8.2.7. Safety Analyses by Demographic Subgroups

As no adverse reactions were reported in IOP-121, demographic subgroup analyses were not performed.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No clinical studies of carcinogenicity were performed for this application, and none were needed.

Human Reproduction and Pregnancy

No new clinical data regarding pregnancy or lactation were submitted, and none were needed.

Pediatrics and Assessment of Effects on Growth

Of the adverse reactions from postmarketing reports listed in Table 21, 14 were reported in pediatric patients. The identity of these reactions was similar to the reactions reported in adults. The incidence of adverse reactions in pediatric patients could not be determined due to the unknown number of patients exposed.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No abuse potential is expected for Isovue.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Available postmarket safety data are discussed in section 8.2.4.

Expectations on Safety in the Postmarket Setting

Due to the long-standing use of Isovue and other formulations of iopamidol for this indication, the safety profile is expected to be similar after approval of this supplement.

8.2.10. Integrated Assessment of Safety

GI adverse reactions such as diarrhea were identified after oral iopamidol administration that were not documented for intravascular Isovue. Because of the limited absorption of iopamidol

from the GI tract, the major systemic safety issue for oral Isovue is hypersensitivity. The overall safety profile is acceptable.

8.3. Statistical Issues

8.3.1. IOP-121

See Sections 8.1.1 and 8.1.1.1 for Study IOP-121 design and analysis results reported by the Applicant.

The FDA statistical reviewer verified the Applicant's analysis results for the primary efficacy endpoint (proportion of patients with adequate anatomic delineation at the patient-level), the secondary efficacy endpoint (proportions of patients with adequate anatomic delineation at the segment-level [stomach, duodenum, jejunum, proximal ileum, and distal ileum]), as well as the inter-reader agreement quantified by Fleiss' general kappa value.

As shown in Table 11, the lower limits of the 95% Wilson confidence intervals (CIs) of the primary efficacy results were less than the pre-specified success threshold of 0.80 for Reader 1 and Reader 2, thus the study did not meet its success criteria of at least two readers exceeding 0.80. However, as shown in Table 16 and pointed out by the FDA clinical reviewer, at the segment-level, the lower limits of the 95% Wilson CIs of the proportion of patients with adequate delineation were greater than 0.80 in proximal ileum and distal ileum for all readers, and in stomach for Reader 3. From a statistical perspective, approval of this drug relies on clinical justification of the acceptability of the study results.

8.4. Conclusions and Recommendations

Results from one adequate and well-controlled study and confirmatory evidence demonstrated the ability of orally administered, dilute Isovue to opacify and delineate the bowel at abdominopelvic CT from clinical perspective. Its safety profile, based on clinical trial data and postmarket and off-label experience, is acceptable. We find the benefit-risk balance for this use to be favorable and recommend approval of this efficacy supplement for CT of the abdomen and pelvis to delineate the GI tract in adults and pediatric patients.

9 Advisory Committee Meeting and Other External Consultations

The review team did not identify any issues that would benefit from discussion at an Advisory Committee meeting.

10 Pediatrics

The Applicant provided a pediatric assessment for patients from birth to 16 years of age. As discussed in section 8.1.1.1, study IOP-121, which provided primary evidence for effectiveness,

included 66 pediatric patients aged 3 years to 16 years and showed similar bowel opacification and delineation as seen in adults. Based on the mechanism of action, which involves transport of the drug with bulk fluid in the gastrointestinal tract, it is reasonable to expect similar effectiveness in children less than 3 years. The dose in these patients was established based on gastric capacity and published experience (Section 6.3.2). Therefore, it is reasonable to label the indication for pediatric patients of all ages.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

Recommended revisions to the finalized Prescribing Information (PI) compared to the Applicant's draft PI and rationale for the changes are provided below.

Indications and Usage

No major changes were made to the proposed indication statement except for replacing (b) (4) with "delineate" to align with efficacy data and clinical utility. The agreed-upon indication statement for the new oral indication reads:

> *"ISOVUE is indicated for CT of the abdomen and pelvis to delineate the gastrointestinal tract in adults and pediatric patients."*

The proposed indication statement encompasses a broader anatomic scope than was directly evaluated in the efficacy studies. While the IOP-121 specifically evaluated Isovue's performance in delineating five distinct segments of the GI tract—namely the stomach, duodenum, jejunum, proximal ileum, and distal ileum—the proposed indication statement broadly claims utility "to delineate the gastrointestinal tract". This broader indication extends beyond the study's defined endpoints to potentially include the colon and rectum, which were not explicitly evaluated in the study. However, the relatively simple mechanism of action of oral Isovue and extensive clinical experience with this use supports the conclusion that imaging performance observed in the studied segments would reasonably extend to the entire abdominopelvic GI tract.

The indication statement of a contrast agent used for structural delineation typically does not use the phrasing "diagnosis of a recognized disease or condition", which is required for the indication statement of human prescription drug labeling by the FDA labeling regulation, 21 CFR 201.57(c)(2). Instead, the indication statement specifies imaging applications and general anatomy or pathology (e.g., lesions) to be visualized with the drug.

Contrast agents used for structural delineation typically improve general visualization of anatomical and pathological structures rather than diagnosing specific diseases. There are usually many potential diseases and conditions that could be imaged in an indicated part of the body, and listing them specifically would not be practical. Furthermore, deciding the appropriateness of contrast agent use for structural delineation in a specific disease setting is considered practice of medicine. Therefore, the phrasing "diagnosis of a disease or condition" has been omitted in accordance with 21 CFR 201.56(d)(4), allowing healthcare providers to apply their clinical expertise in determining appropriate specific disease applications while ensuring the labeling focuses on the scientifically established performance characteristics of the contrast agent itself.

Dosage and Administration

For CT of the abdomen and pelvis with orally administered Isovue, Isovue must be diluted with water or other clear liquids to achieve a final concentration of 6 to 9 mg iodine/mL before patient administration. The volume of diluted Isovue administered is determined by patient age. To enhance usability and reduce potential dosing errors, the proposed dosing tables for adults and pediatric patients have been consolidated into a single, comprehensive table that presents administration volumes in ascending order of patient age. This streamlined approach eliminates the need for healthcare providers to reference multiple tables and provides a clear progression of dose volumes from youngest to oldest patients. The recommended concentrations of diluted Isovue are clearly specified in accompanying footnotes with direct cross-references to detailed dilution instructions, ensuring proper preparation protocols are followed. For simplicity, dilution recommendations and instructions focus on 6 or 9 mg iodine/mL concentrations rather than the entire range between these values.

While the Applicant initially proposed using the 300 mg iodine/mL concentration of Isovue for dilution purposes, the review team determined that any of the four commercially available iodine concentrations (200, 250, 300, and 370 mg iodine/mL) would be acceptable for dilution without compromising safety and efficacy. Consequently, the dilution instruction table has been expanded to include comprehensive preparation guidelines for all four available iodine concentrations, providing healthcare facilities with greater flexibility in inventory management and allowing them to use any concentration available in their clinical setting.

The Applicant proposed using water, purified water, or clear liquids such as apple juice for dilution. However, the proposed (b) (4) recommendation have been removed.

The final dosing and dilution instructions are shown below:

2.5 Recommended Dosage for Oral Procedures in Pediatric Patients and Adults

- *The recommended concentration of diluted ISOVUE is either 6 mg iodine/mL or 9 mg iodine/mL administered orally as shown in Table 4.*
- *See Table 5 for dilution instructions of ISOVUE [see Dosage and Administration (2.6)].*

Table 4: Recommended Volumes of Diluted ISOVUE for Oral Administration for CT of the Abdomen and Pelvis in Pediatric Patients and Adults

Age	***Volume of Diluted ISOVUE‡ to Administer***	***Administration Instructions***
Pediatric patients less than 3 years of age	*50 mL to 300 mL*	*Administer the oral dose approximately 60 minutes*

Age	***Volume of Diluted ISOVUE‡ to Administer***	***Administration Instructions***
Pediatric patients 3 years to 5 years of age	*300 mL to 360 mL*	*before beginning the CT procedure.*
Pediatric patients 6 years to 11 years of age	*360 mL to 500 mL*	
Pediatric patients 12 years of age and older	*500 mL to 1,000 mL*	
Adults		

‡ Prepare diluted ISOVUE solution to a concentration of either 6 mg iodine/mL or 9 mg iodine/mL according to Table 5 [see Dosage and Administration (2.6)].

2.6 Directions for Dilution of ISOVUE for Oral Administration

- *Dilute ISOVUE to 6 mg iodine/mL or 9 mg iodine/mL in water or clear liquids such as apple juice according to Table 5.*
- *Use diluted ISOVUE immediately.*
- *Discard any unused portion after the procedure.*

Table 5: Volumes of ISOVUE and Added Liquid to Dilute ISOVUE for Oral Administration for CT of the Abdomen and Pelvis

Final Concentration of Diluted ISOVUE (mg Iodine/mL)	***ISOVUE***		***Volume of Added Liquid§ (mL)***
	Concentration (mg Iodine/mL)	***Volume (mL)***	
6	*200*	*30*	*970*
	250	*24*	*976*
	300	*20*	*980*
	370	*16*	*984*

Final Concentration of Diluted ISOVUE (mg Iodine/mL)	***ISOVUE***		***Volume of Added Liquid[§] (mL)***
	Concentration (mg Iodine/mL)	***Volume (mL)***	
9	*200*	*45*	*955*
	250	*36*	*964*
	300	*30*	*970*
	370	*24*	*976*

[§]Use water or clear liquids such as apple juice.

Adverse Reactions

The primary safety sources for orally administered Isovue were study IOP-121 and postmarketing safety surveillance data from oral iopamidol use in international markets and off-label in the US, as submitted by the Applicant. Study IOP-121 was not considered to demonstrate any adverse reactions to oral iopamidol. However, in accordance with the FDA labeling regulations and guidances, the Clinical Trials Experience subsection of the ADVERSE REACTIONS section employs the specific terminology "no new adverse reactions" rather than the absolute statement "no adverse reactions" to characterize the safety findings from the efficacy study. This precise language selection aligns with the recommendations outlined in the FDA guidance document, "Adverse Reactions Section of Labeling", which advise against including negative findings in product labeling unless the absence of particular adverse reactions has been convincingly demonstrated through a clinical trial specifically designed with adequate statistical power and appropriate methodology to detect such reactions. This approach ensures that labeling statements reflect the scope and limitations of the available safety data and prevent potential misinterpretation of study findings by healthcare providers. The Clinical Trials Experience subsection reads:

> ***6.1 Clinical Trials Experience***
> *Adverse Reactions from Oral Use in Adult and Pediatric Patients*
> *There were no new adverse reactions from oral use of ISOVUE in adult and pediatric patients [see Clinical Studies (14)].*

In the Postmarketing Experience subsection, adverse reactions reported with orally administered iopamidol products marketed outside of the US or used off-label in the US have been added to the existing list of adverse reactions from intra-arterial or intravenous use of Isovue. The introduction statement now includes the phrase "post approval use of ISOVUE or other iopamidol-containing products by intra-arterial, intravenous, or oral administration" to

indicate that these adverse reactions are derived from multiple sources. The new adverse reactions added to subsection 6.2 are as follows:

> ***Eye disorders**: …eye edema*
> ***Gastrointestinal disorders**: nausea, vomiting, diarrhea, …, esophageal pain, …oral paresthesia, lip swelling*
> ***Skin and subcutaneous tissue disorders**: …urticaria…*

Pediatric Use

A pediatric use statement for the oral indication of Isovue and the basis of approval for pediatric patients were added in accordance with the FDA guidance document, "Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling" (March 2019). The final text reads:

> *The safety and effectiveness of ISOVUE have been established in pediatric patients for oral administration for CT of the abdomen and pelvis to delineate the gastrointestinal tract. Use of ISOVUE for this indication is supported by evidence from an adequate and well-controlled clinical study in adults (n=152) and pediatric patients 3 to 16 years of age (n=66) who underwent CT of the abdomen and pelvis with oral administration of ISOVUE and additional safety data from post-approval use of enteral iopamidol in adult and pediatric patients [see Adverse Reactions (6.2)] and Clinical Studies (14)].*

Clinical Pharmacology

The underlined heading "Absorption" has been added to the Pharmacokinetics subsection to include the pharmacokinetic characteristics of orally administered iopamidol. The final text reads as follows:

> ***12.3 Pharmacokinetics***
> *Absorption*
> *Following oral administration, iopamidol is minimally absorbed from the gastrointestinal tract. Less than 1% of the administered dose is recovered in urine within 12 hours post-dose.*

Additionally, throughout the labeling, existing text has been edited as appropriate to reflect whether the presented information is related to intravascular, oral, or both routes of administration. When information is applicable to both intravascular and oral routes, specific routes of administration were omitted.

Clinical Studies

Additional description of IOP-121 was added. This includes a brief explanation of the study design, demographic information for enrolled subjects, and per reader results for the primary analysis.

Other Prescription Drug Labeling

The oral route of administration has been added to the container labels and carton labeling, provided as a separate submission (supplement-076) in response to our request.

12 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategy is needed for this application.

13 Postmarketing Requirements and Commitment

There are no current postmarketing requirements or commitments for this NDA. No postmarketing requirement or commitment is needed for this application.

14 Division Signatory Comments (DIRM)

Per the multi-disciplinary review findings, this supplemental application supports a new indication for oral use of dilute Isovue injection with CT of the abdomen and pelvis to delineate the GI tract in adults and pediatric patients.

Substantial evidence of effectiveness of oral Isovue for this indication was demonstrated through one adequate and well-controlled trial, Study IOP-121, and confirmatory evidence, (Morgan et al. 2009). Study IOP-121 demonstrated adequate bowel delineation in a clinically meaningful percentage of patients for multiple readers even though it did not meet its predefined but arbitrary success criterion. Deference of the statistical team to this clinical justification is noted. Although comparison to CT images without oral contrast was not performed, bowel opacification by contrast was included in the definition of adequate delineation and is inherently expected to be associated with improved visualization relative to non-opacified bowel. (Morgan et al. 2009) further mitigated the lack of noncontrast comparison by suggesting similar opacification ratings among iopamidol and two other oral contrasts approved to visualize bowel on CT.

The safety profile of oral iopamidol from available clinical trial data and postmarketing experience is relatively benign and supports a favorable benefit-risk balance for the new indication. Given the limited absorption of iopamidol from the GI tract, expected systemic exposure from oral administration is far below that of approved intravascular administration. The existing warning in the prescribing information for hypersensitivity reactions was modified to be applicable regardless of route of administration. Absence of safety concerns from the nonclinical review team is noted. Lack of concerns regarding product quality for this supplement is also noted.

Although colon and rectum were not evaluated in the above mentioned clinical studies, the relatively simple mechanism of action of oral iopamidol and extensive clinical experience with its oral use for CT supports expected extension of observed imaging efficacy in the stomach and small intestine to more distal bowel. Thus, the new indication statement is appropriately broadened to the entire GI tract imaged on CT of the abdomen and pelvis.

While the supporting clinical studies did not evaluate iopamidol in patients younger than 3 years of age, the relatively simple mechanism of action of oral iopamidol also supports extrapolation of efficacy to this age group. Clinical pharmacology concurrence is noted for proposed dosing in this age group based on evidence in the literature, gastric capacity data, and oral contrast guidelines. Clinical pharmacology concurrence is similarly noted for dosing in the other pediatric age groups as well as in adults.

Information regarding the new indication is appropriately integrated into labeling with input from the Division of Medication Error Prevention and Analysis and the remainder of the review team. Dilution instructions and recommended age-based volumes for dosing are presented in a clear and simple manner.

In conclusion, approval of this supplemental application and its associated new indication is recommended.

15 Appendices

15.1. References

Literature

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Guidances

FDA guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019)

ICH harmonised guideline *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)* (November 2016)

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): IOP-121

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 3		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Team Leader	Jonathan Cohen, PhD	ORDPURM/DPTRDPURM	Section: 5	Select one: X Authored ___ Approved
	Signature: JONATHAN E. COHEN -S Digitally signed by JONATHAN E. COHEN -S Date: 2025.10.09 12:43:00 -04'00'			
Nonclinical Division Director	Kimberly Hatfield, PhD	ORDPURM/DPTRDPURM	Sections: 5	Select one: ___ Authored X Approved
	Signature: Kimberly P. Hatfield -S Digitally signed by Kimberly P. Hatfield -S Date: 2025.10.09 12:39:28 -04'00'			
Clinical Pharmacology Reviewer	Shiyu Tang, PhD	OCP/DCPI	Section: 6	Select one: X Authored ___ Approved
	Signature: Shiyu Tang -S Digitally signed by Shiyu Tang -S Date: 2025.10.09 13:38:52 -04'00'			
Clinical Pharmacology Team Leader	Wentao Fu, PhD	OCP/DCPI	Section: 6	Select one: ___ Authored X Approved
	Signature: WENTAO FU -S Digitally signed by WENTAO FU -S Date: 2025.10.09 13:31:30 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Section: 6	Select one: ___ Authored X Approved
	Signature: Signing of behalf of Brian Booth. OLANREWAJU OKUSANYA -S Digitally signed by OLANREWAJU OKUSANYA -S Date: 2025.10.09 13:47:37 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Primary Statistical Reviewer, (DBI)	Zhipeng Huang, PhD	OTS/OB/DBI	Sections:8.3	Select one: X Authored ___ Approved
	Signature: ZHIPENG HUANG -S Digitally signed by ZHIPENG HUANG -S Date: 2025.10.09 14:39:20 -04'00'			
Secondary Statistical Reviewer, (DBI)	Jyoti Zalkikar, PhD	OTS/OB/DBI	Sections:8.3	Select one: X Authored ___ Approved
	Signature: JYOTI ZALKIKAR -S Digitally signed by JYOTI ZALKIKAR -S Date: 2025.10.09 14:44:47 -04'00'			
Deputy Director, Division of Biometrics I, (DBI)	Sue-Jane Wang, PhD	OTS/OB/DBI	Sections:8.2, 8.3, 8.4	Select one: ___ Authored __X_ Approved
	Signature: Suejane Wang -S Digitally signed by Suejane Wang -S Date: 2025.10.09 14:58:02 -04'00'			
Associate Director for Labeling, (DIRM)	Younsook Kim, PharmD	OSM/DIRM	Section: 11	Select one: X Authored ___ Approved
	Signature: Younsook Kim -S Digitally signed by Younsook Kim -S Date: 2025.10.10 08:07:39 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer and Team Leader, (DIRM)	Shane Masters, MD, PhD	OSM/DIRM	Sections: All	**Select one:** __X__ Authored __X__ Approved
	Signature: Shane Masters -S Digitally signed by Shane Masters -S Date: 2025.10.09 16:37:39 -04'00'			
Office Director, (OSM) (Signatory for DIRM)	A. Alex Hofling, MD, PhD	OSM/DIRM	Sections: All	**Select one:** ___ Authored __X__ Approved
	Signature: August Hofling -S Digitally signed by August Hofling -S Date: 2025.10.10 08:04:12 -04'00'			

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/

SHARON P THOMAS
10/10/2025 09:32:38 AM

AUGUST A HOFLING
10/10/2025 10:21:38 AM