CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205383Orig1s000

MEDICAL REVIEW(S)

Division of Medical Imaging Products

NDA 205383; Oraltag (iohexol) (b) (4) Oral Solution

Sponsor: Otsuka Pharmaceutical Development and Commercialization

Reviewer: Harris E. Orzach, MD

Date: March 12, 2015

Addendum to Primary Clinical Review

The NDA application contains a Statement of Financial Certification and Disclosure, stating the following:

"This NDA does not include the reports of any clinical trials sponsored by the applicant, nor did the applicant contract with one or more clinical investigators to conduct the published studies summarized in this NDA. Thus, the requirements of 21 CFR Part 54 do not apply.

The applicant's assessment is correct and fulfills the certification and disclosure requirement. No regulatory action is needed.

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/s/

HARRIS E ORZACH
03/17/2015

LIBERO L MARZELLA
03/17/2015

Division of Medical Imaging Products **February 26, 2015**

New Drug Application (NDA 205383)

NDA Resubmission – Amendment to Original NDA Submission, Sequence 0015

Product: Iohexol (b) (4) Oral Solution (Oraltag)

Sponsor: Interpharma Praha, a.s. (US agent: Otsuka Pharmaceutical Development & Commercialization)

Reviewer: Harris E. Orzach, M.D.

Recommendation for regulatory Action:

The outstanding CMC and inspectional issues have been addressed in the resubmission. The labeling requires extensive revisions and is under review.

I recommend approval of this supplement from the clinical perspective provided that the applicant agrees with the labeling changes recommended by FDA.

Summary of Regulatory History:

This is a resubmission of NDA 205383, originally submitted March 20, 2013. OralTag is an iodine-based oral contrast agent, which is used to opacify the gastrointestinal tract, for abdominal and pelvic CT scanning. The drug, contains the same active ingredient as prepared solutions of Omnipaque 300 (iohexol), which is the reference listed drug (RLD) for oral use. The physicochemical properties (density, osmolality and viscosity) of iohexol (b) (4) oral solution (b) (4) when mixed with various solutions for administration. The original clinical reviewer, Barbara Stinson, D.O., recommended approving the 505(b)(2) NDA for the product, which at that time was called " (b) (4) This was based on the FDA's previous finding of safety and effectiveness of Omnipaque, which was approved under NDAs 18,956 and 20,608.

However, the original NDA was not approved, and the Division of Medical Imaging Products took a complete response action. Dr. Milagros Salazar, the CMC reviewer, determined that the NDA did not meet the CMC regulatory requirement (21 CFR 314.50), because the manufacturing equipment and the drug product used for the stability study are not representative of the commercial production. In addition, the cGMP status of the packager of the drug product (Ultra Seal Corporation) cannot be determined, because the (b) (4) to be used for commercial production are under construction.

In response to an information request, the manufacturer explained that subsequent to submitting the NDA, it was found that (b) (4) It was decided to

assemble (b) (4) dedicated to commercial production of iohexol (b) (4) oral solution. Batch analysis and stability studies submitted in the present application are not acceptable, (b) (4) .

CMC:

I agree with the CMC reviewer's assessment that all the CMC issues have been addressed

The applicant states that in the resubmission, they have addressed the issues documented in the Complete Response letter issued by the FDA. Specifically:

1. The manufacturing facility, Ultra Seal (USC) in New Paltz, New York, has done the following:

   - Installation and qualification of the manufacturing equipment to be used for commercial production.
   - Release testing (b) (4).
   - Preparation of the validation protocol.

2. No significant changes have been made to (b) (4), used for commercial production, compared to (b) (4) Proper manufacturing conditions are maintained, with no change in manufacturing process flow.

3. Appropriate batch analysis and stability data provided for OralTag manufactured at the drug product site.

4. Stability results of batches produced on (b) (4) are comparable to those on (b) (4).

5. Post-approval stability program instituted as directed, with testing of free iodine and free iodide at each testing interval.

6. Appropriate photostability testing instituted as directed.

The FDA Inspector determined that the Ultraseal facility in New Paltz, New York was acceptable.

Clinical:

<u>Efficacy</u>
No new efficacy data were required and none were submitted.

I agree with the risk/benefit assessment by the clinical reviewer of the original application (Barbara Stinson, D.O.). The reviewer determined that the use of iodinated contrast during opacification of the GI tract during CT examination in adult and pediatric patients is supported by practice guidelines, and the literature. Notably, this preparation is not suitable for radiological pass-through exams of the GI tract. To

document the safety profile of iohexol, the applicant conducted a clinical literature search for both oral and intravenous usage of Ominpaque. Based on the low systemic absorption of oral iohexol, the primary focus of safety and tolerability was intravascular, primarily the intravenous route. Data support the safety and tolerability of iohexol for use as an oral agent. The clinical reviewer recommended approval from the clinical perspective.

Safety Update

With respect to safety the applicant submitted the required safety update.

After the original NDA, a 120 day safety update was performed, up to cutoff date of April 30, 2013. Literature search during this period showed no new safety concerns for Iohexol oral administration, that may reasonably effect proposed drug labeling for Iohexol (b) (4) Oral Solution (Oraltag).

Final Safety Update (cutoff date April 30, 2014) was performed through conduct of supplemental literature search to identify recently published literature relevant to the safety review of oral Iohexol. No new safety concerns were detected that may reasonably affect drug labeling. The applicant concludes that data evaluated in this final safety update continue to support the overall safety and tolerability of Iohexol (b) (4) Oral Solution for use in adults and children as an opacification agent during CT of the abdomen and pelvis. I agree with that assessment.

Table 1 summarizes the numbers of patients in various indications and age groups for whom safety information from the literature was derived.

Table 1 Exposure Data from Published Articles Pertinent to Summary of Clinical Safety

Study Grouping	Original NDA	120-Day Safety	Final Safety Update
CT in Adults (Oral)	278	444	114
X-ray Radiography in Adults (Oral)	152	NA	1,978
CT in Pediatrics (Oral)	557	NA	86
X-ray Radiography in Pediatrics (Oral or rectal)	493		

IV Healthy Volunteers	36	35	NA
Intravascular Adults and Pediatrics (focus on IV)	>49,000	~27,770	~7,873
IV Adults and Pediatrics (focus on CIN)		~21,953	~1,117
IV GFR Biomarker Studies in Special Patient Groups	27	2,467	~7,400

No deaths or SAEs related to oral administration of iohexol were reported in the published studies reviewed for submission in the Original NDA, the 120-Day Safety Update or this Final Safety Update. The Adverse Events section of the proposed Draft Labeling is based on the approved labeling for OMNIPAQUE . No revisions are proposed based on this Final Safety Update

Labeling:

With regard to the labeling, Dr. Stinson recommended [redacted] (b) (4) . The reviewer reserved comment on labeling because the application was not approvable due to CMC deficiencies.

In an information request letter dated 12/24/2013, FDA recommended a number of revisions to the container and carton labels, and requested additional information from pharmacology studies cited in the label.

Multiple revisions to the labeling are necessary. [redacted] (b) (4) .

The applicant will need to agree with the recommended labeling changes before an approval action is taken.

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/s/

HARRIS E ORZACH
02/27/2015

LIBERO L MARZELLA
02/27/2015
I concur with Dr. Orzach's assessment and recommended action.

Summary Review for Regulatory Action

Date	1/6/2014
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA # Supplement #	205383 0
Applicant Name	Interpharma Praha
Date of Submission	3/11/2013
PDUFA Goal Date	1/11/2014
Proprietary Name Established (USAN) Name	OralTag Iohexol
Dosage Forms Strength/Route of Administration	[redacted] (b) (4) Solution 9.7 g iohexol (4.5 g of iodine content) in a 20 ounce beverage bottle to be reconstituted with a liquid for oral administration
Proposed Indication	Iohexol [redacted] (b) (4) Oral Solution is indicated for oral use in adults and in children as an opacification agent during computed tomography of the abdomen and pelvis. [redacted] (b) (4)
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Barbara A Stinson M.D.
CMC Review	Milagros Salazar Driver Ph.D.
Pharmacology Toxicology Review	Sally J Hargus Ph.D.
Clinical Pharmacology Review	Burns Safaa Ph.D.
Biopharmaceutics	Tien-Mien Chen Ph.D.
Microbiology Review	Jessica Cole Ph.D.
Statistical Review	Satish Misra Ph.D.
CDTL Review	Alex Gorovets M.D.
OSE/DMEPA	Kevin Wright Pharm. D.
DGMPA Establishment Review	Robert H Wittorf Pharm. D.

NDA = New Drug Application
OND = Office of New Drugs
CMC = Chemistry Manufacturing and Controls
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
CDTL = Cross-Discipline Team Leader
DGMPA = Division of Good Manufacturing Practice Assessment

Reference ID: 3432370

1. Introduction

The topic of this Division Director summary review is NDA 205383 for OralTag (Iohexol) (b) (4) Oral Solution submitted by Interpharma Praha. OralTag is a non-ionic water-soluble radiographic contrast agent proposed for oral use in computed tomography (CT) of the abdomen and pelvis in adults and children (b) (4)

The present application is submitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and proposes to rely upon published literature and FDA's findings of safety and efficacy for the reference listed drug Omnipaque (Iohexol Solution for Injection). NDA 18956 for Omnipaque is held by GE Healthcare and was approved in 1985 for use in adults and in 1988 for use in children. The indication sought for OralTag is very narrow compared with the indications for Omnipaque which include intravascular, intrathecal, oral, rectal, and body cavity radiographic imaging.

The product OralTag is the drug substance (iohexol) packaged in a 20-ounce polyethylene terephthalate bottle with a polypropylene cap. Each bottle contains 9.7 grams of iohexol equivalent to 4.5 grams of iodine and is sealed in a foil (b) (4) pouch. The amount of iohexol allows the user to prepare the standard concentration of 9 mgI/mL of iodine in a volume of 500 mL of fluid and also allows other standard concentrations (12, 15, 18 and 21 mgI/mL) to be prepared by adding fluid (375, 300, 250, and 214 mL) to the indicated fill lines premolded and labeled on the bottle.

For the purpose of this review, the most important differences between OralTag and the reference listed product Omnipaque for oral use are shown in the table below. I concur with the assessment by the FDA reviewers that these relatively minor differences in the products will not affect the extrapolation of safety and effectiveness of Omnipaque to OralTag.

Table 1. Comparison between OralTag and Omnipaque

	Oral Tag for oral use	**Omnipaque for oral use**
Drug substance	iohexol	iohexol
Excipients	none	tromethamine, Na_2Ca EDTA, HCl or NaOH
Dosage form	(b) (4) solution	solution for injection
Iodine concentration in reconstituted solution	9 - 21 mgI/ml	6 - 21 mgI/ml
Indication	only GI opacification	GI opacification or GI diagnosis (pass-through)
Intravenous (IV) iodinated contrast	(b) (4)	GI opacification only with IV contrast

The key outstanding regulatory issues in this application are related to product manufacturing. The application does not meet the regulatory requirements (21 CFR 314.50) because the batch

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analysis and stability studies submitted in the present submission are not acceptable; the (b) (4) used to manufacture the NDA lots will not be used for (b) (4) of the iohexol powder. The cGMP status of the establishment (Ultra Seal Corporation) that will carry out the (b) (4) operations cannot be determined because the (b) (4) intended for use for commercial production are not ready for inspection. These issues could not be resolved during the present review cycle and will result in a complete response action.

Labeling issues have been identified and many of them have been communicated to the applicant. The revised labeling submitted on January 6, 2014 appears to have addressed a number of these issues. Agreement on the remaining labeling issues is anticipated.

2. Background

The NDA clinical reviewer Dr. Barbara Stinson and the CDTL reviewer Dr. Alex Gorovets have summarized the extensive clinical experience with the use of "dilute" concentrations of iohexol (Omnipaque) administered orally for CT studies as an aid to delineate the GI tract and distinguish bowel from other normal or abnormal structures in the abdominal and pelvic cavities.

The reviewers make clear that, at the concentrations proposed in this application, iohexol is not suitable for " pass-through" diagnostic examination of the GI tract and the applicant will need to revise OralTag labeling to make this limitation clearer. The reviewers also point out that the approved labeling for the listed drug Omnipaque recommends the concomitant use of oral and intravenous iohexol for CT studies of the abdomen. On the other hand, the application for OralTag proposes the use of oral iohexol (b) (4) .

The reviewers consider iohexol to be less likely to induce fluid shifts (due to more favorable osmolarity) and to be more palatable compared to the other iodinated contrast agents approved for oral use for abdominal CT scans. The principal rationale for the development of OralTag vis-à-vis Omnipaque appears to be convenience of reconstitution.

3. CMC/Microbiology/Establishment Inspection

CMC

I concur with the conclusions reached by the CMC reviewer Dr. Milagros Salazar that the application cannot be approved.

Dr Salazar determined that the manufacturing, testing, and packaging of the drug substance by Interpharma Praha (under Drug master File # 26641, reviewed July 22, 2013) are acceptable.

Dr. Salazar also determined that the NDA does not meet the CMC regulatory requirement (21 CFR 314.50) because the manufacturing equipment and the drug product used for the stability

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study are not representative of the commercial production. In addition the cGMP status of the packager of the drug product (Ultra Seal Corporation) cannot be determined (b) (4) .

In response to a CMC information request, the manufacturer explained the lack of preparedness for inspection as follows. Subsequent to submitting the NDA, the manufacturer determined that (b) (4). The decision was made to assemble (b) (4) The FDA CMC reviewers found the proposal for qualification of the (b) (4) including comparability between batches produced (b) (4) to be generally acceptable. However the batch analysis and stability studies submitted in the present application are not acceptable (b) (4)

Microbiology
I concur with the FDA reviewer's recommendation to approve OralTag from the microbiology product quality perspective.

The reference listed drug, Omnipaque is provided as a sterile solution for injection. On the other hand the proposed drug product is a non sterile (b) (4) reconstitution with water or a beverage. The microbiology reviewer Dr. Jessica Cole determined that the microbiological quality of the drug product is controlled by an adequate testing protocol and that the microbial limits specification is acceptable.

Establishment
I concur with the recommendation by the Division of Good Manufacturing Practice Assessment (DGMPA) to withhold approval of the NDA.

The FDA New York District Office investigators conducted a pre-approval inspection at the Ultra Seal Corporation establishment from October 1 to October 7, 2013. The facility will perform (b) (4) operations for OralTag. DGMPA reviewed the establishment inspection report by the District Office and also the letter provided by the manufacturer explaining when (b) (4) equipment would become available and qualification activities (b) (4) would begin. DGMPA determined that the establishment demonstrated a lack of capacity to manufacture the drug product. (b) (4)

4. Nonclinical Pharmacology/Toxicology

I concur with the recommendation by the pharmacology/toxicology reviewer Dr. Sally Hargus that the application be approved from a non-clinical perspective based on previous findings by FDA for the reference listed drug. No new non-clinical studies were necessary and none were provided in the application.

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5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer Dr. Safaa Burns that the application is acceptable from the clinical pharmacology perspective provided that labeling revisions are considered by the applicant.

During the review process Clinical Pharmacology asked the applicant to consider a more clinically meaningful presentation of the dose of OralTag to be administered in terms of grams of iodine or volume or both based on current clinical practice. For example the Dosage and Administration section in both adults and children might recommend the use of the same concentration of OralTag. (b) (4)

Dr Burns determined that there are no clinical pharmacology findings as no new clinical pharmacology studies were conducted in support of this application. The proposed use of OralTag as an oral contrast agent only requires the drug to be present in the gastrointestinal tract. Hence evaluation of systemic bioavailability following oral administration is not needed. The applicant submitted published data on the oral administration of marketed iohexol products, including a study in a pediatric population and three studies in which oral iohexol was used to assess bowel permeability in patients with inflammatory bowel disease. The applicant also submitted published data on intravenously administered iohexol including PK studies in healthy volunteers, studies in patients with renal impairment and a study in lactating women to estimate the amount of iohexol excreted into breast milk. Literature reports of studies of the effect of iohexol on erythrocytes, coagulation and platelet aggregation were also submitted. Dr Burns determined that review of these studies was not needed because this 505(b)(2) application is for an indication already approved for Omnipaque.

Biopharmaceutics

I concur with the recommendation by the Biopharmaceutics reviewer Dr Tien-Mien Chien that this NDA be approved.

Dr Chien's review focused on the biowaiver request and the *in vitro* stability data of the oral solution mixed with various beverages. Dr Chien determined that OralTag is the same as Omnipaque IV solution for oral administration (the reference product) in terms of the active drug ingredient, concentration, and dosage form. Dr Chien notes that Omnipaque oral solution contains minor inactive ingredients intended for parenteral dosage form stability and these ingredients would have no biological importance for a product reconstituted in large volume as an oral solution. Dr. Chien thus determined that OralTag meets criteria (21 CFR 320.22) for a waiver of evidence of *in vivo* bioavailability or bioequivalence. No dissolution data were submitted in the application and none were required because iohexol is a BCS Class 3 (high solubility with low permeability) drug substance. Dr. Chien concluded that OralTag will have efficacy and safety profiles similar to those of the reference product (Omnipaque oral solution) as a single use oral contrast agent.

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6. Clinical Microbiology

This section is not needed for this application. No clinical microbiology data were included in the submission.

7. Clinical/Statistical-Efficacy

Statistical

I concur with the assessment by the statistical reviewer Dr. Misra that no statistical review is necessary. No clinical studies have been conducted in support of this application. Available summaries of the individual publications are provided. Methods to combine information using Meta Analyses were not explored.

Clinical

I concur with the recommendation by the clinical reviewer Dr. Stinson and the CDTL reviewer Dr. Gorovets that this application be approved pending modification to the product labeling.

Dr. Stinson states that the performance characteristics of iohexol as an oral agent to opacify the GI tract in CT imaging and the supportive data from x-ray radiography are well understood. I agree with the reviewer's assessment that the relatively minor differences between the formulation of OralTag and the reference listed product Omnipaque (in terms of excipients and iodine concentration) do not have any implication for the performance of orally administered iohexol for GI opacification. The findings of efficacy for dilute Omnipaque administered orally can therefore be extrapolated to OralTag.

The undiluted solution of Omnipaque (350mgI/ml) is indicated for oral administration to support x-ray (pass through) exams of the gastrointestinal (GI) tract and the diluted solution (6-21 mgI/mL) is indicated for oral administration during CT of the abdomen and/or pelvis. On the other hand OralTag is not intended for pass through examination and the product presentation will generally not allow reconstitution to a strength and volume needed for this type of examination. The labeling needs to make this limitation clearer

I agree with the reviewers that the data on the usefulness of OralTag alone for CT examination of the abdomen and pelvis (b) (4) have not been provided. Therefore the labeling may need to be revised to specify that OralTag be used concomitantly with another approved iodinated contrast agent.

8. Safety

I concur with the clinical reviewer's and the CDTL's assessments that the data provided support the safety and tolerability of iohexol for use as an oral agent. To assess the safety profile of iohexol, the applicant conducted a search of the clinical literature for both oral and injection usage of Omnipaque. Based on the very low systemic absorption of oral iohexol (0.1-

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0.5% in normal GI tract), most of the adverse reactions are associated with parenteral administration. No new safety issues have been identified for the proposed use of orally administered iohexol.

9. Advisory Committee Meeting

No advisory committee meeting is necessary.

10. Pediatrics

The application triggers the requirement for pediatric assessment of OralTag under the Pediatric Equity Research Act (PREA) as a new dosage form. The FDA's Pediatric Review Committee agreed that an assessment has been presented in pediatric patients (b) (4) because it was previously appropriately labeled.

11. Other Relevant Regulatory Issues

With regard to Post-market Requirements and Commitments (PMC/PMR), I concur with the recommendation of the primary reviewers (clinical, clinical pharmacology, and drug safety) that no PMC or PMR are necessary.

12. Labeling

The FDA DMEPA reviewer (Dr. K. Wright) found the proposed proprietary name to be conditionally acceptable from a safety and promotional perspective. I concur with that assessment. The applicant was informed of that determination.

DMEPA determined that the proposed container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Detailed recommendations to achieve these objectives were sent to the applicant and a revised labeling appears to have addressed many of these issues.

Complete review of prescribing information, carton and immediate container labels has been deferred. Patient labeling and medication guide are not needed and none were considered.

13. Decision/Action/Risk Benefit Assessment

I concur with the recommendation by the Office of New Drug Quality (ONDQA) and by the Division of Good Manufacturing Practice Assessment (DGMPA) to withhold approval of the NDA because of the finding that the batch analysis and stability studies submitted in the present submission are not acceptable and because of lack of capacity of the establishment that

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will perform the [redacted] (b) (4) operations to manufacture the drug product. [redacted] (b) (4) [redacted].

For these reasons the Division of Medical Imaging Products will take a complete response action.

I concur with the recommendation made by the FDA CDTL reviewer Dr. Gorovets and by primary and secondary reviewers in pharmacology/toxicology, clinical pharmacology, biopharmaceutics, clinical, and safety disciplines, that this application could be approved pending resolution of labeling issues identified by preliminary review of prescribing information and container labeling.

No REMS, PMC or PMR are needed and none were considered.

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/s/

LIBERO L MARZELLA
01/06/2014

Cross-Discipline Team Leader Review

Date	October 29, 2013
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA #	205383
Applicant	Interpharma Praha
Date of Submission	March 11, 2013
PDUFA Goal Date	January 11, 2014
Proprietary Name / Established Name	OralTag/Iohexol (b) (4) Oral Solution
Dosage forms / Strength	Powder (4.5 g of iodine content in a beverage bottle) to be reconstituted with a liquid for oral administration
Proposed Indication(s)	Oral use in adults and in children as an opacification agent during computed tomography of the abdomen and pelvis. (b) (4) (b) (4)
Recommended:	*Complete Response*

1. Introduction

The subject of this Cross Disciplinary Team Leader (CDTL) review is the New Drug Application (NDA) 205383 for OralTag, or Iohexol Powder, an iodinated contrast agent proposed for oral use during abdominal/pelvic Computed Tomography (CT) examinations.

The applicant is Interpharma Praha, represented in the US by Otsuka Pharmaceutical. The application is a 505(b) (2) with the applicant relying on the previous findings by the FDA of safety and effectiveness for the approval of the listed drug, Omnipaque (Iohexol) Injection, but only and specifically for its oral administration. Omnipaque, which is manufactured by GE Healthcare and marketed in the US since 1985, is a sterile solution originally developed as a parenteral product and is since approved for use as a contrast agent given by intrathecal, intravascular or oral administration for a variety of indications. The only approved indication for Omnipaque that is proposed for OralTag is its oral, therefore non-sterile, use to help delineate loops of bowel during an abdominal CT examination. The applicant also presents literature based clinical data in support of the proposed indication.

The proposed indication for OralTag is as follows: (b) (4)

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(b) (4)

This review document addresses the evidence submitted by the applicant in support of the stated claim and whether the clinical data presented by the applicant are needed for the drug approval. The document refers to analyses and review findings from multiple disciplines recognizing that the main determinants here are the product's chemistry and reliability of the control of its manufacturing. During the review process, no significant disagreements have been encountered among the reviewers.

2. Background

Computed tomography of abdomen and pelvis routinely requires administration of oral contrast to delineate the loops of bowel to differentiate them from adjacent structures be it a pathological mass or a normal anatomy. Historically the most commonly used oral contrast was barium. However it is known that barium sulfate suspensions may clump in the GI tract thereby causing imaging artifacts and their use is contraindicated in patients with a suspicion of bowel perforation. Additionally, when used orally, aspiration of barium into the lungs may be lethal. It is also known to cause constipation and impaction.

Gastrografin and Gastroview are the two water soluble, iodine-based oral contrast agents approved for use with CT and represent alternatives to barium. However these drugs have high osmolarity and may cause fluid shifts leading to dehydration as well as pulmonary edema if aspirated. They are also not known to be well tolerated because of their taste.

Iohexol, or Omnipaque, is a more recently developed iodinated contrast agent of lower osmolarity. In addition to its favorable properties for use in the GI tract in case of a perforation or an aspiration, Omnipaque is reported to have a neutral taste and to be better tolerated with less unpleasant side affects than the other agents.

Omnipaque, in the same formulation as approved for intra vascular administration, can be given orally undiluted for use in the diagnostic pass-through radiographic studies of the GI tract. But if diluted it can be used simply for bowel delineation in the CT studies of abdomen and pelvis.

The current applicant claims to have developed a powder form of Iohexol as an agent essentially analogous to Omnipaque which once reconstituted with water or some beverage would be equivalent to the diluted solution of Omnipaque and can then be used similarly during CT examinations. In such use, just as oral Omnipaque for bowel delineation in CT, it would not be for diagnosing any GI conditions but simply for clarifying the existing anatomy.

It should be noted however that Omnipaque is approved for oral use in conjunction with its intravenous use in CT examinations rather than for oral use alone. This issue has been raised at the pre-NDA meeting and the applicant was encouraged to develop a line of evidence based on the existing literature and practice guidelines which would support an apparent expansion of the oral use claim for Iohexol.

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Another related regulatory issue is that although in practice oral Omnipaque is likely being used with other iodinated agents administered intravenously it is labeled for use with intravenous Omnipaque. No clinical studies are cited in the Omnipaque label to better understand the basis for such a claim. Again, a literature based evidence of oral Omnipaque use with other agents given IV would be helpful here as well. Of note, no other iodinated contrast agent approved for use as an IV contrast with abdominal/pelvic CT is also approved for oral use for bowel delineation. (It is all presumably because of taste.)

3. CMC/Device

The drug product in the Iohexol powder consists only of the active pharmacological ingredient (API), the drug substance Iohexol, with no other excipients. It is a non sterile product that comes in as 9.7 g of Iohexol, which corresponds to 4.5 g of Iodine, in graduated 20 oz. bottle. After reconstitution the proposed concentrations are 9, 12, 15, 18 and up to 21 mgI/mL. Adequate solubility of Iohexol Powder has been shown with a variety of beverages and very similar to that of Omnipaque. Other measured properties have been also reported to be very similar.

The initial assessment by the primary CMC reviewer, Dr. Milagros Salazar, was consistent with the probable recommendation for approval pending some additional stability data and the results of manufacturing inspections.

However, the inspectional results, which have just come in, reveal that at the only existing manufacturing site (b) (4) . The resulting recommendation from the Office of Compliance is Withhold.

The discovery that (b) (4) It is not clear, for example, from where the production and stability batch data included in the NDA have originated and under what conditions the provided in the NDA data were obtained. (b) (4) Information requests from the CMC and Compliance staff are being sent to the applicant at this time. In addition to resolving data related questions, once the (b) (4), the inspections will have to take place and results then evaluated.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Sally Hargus has recommended approving this NDA based on FDA's previous finding of safety and efficacy for Omnipaque.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer, Dr. Safaa Burns, plans on recommending the approval of this NDA, also based on it being a 505(b) (2) application. No new clinical pharmacology data have been presented by the applicant.

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As per Omnipaque label, orally administered Iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5% of the oral dose is excreted by the kidneys. The use of this oral contrast agent requires the drug, in fact, to be present in the gastrointestinal tract rather than to be absorbed. Therefore, systemic bioavailability following oral administration is not a prerequisite for the drug's therapeutic indication for CT imaging of the abdomen. The requested waiver (a "biowaiver") of the requirement for measuring in vivo bioavailability or demonstrating in vivo bioequivalence is being considered and will like be granted.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

This is a 505 (b) (2) application which relies primarily on the information presented in the listed drug's labeling. Based on the CMC confirmation, which is extremely important here, that after reconstitution it is the same Iohexol as in orally given diluted Omnipaque for bowel delineation, then, conceptually, this is all that is needed for the drug's approval for the same indication. One has to take into an account formulation differences and a slightly different range of iodine concentrations available for oral administration, which why it is not a generic and why the 505 (b) (2) pathway is appropriate here.

However there are some subtle but potentially significant differences in the proposed indication for OralTag as compared to the approved indication for an oral administration of diluted Omnipaque.

<u>Omnipaque label</u>
The listed drug, Omnipaque, is approved for multiple indications. Among its several intravascular indications it is approved for an intravenous use with CT. The specific formulations approved for such use are 240, 300 and 350 meaning that the strength of the Omniscan solution is 240 mg of iodine per mL, 300 or 350. A dose recommended for any particular imaging is expressed as an amount of iodine, usually in grams (gI), and also frequently listed as a volume of a solution of a given strength.

So for CT related indications, Omnipaque label states that Omnipaque 350 is indicated in <u>adults</u> for "contrast enhancement for computed tomographic head and body imaging" and for body imaging gives a dose range of 60 – 100 mL which is <u>21 – 35 gI</u>. It goes on to say that Omnipaque 300 is also indicated in adults for "contrast enhancement for computed tomographic head and body imaging" and gives for body imaging a dose range of 50 – 200 mL (<u>15 – 60 gI</u>). It then states in the section on INDIVIDUAL INDICATIONS AND USAGE—Oral Use, which is further discussed throughout this document, that in conjunction with oral administration, "the recommended dosage of <u>Omnipaque 300</u> administered intravenously is 100 mL to 150 mL" which is only <u>30 – 45 gI</u>. Therefore it appears that, whereas there are several dose ranges for iodine amount listed in the Omnipaque label for body CT imaging, a more specific intravenous dosing recommendation is provided when it is used as a component of body imaging together with oral Omnipaque. The Omnipaque label also provides a specific

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timing recommendation for the oral dose to be administered "about 20 to 40 minutes prior to the intravenous dose and image acquisition."

For children, the Omnipaque label recommends an intravenous use for abdominal CT, listing it only in the section for use in conjunction with the oral use of Omnipaque, with a dosing range provided as 1 to 2 mL/kg of either Omnipaque 300 or 240 not to exceed 28 gI as a maximum dose. It also recommends that the oral dose is "administered about 30 to 60 minutes prior to the intravenous dose and image acquisition".

For oral use, undiluted and at a higher strength (Omnipaque 350 at a concentration of 350 gI per mL) the listed drug is indicated in adults for use in oral pass-thru examination of the gastrointestinal tract which is essentially an upper or lower GI (diagnostic) series with a water soluble contrast instead of barium. This indication is not a subject of this application and although the applicant has included literature related to this indication it is not being considered in this review document.

For oral Omnipaque, diluted for use with CT, the indications are as follows:

Omnipaque diluted to concentrations from 6 mgI/mL to 9 mgI/mL administered orally in conjunction with Omnipaque 300 at a concentration of 300 mgI/mL administered intravenously is indicated in adults for contrast enhanced computed tomography of the abdomen.

OMNIPAQUE diluted to concentrations from 9 mgI/mL to 21 mgI/mL administered orally in conjunction with OMNIPAQUE 240 at a concentration of 240 mgI/mL or OMNIPAQUE 300 at a concentration of 300 mgI/mL administered intravenously is indicated in children for use in contrast enhanced computed tomography of the abdomen.

The Omnipaque label goes on to say that "dilute oral plus intravenous Omnipaque may be useful when unenhanced imaging does not provide sufficient delineation between normal loops of the bowel and adjacent organs or areas of suspected pathology." It does not say anywhere that oral Omnipaque may be administered "with or without" concomitant intravenous contrast administration as is being claimed in the OralTag application. Omnipaque is also not identified anywhere as an "opacification agent".

The Omnipaque label also provides recommendations on volumes of oral drug administration to which a stock solution of Omnipaque is to be diluted to reach a desired final concentration in mgI per mL, for both children and adults. The label cites such beverages like water, "carbonated beverage", milk or "juice" for use in dilution. Notably, the applicant provides recommendation on reconstitution of OralTag, the powder form of Iohexol, using similar beverages and ending up with similar concentrations and volumes except for a concentration lower that 9 mgI/mL.

Published Literature

The applicant has provided five published studies on the use of diluted oral Iohexol for abdominal and pelvic CT in adults and three studies on such use in children. The studies have

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been presented by Dr. Barbara Stinson, the primary clinical reviewer, at the midcycle meeting and have been thoroughly discussed in her review document. They are not being reproduced again here. Of note, the two most recent studies in adults appear to be adequate and well controlled.

However, none of the studies address the use of dilute oral Iohexol alone for bowel delineation in abdominal CT. Iohexol in all these studies appears to be in the form of Omnipaque and whenever mentioned administered concomitantly with an intravenous contrast. The studies primarily assess taste and tolerability of oral Iohexol in comparison to other oral contrast agents. Whenever bowel "opacification" has been assessed in these studies, using a subjective scale or Hounsfield units, it has been used just for a comparison among the agents so it has not been possible to ascribe any clinical meaningfulness to any particular value obtained.

So the submitted publications do not appear to justify the proposed "opacification" claim and do not provide substantial evidence of effectiveness of oral Iohexol in bowel delineation without a concomitant use of intravenous contrast during an abdominal CT examination. Of note, the review of this application did not involve a statistical evaluation of the submitted published literature because, while reviewed clinically, the data were not found to be applicable to the proposed indication.

This reviewer agrees with the applicant's claim that given the chemical similarities the evidence of efficacy of OralTag can be extrapolated from the efficacy of dilute oral Omnipaque as found by the FDA in the approved label but not with what appears to be an attempt by the applicant to expand the approved indication.

8. Safety

The assessment of safety of OralTag is based on FDA's finding of safety of oral dilute Omnipaque as described in the product labeling. The product has been extensively used throughout the world with a well established safety profile typical for an iodinated contrast agent. Most of the adverse events even when they occur are associated with parenteral administration.

9. Advisory Committee Meeting

There have been no plans for an Advisory Committee meeting.

10. Pediatrics

The applicant has requested, and this reviewer agrees with the request, for a full pediatric waiver because this is a 505(b) (2) application based on the prior FDA approval for use of Omnipaque in all pediatric age groups.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

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12. Labeling

The review team has expressed an opinion early in the review process that having a word "oral" in the name would be preferable for this product. (b) (4) as a proprietary name has been rejected. OralTag is being accepted.

A systematic review of labeling has not been completed yet but certain issues would still have to be addressed. These mostly relate to the indication statement itself. Specifically the claim would have to be worded similarly to the approved claim for the dilute oral Omnipaque.

A concomitant use with IV contrast agents other than Omnipaque might be acceptable if iodine amounts and dosing recommendations are similar as they appear to be. However, while oral Omnipaque might be used off label for abdominal CT in some circumstances alone without an IV agent there are no apparent data to support such an indication. When a non-contrast CT is used, for a renal stone evaluation or sometimes in appendicitis, it is usually without any contrast, oral or IV.

The issue of timing of oral administration in relation to timing of IV administration would also have to be addressed. Certain limitations of use might have to be emphasized: OralTag is not a diagnostic agent and it is not to be used for radiographic pass-through GI examinations.

13. Recommendations/Risk Benefit Assessment

Based on the newly developed manufacturing compliance issues this reviewer recommends a Complete Response. The applicant has not begun manufacturing the product which not only raises a concern about the whole process but also questions the veracity and the origin of the submitted chemistry data. A decision of approving this particular product through a 505b2 application rests entirely on such data.

From a clinical standpoint the application could be approved with the indication wording consistent with that of the approved listed drug.

No REMS or Postmarketing study commitments are being planned.

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/s/

ALEXANDER GOROVETS
10/29/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205383
Priority or Standard	Standard
Submit Date(s)	March 20, 2013
Received Date(s)	March 2013
PDUFA Goal Date	January 20, 2014
Division / Office	DMIP/ODE IV/OND/CDER
Reviewer Name(s)	Barbara Stinson
Review Completion Date	September 9, 2013
Established Name	Iohexol (b) (4) Oral Solution
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Oral Solution for GI Tract Opacification
Applicant	Interpharma Praha, a.s.
Formulation(s)	Powder (9.7 g, iodine content 4.5 g) in a beverage bottle of 20 ounce volume
Dosing Regimen	To be reconstituted with a liquid for oral administration of iodine concentrations ranging from 9 to 21 mgI/mL
Indication(s)	Iohexol (b) (4) Oral

	Solution is indicated for oral use in adults and in children as an opacification agent during computed tomography of the abdomen and pelvis. Iohexol [redacted] (b) (4) Oral Solution may be used with or without concomitant intravenous administration of a radiopaque contrast agent to delineate between normal loops of bowel and adjacent organs or areas of suspected pathology.
Intended Population(s)	Adults or children undergoing CT of the abdomen and pelvis, for delineation between normal loops of bowel and adjacent organs or areas of suspected pathology

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval with no postmarketing commitments.

The clinical reviewer recommends approving the 505(b)(2) NDA for (b) (4) a GI tract opacification agent for use in abdominal and pelvic CT scans. The main purpose of this application is to provide an alternate product to opacify the GI tract during abdominal and pelvic CT scans. The solution administered contains the same active drug ingredient in the same concentration and dosage form as prepared solutions of Omnipaque 300 (iohexol) which is the reference listed drug (RLD) for oral use. The indication is similar to the CT indication for oral use of the listed drug but differs in that the approved indication of the listed drug combines oral administration in conjunction with intravenous administration of the same drug. (b) (4) .

1.2 Risk Benefit Assessment

The overall assessment of risks and benefits of (b) (4) favors the approval of the drug and adoption of an indication for oral use in CT exams to opacify the GI tract. For drug usage, the assessment favors adoption of language proposed by the applicant which indicates an oral route of administration to opacify the GI tract, similar to the route of administration used for the Omnipaque 300 in adults and Omnipaque 300 or 240 in children, but which does not necessitate administration of this drug in conjunction with an intravenous injection of this same drug. The physicochemical properties, (density, osmolality, viscosity), of iohexol (b) (4) oral solution (b) (4) when mixed with various solutions for administration and support the recommendation for approval.

The sterile listed drug is approved for a wide variety of indications and routes of administration in adults and children including intrathecal myelography, intravascular injection (both intra arterial and intravenous), oral ingestion (both pass through and CT exams), and injection into body cavities for example hysterosalpingography, arthrography, and voiding cystourethrography. The performance characteristics of iohexol as an oral agent to opacify the GI tract in CT imaging and the supportive data from x-ray radiography have been extensively studied. The undiluted solution of Omnipaque is indicated for oral administration to support x-ray(pass through) exams of the gastrointestinal (GI) tract and the diluted solution (6-21 mgI/mL) is indicated for oral administration during CT of the abdomen.

Approval is supported by the routine use of orally administered dilute contrast media for opacification of the gastrointestinal tract during abdominal computed tomography (CT). The use of iodinated contrast media for this purpose is supported by the American College of Radiology publication, (ACR Manual on Contrast Media Vs. 8, American College of Radiology, Committee on Drugs and Contrast Media, 2012), which states that approximately 35% of abdominal CT exams currently performed in the United States are performed using iodinated contrast media. The proposed indication inclusive of abdominal and pelvic procedures, (abdomino-pelvic exams) has been described in recent literature and CPT codes, as presented by the applicant, reflect the increased frequency of both exams in current practice, (AAPC Get the Latest on Abdomen and Pelvis CT Scan Codes, August 18, 2011. Accessed 2012. http://news.aapc.com/index.php/2011/08/get-the-latest-on-abdomen-and-pelvis-ct-scan-codes/.). Publications (McNamara MM et.al. Oral contrast media for body CT: comparison of diatrizoate sodium and iohexol for patient acceptance and bowel opacification. AJR AM J Roentgenol. 2010 Nov; 195 (5): 1137-41. and Petersen CM, et al. Prospective randomized trial of iohexol 350 versus meglumine sodium diatrizoate as an oral contrast agent for abdominopelvic computed tomography. J Comput Assist Tomogr. 2011 Mar-Apr; 35 (2): 202-5.) lend additional support to this terminology.

When all routes of administration, all strengths, all clinical settings, and all indications are considered, according to IMS, (IMS Health Data, 2012), an estimated (b) (4) patients in the US are exposed to iohexol annually.

Omnipaque was first approved in 1985. The applicant conducted a literature search to document both the efficacy and safety of the listed drug Omnipaque. The search included supportive efficacy data from published trials of orally administered iohexol in the adult and pediatric population. To document the safety profile of iohexol, the applicant conducted a clinical literature search for both oral and injection usage of Omnipaque. Based on the low systemic absorption of oral iohexol, the primary focus of safety and tolerability was intravascular, primarily the intravenous route. Data support the safety and tolerability of iohexol for use as an oral agent.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

The subject of this clinical review is the 505 (b)(2) New Drug Application (NDA) from Interpharma Praha, a.s. for the diagnostic imaging product (b) (4) (Iohexol (b) (4) Solution), which is an iodinated contrast material used to opacify the GI tract for abdomino-pelvic CT scans.

The reference listed drug, Omnipaque, which is manufactured by GE Healthcare was first approved in 1985 and is provided in five iodine concentrations for intrathecal, intravascular, and oral/body cavity use, with most indications approved for both adults and children. It is provided as a sterile solution packaged to meet the requirements for a parenteral product.

The presentation of Iohexol (b) (4) Solution has been differentiated from the listed drug. For the current application, the applicant has manufactured the drug substance as a powder to be dispensed in a bottle as a unit dose presentation that will contain 9.7 grams of iohexol drug substance, equivalent to 4.5 grams of iodine. The powder which will be contained in a bottle will be dissolved in water or a beverage to achieve the desired concentration for a radiographic procedure. Unlike the listed drug, Iohexol (b) (4) Solution will only be indicated for oral use and will only be indicated for abdomino-pelvic CT exams. (b) (4)

The proposed indication is: (b) (4) ."

The application contains data to support in vivo bioequivalence of Iohexol (b) (4) Oral Solution to the listed drug. No nonclinical or clinical studies were conducted in support of this application. The application relies on the FDA's previous finding of safety and effectiveness from the approval of Omnipaque.

Reviewer's Comment: Clinical recommendation for the indication is as a contrast agent, may state that agent will opacify the GI tract .

2.1 Product Information

The established drug name is Iohexol for Oral Solution. The proposed trade name is (b) (4)®. The reference listed drug is Omnipaque™.

The drug substance will be manufactured as a non-sterile powder with 9.7 grams of iohexol (4.5 grams iodine) per unit dose bottle. Iohexol, the active ingredient in the listed drug Omnipaque, is the same active ingredient that is contained in Iohexol (b) (4) Solution. The drug will be administered as an oral solution that upon dissolution of the powder in water or a beverage will yield a similar concentration and volume as the listed drug and will have similar local availability of the active ingredient.

The reference listed drug, (RLD), Omnipaque is approved as a sterile solution for injection, (NDAs 18,956 and 20,608). The proposed drug product is a non sterile powder for reconstitution with water or a beverage. It is highly soluable. It contains the same active ingredient as the RLD and may be reconstituted to contain iodine in concentrations similar to the RLD. The proposed drug formulated as a powder contains 9.7 grams of iohexol per bottle which is equivalent to 4.5 grams of iodine. When reconstituted for oral use, the concentration ranges from 9 to 21 mgI/mL with standard concentrations being 9, 12, 15, 18, and 21 mgI/mL, compared to 6 to 21 mgI/mL for the RLD. The physicochemical properties of the Iohexol (b) (4) Oral Solution and the RLD in various beverages are comparable. The proposed drug has no excipients. The RLD drug contains excipients necessary for parenteral injection such as substances for solution stability and pH adjustment.

2.2 Currently Available Treatments for Proposed Indications

Oral contrast agents are routinely used to opacify the GI tract during CT imaging. The barium sulfate suspensions and water-soluable iodinated contrast agents that are used for this purpose allow visualization of the GI tract based on their ability to attenuate x-rays.

Barium sulfate suspensions tend to desiccate and may clump in the GI tract thereby causing imaging artifacts. In addition, their use is contraindicated in patients with a suspicion of perforation due to the associated inflammatory response. Water soluable iodinated contrast agents on the other hand are absorbed after GI leakage and are excreted by glomerular filtration and are eliminated unchanged through the kidneys. Additionally, in the upper GI tract, perforations/aspiration of barium into the lungs may be lethal.

All of the approved water soluable products are based on derivatives of tri-iodo-benzoic acid (a benzene molecule with 3 iodine iodine atoms attached). Early developed products dissociate into more than one particle in solution and are referred to as ionic

agents. The more recently developed compound, iohexol, does not dissociate (i.e. it is non-ionic) and thus has a lower osmolality at equivalent iodine concentrations. The group of contrast agents having this property are referred to as low osmolar contrast media which is a property that is primarily relevant for injection and not relevant for oral administration.

In addition to its favorable properties for use in the GI tract when perforations or aspiration exist, iohexol is reported to have a neutral taste and to be better tolerated with less unpleasant side affects than the ionic agents.

Gastrografin™, MD-Gastroview™, and Omnipaque™ are currently in use as water soluable iodinated contrast agents that are approved for oral administration. The first two agents are considered to be high osmolality ionic agents. Omnipaque™ is a low osmolality nonionic agent. The first two of the currently marketed agents are sold as concentrated solutions that must be diluted before oral administration for CT procedures. Four Omnipaque™ concentrations are approved for oral administration. Three of these are diluted before use.

The applicant believes that there is an unmet need for a contrast product that is specifically packaged for oral administration and that has easy to follow dosage and administration instructions and proposes marketing Iohexol Powder as a pre-measured unit dose product in a bottle that will indicate the amount of diluent to add in order to achieve the required concentration of iodine or volume of solution for a CT imaging procedure.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substance testing and stability manufacture will be in the Czech Republic.

The drug product manufacturing site (b) (4) is in New Paltz, New York (Ultra Seal Corporation) and drug product release will be performed in (b) (4)).

2.4 Important Safety Issues With Consideration to Related Drugs

Several published studies of orally administered iohexol to adult patients undergoing CT or x-ray follow through exam demonstrated a low incidence of adverse events. When administered orally, the drugs may be associated with mild GI symptoms.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Iohexol (b) (4) Oral Solution was submitted to the FDA as IND 114,359. The pre-NDA meeting was held on March 20, 2012 to discuss the applicant's intent to seek approval for Iohexol Powder as an oral contrast agent for use in computed tomographic (CT) imaging of the gastrointestinal (GI) tract and to discuss the drug and reach agreement on the proposed regulatory pathway for this process.

Prior to submission of the NDA on March 20, 2013, the applicant discussed additional pre-submission concerns with FDA CMC and Clinical Pharmacology reviewers.

The NDA was submitted on March 20, 2013 and was designated for standard review.

2.6 Other Relevant Background Information

The applicant's plans to submit a 505(b)(2) application for marketing approval of Iohexol Powder were discussed at the pre-NDA meeting. The application relies on the findings of safety and efficacy from the approval of the listed drug Omnipaque for oral administration. Both drugs contain the same active ingredient (iohexol). The applicant does not have a right of reference to the Omnipaque safety and efficacy data. The applicant reviewed literature published since the last date of the listed drug labeling and submitted updated safety and efficacy information for the oral use based on the published literature. The applicant believes that the safety and efficacy profile of the Iohexol Powder will be similar to that which has already been demonstrated for Omnipaque.

Omnipaque was first approved in the US in 1985 as a radiographic contrast medium with multiple indications, concentrations, and doses including for oral use as a contrast agent in the GI tract during CT exams. When orally administered, it has been shown to be poorly absorbed from the normal GI tract and excreted largely unchanged in the feces. Concentrated (non-diluted) solutions administered orally are used to study radiographic pass through studies of the GI tract. Diluted solutions are used in CT studies. Both the undiluted and diluted solutions are used in children as well as adults. Safety has been established for intravenous, intra-arterial, and intrathecal use in addition to oral use.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission is a 505(b)(2) relying in part on literature articles. The application noted details of the search strategy, the search terms, complete output of the literature search, and copies of references cited in summaries. No inspections were conducted

for purposes of data evaluation. The applicant did not perform meta-analyses of the data.

3.2 Compliance with Good Clinical Practices

None of the submitted literature articles report on trials conducted by the applicant.

3.3 Financial Disclosures

None submitted or required.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The proposed drug, Iohexol (b) (4) N,N'-Bis(2,3-dihydroxypropyl)-5[N-2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide} in solution contains the same active drug ingredient in the same concentration and dosage form as the reference listed drug Omnipaque™. (b) (4) are the proposed regulatory starting materials as they are commercially available and are well characterized in the literature and are stable chemical entities. The DMF in the submission contains detailed information on the (b) (4)

The applicant is seeking a waiver of the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of the proposed drug product Iohexol (b) (4) Oral Solution. In support of this request, the applicant summarized provisions of 21 CFR Part 320.22(b)(3) which are reproduced in Table 1 below.

Table 1: Criteria for Waiver of In Vivo Bioavailability or Bioequivalence*

Criteria	Relevant Clause of 21 CFR 320.22(b)(3) and Location of Supporting Rationale
The drug product administered to the patient is an oral solution and	21 CFR 320.22(b)(3)(i); See Section 1.12.15.2
The active drug ingredient in the solution for administration is present in the same concentration and dosage form as the listed drug upon dissolution to obtain similar concentrations and volumes for oral administration, and	21 CFR 320.22(b)(3)(ii); See Section 1.12.15.3
The drug product contains no inactive ingredients or a change in formulation from the listed drug that may significantly affect systemic or local availability of the active drug ingredient for this locally acting product.	21 CFR 320.22(b)(3)(iii); See Section 1.12.15.4

* Reproduced from NDA 205383, Module 1, Section 1.12.15.1, page 4; sections refer to NDA.

The table provides the rationale for the applicant's request and cites the appropriate supportive sections of the NDA. Iohexol, the active ingredient in the listed drug Omnipaque, is the same active ingredient that is contained in Iohexol (b) (4) Solution. The drug will be administered as an oral solution that upon dissolution of the powder in water or a beverage will yield a similar concentration and volume as the listed drug and will have similar local availability of the active ingredient. Omnipaque is supplied as a concentrated liquid that is diluted in water or a beverage to achieve a desired concentration. Iohexol (b) (4) Oral Solution contains no inactive ingredients or excipients and the drug substance (b) (4) This differs from Omnipaque which requires excipients such as those for stability and pH adjustment based on its parenteral use. The intended use of Iohexol (b) (4) Oral Solution as an opacification agent during computed tomography (CT) for visualization of the abdomen and pelvis requires the drug to be present and remain locally in the gastrointestinal (GI) tract with no requirement for systemic oral bioavailability. This is consistent with the known bioavailability profile for Iohexol which has minimum systemic bioavailability after oral administration.

The reference listed drug, (RLD), Omnipaque is approved as a sterile solution for injection, (NDAs 18,956 and 20,608). The proposed drug product is a non sterile (b) (4) reconstitution with water or a beverage. It is highly soluble. It contains the same active ingredient as the RLD and may be reconstituted to contain iodine in concentrations similar to the RLD. The proposed drug formulated as a powder contains 9.7 grams of iohexol per bottle which is equivalent to 4.5 grams of iodine. When reconstituted for oral use, the concentration ranges from 9 to 21 mgI/mL with standard

concentrations being 9, 12, 15, 18, and 21 mgI/mL, compared to 6 to 21 mgI/mL for the RLD. The physicochemical properties of the Iohexol (b) (4) Oral Solution and the RLD in various beverages are comparable. The proposed drug has no excipients. The RLD drug contains excipients necessary for parenteral injection such as substances for solution stability and pH adjustment.

The drug substance testing and stability manufacture will be in the Czech Republic. It is a non-sterile powder with 9.7 grams of iohexol (4.5 grams iodine) per unit dose bottle.

The drug product manufacturing site (b) (4) is in New Paltz, New York (Ultra Seal Corporation) and drug product release will be performed in (b) (4) The drug will be packaged in a 20 ounce polyethylene bottle that has a lined polypropylene cap. Each bottle will be individually sealed in a (b) (4) foil (b) (4) pouch. The product will be reconstituted to an appropriate concentration by filling the bottle to the indicated line on the bottle's label.

The solution is stable in simulated gastric fluid for 90 minutes and in simulated intestinal fluid for 3 hours at 37 ^{0} C. The applicant proposes a 24 month shelf life for the product. Stability studies and analysis of stability data is ongoing.

CMC recommendation at the midcycle has been for approval.

The CDER Bioequivalence team assessment at the midcycle has been that iohexol powder bioequivalence/bioavailability is identical to the RLD Omnipaque.

4.2 Clinical Microbiology

The applicant conducted post-constitutional hold studies where the drug product was reconstituted in tap water and growth at 48 hours was compared to tap water alone. The microbiological stability of the reconstituted drug product after short term storage at room temperature (48 hours) demonstrated no greater microbial risk than standard tap water. Drug product testing for microbial limits at release was appropriate and the proposed microbial limit drug testing was considered adequate.

The microbiology recommendation at the midcycle has been for approval.

4.3 Preclinical Pharmacology/Toxicology

Extensive literature pertaining to nonclinical and clinical testing suggests that nonionic imaging agents such as iohexol are associated with fewer side effects than ionic contrast media, (CM), particularly when administered parenterally. Studies have demonstrated potential safety and tolerability advantages to the lower osmolality of the nonionic agents. Safety concerns are predominantly associated with a parenteral route

of administration. In vitro studies demonstrate that iohexol is a relatively inert compound. Due to low bioavailability when administered orally, there is a lower potential of iohexol to induce adverse events.

The pharmacology, toxicology, and pharmacokinetic evaluation of Iohexol (b) (4) Oral Solution was based on a comprehensive review of the nonclinical literature for iohexol (Omnipaque as the RLD) administered via various routes of administration and doses in multiple animal species and on prior regulatory approvals.

Central nervous system effects ranged in severity depending on the route of administration with subarachnoid (SA) injection having a greater effect than intravenous (IV) or intraarterial (IA) injection. Minimal respiratory effects were observed in rabbits and dogs after SA and IV administration. Smooth/skeletal muscle contraction was not affected by iohexol administration in a variety of in vitro and animal models. There were minimal/transient effects on renal hemodynamics after IV administration in rats, dogs, and pigs. Cardiovascular effects after IA or IV administration to rats, rabbits, dogs, and pigs were more consistent and more serious, for example ventricular fibrillation when injection was direct into the coronary arteries or the aorta. The serious effects were likely a result of high local concentrations. However, in general, direct injection of a short bolus dose of iohexol into the coronary artery produced only minimal and transient effects. More significant effects occurred in studies employing prolonged infusions. Generally, iohexol injection decreased vascular resistance, had positive inotropic effects, and caused no changes or minimal changes in heart rate with effects of decreased vascular resistance.

The applicant noted that in general the primary, secondary, and safety pharmacology reports demonstrated that iohexol causes minimal or undetectable effects after IV administration. Localized administration such as coronary artery or SA injection was associated with more serious pharmacological effects and was likely due to injection of a large volume of fluid with higher osmolality than body fluid rather than a true pharmacological effect. Based on the low bioavailability of iohexol after oral administration, only a fraction of the administered dose is absorbed into the systemic circulation which is then diluted in the systemic circulation and according to the applicant likely to cause only mild, transient, and fully reversible effects, if any, based on the limited pharmacological effects that are observed after IV administration.

After administration into a body cavity, iohexol disperses within the cavity which then is displayed as an opaque image at the time of the radiographic imaging procedure. Following oral administration of Iohexol (b) (4) Oral Solution, a limited fraction is expected to be absorbed based on low oral bioavailability in animals. GI tract obstruction and severe GI tract injury were shown to increase absorption. Studies in rats, rabbits, and dogs showed that iohexol was not metabolized in the body and was eliminated in the urine as the parent molecule after IV administration. Studies in nephrectomized pigs confirmed renal excretion as the predominant mechanism for the

elimination of systemically-induced iohexol with low extra renal clearance noted. As noted, following oral administration of Iohexol (b) (4) Oral Solution, a limited fraction was absorbed and eliminated via urinary excretion. The remainder was primarily eliminated in the feces.

I-125 iohexol was used to study placental transfer and mammary excretion following IV administration to rats. Placental transfer in mid and late gestation was minimal. Absorption from the GI tract of suckling animals was low, with concentrations of about 0.9 µg/mL measured in the blood corresponding to 1/15 of the concentration that is measured in maternal whole blood at 1 hour post injection.

Mortality in mice and rats was studied following single IV administration and was noted to increase with increasing dose with no mortality observed at lower doses. Based on exposure level of greater than 75 times the maximum human oral dose of Iohexol (b) (4) Oral Solution, this is not considered relevant. Single IV iohexol administration studies in beagle dogs did not result in any deaths and related clinical effects were minimal.

Single SA injections of 0.5 or 1.0 gI/kg iohexol in rats were associated with decreased locomotor activity and ptosis but no deaths. Intracisternal administration to rats, dogs, rabbits, and monkeys did not result in any deaths, convulsions, preconvulsive behavior, or adverse effects. In mice, after intracisternal injection ataxia, dyspnea, and decreased motor activity were observed, with no deaths. Oral administration of iohexol to rats and mice at doses at least 133 times the human oral dose was associated with minimal adverse findings and no deaths.

Repeat IV dose toxicity studies conducted in rats demonstrated changes in the liver and kidneys to include vacuolation of renal tubular epithelia and hepatocytes. Additional repeat IV and intracisternal repeat dose toxicity studies in mice, rats, dogs, and monkeys showed similar findings in the liver and kidneys especially at high doses. In rats, in vitro and in vivo studies after IV iohexol administration demonstrated increased histopathologic effects in the kidneys including increased hypoxic injury to medullary thick ascending limbs (mTALs) leading to cytoplasmic damage in proximal convoluted tubule (PCT) cells.

Iohexol was not genotoxic in a battery of genotoxicity assays. Iohexol did not show any mutagenic potential in either mice or guinea pigs. IV administration of iohexol in reproductive and developmental toxicity studies in rats and rabbits demonstrated no effect on male fertility and no embryotoxic or teratogenic potential at doses up to 4.0 gI/kg/day.

In summary the applicant noted the following:

- Acute dose studies: minimal toxicity of iohexol after oral administration, relatively low toxicity following IV administration

- Single and repeat dose studies: minimal progression of toxicity, most effects reversible
- High IV dose effects in rodents: decreased locomotor activity, hydrothorax, ascites, pulmonary edema
- IV administration to dogs: vomiting, hemoglobinuria, dehydration, loss of appetite, vacuolation of renal tubular epithelia, and hepatocytes, hemosiderin deposits in Kupffer cells, lower red blood cell count, higher white blood cell count
- Oral administration to rodents: transient decreased locomotor activity and diarrhea, no additional effects

The preclinical pharmacology/toxicology team recommendation is for approval with no need to conduct further preclinical studies based on prior approval of the RLD Omnipaque.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The drug is a GI tract opacification agent for use in CT scans. After administration, it remains locally in the GI tract. It acts by attenuating radiographic imaging during CT scans. In a retrospective study using an emergency room medical records system to identify CT scans performed with enteric contrast media, following oral administration, iohexol was reported to reach the small bowel in an average of 1:39 hours, the cecum in 2:03 hours, and the rectum in 2:24 hours, (Ortiz-Romero S, Yim A. E089. Comparison of bowel transit time and emergency room turnaround time of oral iohexol versus diatrizoate solution. AJR Am J Roentgenol. 2011 May; 196(5): Suppl. A120-A134.).

4.4.2 Pharmacodynamics

As noted in the pharmacokinetic section below, systemic absorption of an oral dose is low but increased urinary excretion is noted in patients with inflammatory bowel disease as a result of increased intestinal mucosa permeability. The permeability alterations were found to be more frequent in patients with Crohn's Disease as versus patients with ulcerative colitis.

4.4.3 Pharmacokinetics

No new pharmacokinetic studies were conducted since published studies and the prior regulatory approval of Omnipaque adequately characterize the pharmacokinetics and metabolism of iohexol after various routes of administration including oral administration. According to the prescribing information for the RLD as noted in Table 2 below, human oral bioavailability is low with 0.1 to 0.5% of the oral dose excreted by the

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kidneys. Systemic exposure following oral administration is very low but may be increased in patients with inflammatory bowel disease and GI tract injury. When administered orally, all unabsorbed iohexol is eliminated in the feces and any absorbed fraction is not metabolized and is eliminated via renal excretion as iohexol.

Table 2: Omnipaque Bioavailability Following Oral Administration; Section III: Clinical Pharmacology, 2nd Paragraph*

CLINICAL PHARMACOLOGY—Oral/Body Cavity Use
Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5 percent of the oral dose was excreted by the kidneys. This amount may increase in the presence of bowel perforation or bowel obstruction. Iohexol is well tolerated and readily absorbed if leakage into the peritoneal cavity occurs.

Source: {OMNIPAQUE, 2010}.

*Reproduced from NDA 205383, Module 2, Section 2.7.1, page 6; Source: Omnipaque Label, 2010

The applicant conducted a literature search and identified studies relevant to bioavailability and biopharmaceutics (pharmacokinetics) for both the oral and intravenous route of administration. The literature search included a few published studies that assessed the bioavailability of iohexol following oral administration and several studies that examined the use of iohexol as a biomarker of intestinal disease or of organ function (glomerular filtration rate[GFR]), and studies that describe pharmacokinetic assessments of iohexol following IV administration. Summaries of these referenced studies follow.

A study conducted by Langer, (Langer R, et al. Absorption of nonionic contrast media after oral administration. 21st Congress ESPR, Florence 1984), in 3 infants analyzed urine iodine after oral administration of diluted iohexol 300 mgI/mL and concluded that absorption after oral administration was less than 1%.

3 articles cited, (Halme L, et al. Increased urinary excretion of iohexol after enteral administration in patients with ileal Crohn's disease. A new test for disease activity. Acta Radiol. 1993 May; 34(3): 237-41; Halme L, et al. Urinary excretion of iohexol as a marker of disease activity in patients with inflammatory bowel disease. Scand J. Gastroenterol. 1997 Feb; 32 (2): 148-52; Gerova VA, et al. Increased intestinal permeability in inflammatory bowel diseases assessed by iohexol test. World J Gastroenterol. 2011 May 7; 17(17): 2211-5.), tested urinary excretion of oral iohexol as a biomarker of inflammatory bowel disease and supported increased absorption of iohexol in patients with bowel inflammation and mucosal cell damage. Urinary excretion of Omnipaque was measured following administration and was found to be higher in patients with active disease as versus patients with quiescent disease or healthy controls and there was a positive correlation with disease activity and extent. Gerova's study measured serum and urine levels of iohexol assessing the relationship between intestinal permeability and disease activity and showed elevated serum and iohexol

concentrations at 3 and 6 hours for both Crohn's Disease and ulcerative colitis patients compared to healthy controls with significant elevation at both time points for the Crohn's Disease patients and at 6 hours for the ulcerative colitis patients. Patton, (Patton WL et al. Worsening enterocolitis in neonates: diagnosis by CT examination of urine after enteral administration of iohexol. Pediatr Radiol. 1998 (29): 95-99), used CT to study necrotizing enterocolitis in 3 infants after oral administration of iohexol and suggested that the CT attenuation coefficient of urine may be used to evaluate disease.

In addition to oral administration for use as a biomarker for disease activity in inflammatory bowel disease, intravenously administered iohexol has been used as a biomarker of glomerular filtration rate in several studies to assess the impact of pharmaceuticals on renal function in healthy volunteers and patients. Schwartz GJ et al. Glomerular filtration rate via plasma iohexol disappearance: pilot study for chronic kidney disease in children. Kidney Int. 2006 Jun;69(11):2070-77 investigated and validated the feasibility, accuracy, and precision of iohexol plasma disappearance as a useful measure of GFR in children. There was close agreement between GFR measured by inulin clearance and documented correlation between iohexol clearance and Cr-51-EDTA plasma clearance.

The literature search by the applicant yielded 5 published studies of PK trials with intravenously administered iohexol in healthy volunteers, 3 publications of the renal effects of iohexol in patients, two published trials conducted to evaluate the effects of impaired renal function on the PK of iohexol, a trial conducted in lactating women to estimate the amount of iohexol excreted into breast milk, a study on coagulation, fibrinolysis, and platelet function, and a study of iohexol effects on gall bladder volume.

Phase 1 pharmacokinetic trials of iohexol administered via IV route to healthy volunteers were conducted in the early 1980's. The applicant summarized five of these studies in the submission. Following intravascular injection, iohexol distributed into the extracellular fluid with a mean volume of distribution consistent with distribution restricted to circulation. Peak urine concentrations were noted one hour post dosing with 90% to 100% of the IV administered dose recovered unchanged in the urine within 24 hours. No iohexol was detected beyond 2 days after dosing. Total body clearance of iohexol was close to values for Cr-51-EDTA clearance, which demonstrated that excretion is mainly by glomerular filtration. Across the doses tested, the mean iohexol concentrations reported for renal clearance and for total body clearance supported the finding that iohexol is primarily cleared via urine.

Blood and urine analyses detected no metabolites. The negligible metabolism was substantiated by the similarity in renal and total body clearance. The label for the RLD notes that intravascular iohexol displays a low affinity for serum or plasma proteins and that it is poorly bound to serum albumin. It is further noted that no significant metabolism, deiodination, or biotransformation occurs.

In summary, the phase-1 PK studies all supported renal excretion as the route of elimination of iohexol.

Several studies have been conducted to evaluate the effects of iohexol on measurements of renal function in healthy volunteers and patients. Jacobsen, (Jacobsen JA et al. Renal effects of nonionic contrast media after intravenous, cardiac, and lumbar aortic injections. Invest. Radiol. 1990a Sep; 25 Suppl 1:S136-6; Jakobsen JA, Berg KJ. The influence of iodinated contrast media on renal function, with special reference to iopentol. In: Laerum, F, Kendall B, editors. Iopentol. Clinical Trials with a new non-ionic contrast medium. Norway: 1990b. p. 63-72; Jakobsen JA et al. Renal effects of iopentol amd iohexol after intravenous injection. Acta Radiol. 1991 Jul; 32(4):320-4.) conducted and published studies comparing iohexol to iopentol in the 1990-91 time frame. Using patients with normal renal function, renal function (serum creatinine levels and creatinine clearance) was studied after IV administration of iohexol and iopentol for abdominal CT. Renal function remained unchanged for up to 48 hours. There were minor effects on glomerular filtration rate, (increased serum beta 2 - microglobulin [β_2–MG]). A low incidence of acute renal failure was observed, being noted in one patient who had been administered iohexol. There were significant but transient increases in N-acetyl-beta-glucosamidase (NAG) and alkaline phosphatase (ALP) excretion which were also seen in healthy subjects. Intraarterial (IA) administration of iohexol was associated with elevation of serum creatinine at 24 hours. Increases in NAG and ALP were observed in all the IV CT and IA studies that were conducted. The authors concluded that effects on renal tubular function were of minor clinical importance and that no clinically significant differences were detected between iohexol and iopentol.

Nossen in Nossen JO et al. Elimination of the non-ionic x-ray contrast media iodixanol and iohexol in patients with severely impaired renal function. Scand J Clin Lab Invest. 1995 Jul;55(4):341-50 evaluated the pharmacokinetics of intravenously administered iohexol on patients with impaired renal function or diabetic nephropathy. Nossen reported a mean elimination half life of 27 hours which is considerably longer than that reported for healthy volunteers with a 6.1% recovery of iohexol in feces and 74.8% recovery in urine after 5 days as versus studies by Olsson B et al. Human pharmacokinetics of iohexol: a new nonionic contrast media. Invest Radiol. 1983 Mar-Apr; 18(2): 177-82 who concluded that almost 100% of the administered dose was recovered in the urine of healthy volunteers. Glomerular filtration was noted as the main excretory pathway but with markedly reduced elimination rate with severely impaired renal function. Apelqvist P et al. The effect of the non-ionic contrast medium iohexol on glomerular and tubular function in diabetic patients. Diabet Med. 1996 May;13(5):487-92 conducted a study in patients with diabetic neuropathy to determine the acute and chronic effects of iohexol 300 mgI/mL on renal function and found 89% of patients had an increase in serum creatinine levels, peaking at 24-48 hours post arteriography procedure. 9% of these patients had an increase of more than 50%. No patients required dialysis and at 30 days no patients showed differences in serum

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creatinine or other parameters relative to samples taken prior to administration of contrast media. Additionally, a significant decrease in creatinine was noted two days after the procedure.

In summary, studies indicate that patients with reduced renal function have alterations in elimination and clearance rates after administration of intravascular iohexol.

A single study by Nielsen in 1987, (Nielsen ST et al. Excretion of iohexol and metrizoate in human breast milk. Acta Radiol. 1987 Sep-Oct;28(5): 523-36.). which was conducted to measure the amount of iohexol excreted in breast milk of lactating women following IV injection of iohexol found small amounts excreted into breast milk and calculated a mean milk half life of 28 hours concluding that the long half life observed in breast milk indicated the presence of a second elimination phase from plasma for iohexol. This amount represents 0.5% of the maternal dose given. This is in contrast to American College of Radiology estimates of 0.01% based on reports for metrizamide. In the clinical overview, the applicant reproduced the calculation used by Neilsen calculation and calculated an IV pediatric dose and an oral dose for CT exam of an infant less than 3 years old and a 3.5 kg weight infant after maternal dose to an IV exposure to be 0.13% of the recommended amount to be administered to a young child for CT of the abdomen or pelvis.

Following IA administration of iohexol or metrizoate, the result of the coagulation and fibrinolysis test parameters were within normal ranges with the exception of a prolonged prothrombin time for both contrast media (pooled results), attributed to the heparin that was used to flush the arteriofemoral catheter. Platelet counts were reduced after the procedure. In this study, Stormorken H et al. Effect of various contrast media on coagulation, fibrinolysis, and platelet function. An in vitro and in vivo study. Invest Radiol. 1986 Apr; 21(4): 348-54 concluded that iohexol was more biocompatible than the ionic contrast agents and that concentrations reached in vivo during a normal imaging study may not be high enough to elicit any clotting or aggregation effects.

When patients with known gall bladder disease were administered IV or oral contrast and compared to a control group of patients who received no contrast, sonographic exams of the gall bladder showed a significant mean contraction of gall bladder volume 10-15 minutes after administration of contrast, (Khan O et al. Contrast material and gall bladder kinetics: implications for same day sonography after intravenous pyelography or CT scanning. J Ultrasound Med. 1999 Nov;18(11):763-7.

The clinical literature search, according to the applicant, did not yield any information related to drug interactions in humans. The approved labeling for the RLD contains information about drug/laboratory test interactions related to the following. If iodine containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine binding capacity of thyroid tissue may be reduced up to two weeks after contrast medium administration. Thyroid function tests which do not depend on iodine

estimation such as T3 resin uptake are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many drugs therefore no other pharmaceuticals should be admixed with contrast agents.

Reviewer's Comment: No formal Clinical Pharmacology review was performed for (b) (4) based on assessment by the Bioequivalence Team of identical properties to the RLD Omnipaque.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The literature search includes 173 published studies on the oral administration of iohexol and 67 published studies on iohexol in abdominal/gastrointestinal CT with injection as the route of administration. In adults, 5 published reports demonstrating the efficacy of iohexol administered orally for CT examination of the abdomen and pelvis and 3 published reports for radiography pass through examinations were included for review. In children, 3 published reports demonstrating the efficacy of iohexol administered orally for CT examination of the abdomen and pelvis and 5 published reports for radiography GI studies were included for review.

In addition to the literature search for oral administration of iohexol, general information sources for the NDA included the approved labeling for Omnipaque, clinical practice guidelines for low osmolar contrast material and CT, and a clinical literature search for the use of iohexol for injection. PK of IV iohexol, safety of IV iohexol, and safety of intravascular iohexol in special groups and situations was included in the clinical literature search for use of iohexol as an injection.

Table 3 reproduced from the NDA submission provides a description of the published clinical efficacy studies in the adult and includes the number of patients, reason for examination, contrast media used and number of males and females in the study that received contrast, mean or median age, and concentration and volume of study drug(s). Table 4 also reproduced from the NDA submission, provides a similar description for the pediatric population.

Section 6.1.2 contains summary demographic data. Study details will otherwise be reviewed and summarized with conclusions in section 6.2.

Table 3: Description of Published Clinical Efficacy Studies-Adult Population*

First Author, Year	Population				Study Drugs	
	Number	Examination	Gender (M / F)	Mean or Median Age (Range or Standard Deviation)	Concentration (mgI/mL)	Volume (mL)
Lonnemark,1993	Adult N = 30 (10 / group)	Patients referred for CT of the abdomen	Diatrizoate 9 mgI/mL: 7M / 3F Iohexol 9 mgI/mL (aqueous): 6M / 4F Iohexol 9 mgI/mL (viscous): 6M / 5F	Diatrizoate 9 mgI/mL: 50 (28 - 79) y Iohexol 9 mgI/mL (aqueous): 53 (30 - 81) y Iohexol 9 mgI/mL (viscous): 62 (34 - 85) y	Diatrizoate 9 mgI/mL Iohexol 9 mgI/mL (aqueous) Iohexol 9 mgI/mL (viscous)	Diatrizoate diluted from 320 mgI/mL; Iohexol diluted from 350 mgI/mL; Total volume = 800 mL
Lonnemark, 1995	Adult N = 30 (10 / dose)	Patients referred for CT of the abdomen	Iohexol 4.5 mgI/mL: 6M / 4F Iohexol 6.75 mgI/mL: 7M / 3F Iohexol 9 mgI/mL: 8M / 2F	Iohexol 4.5 mgI/mL: 49 (21 - 71) y Iohexol 6.75 mgI/mL: 50 (31 - 70) y Iohexol 9 mgI/mL: 49 (26 - 66) y	Iohexol 4.5 mgI/mL Iohexol 6.75 mgI/mL Iohexol 9 mgI/mL	Iohexol diluted from 350 mgI/mL Total volume = 800 mL
Diederichs, 2007	Adult N = 160 (30 / CM group; 160 controls)	Patients referred for routine staging for tumor aftercare	All groups: 90M / 61F	All groups: 61 (28 - 82) y	Amidotrizoate 300 mgI/mL Diatrizoate 360 mgI/mL Ioxithalamate 300 mgI/mL Iopromide 300 mgI/mL Iohexol 300 mgI/mL Iotralan 300 mgI/mL	Diatrizoate was administered in 4% aqueous solution; Ioxithalamate, iopromide, iohexol, and iotralan were administered in 5% aqueous solution.
McNamara, 2010	Adult N = 300 Iohexol, n = 149; Diatrizoate, n = 151	Patients referred for abdominal - pelvic CT	Both groups: 184M / 116F	Both groups: 56 (19 - 92) y Iohexol: 56.7 y Diatrizoate: 56.2 y	Iohexol 9 mgI/mL Diatrizoate 9.17mgI/mL	Iohexol diluted from 350 mgI/mL; Diatrizoate sodium 26 mL in 1000 mL) Total volume = 900 mL
Peterson, 2011	Adult N = 100 Iohexol, n = 49; Diatrizoate, n = 51	Patients referred for abdominal – pelvic CT	Iohexol: 23M / 26F Diatrizoate: 20M / 31F	Iohexol: 51.6 ± 12.1 y Diatrizoate: 52.4 ± 10.5 y	Iohexol 8 mgI/mL Diatrizoate 8 mgI/mL	Iohexol diluted from 350 mgI/mL; Diatrizoate diluted from 370 mgI/mL Total volume = 1000 mL
Kinnunen, 1989	Adult N = 58 71 examinations: Iohexol, n = 35; Diatrizoate, n = 36	Patients referred for follow-through examinations	NA	Iohexol: 61.8 ± 18.0 y Diatrizoate: 63.7 ± 12.9 y	Iohexol 350 mg/mL Diatrizoate 370 mg/mL	100 mL
Laerum, 1991	Adult N = 96 Iohexol, n = 52; Iopentol, n = 44	Patients referred for small bowel obstruction follow-through examination	Iohexol: 24M / 28F Iopentol: 20M / 24 F	Iohexol: 56.8 (19.1) y Iopentol: 63.8 (16.8) y	Iohexol 350 mgI/mL Iopentol 350 mgI/mL	Mean ± SD (range): Iohexol: 195 ± 13 mL (130 - 200) Iopentol: 186 ± 29 mL (100 - 200)

Jobling, 1999	Adult N = 42 (52 examinations)	Patients referred for small bowel follow-through examinations	NA	NA	Iohexol 350 mg/mL	100 mL

F = female; M = male; NA = information not available; y = year.

*Reproduced from NDA 205383, Module 2, Section 2.7.3, Summary of Clinical Efficacy, pages 41-43

Table 4: Description of Published Clinical Efficacy Studies-Pediatric Population*

Smevik, 1985	Pediatric N = 32	Infants and children referred for abdominal CT for malignant disease	13M / 19F	Median 142 wk (31 wk – 13 y) 15 patients < 2 years	Iohexol 7 mgI/mL	Diluted from 350 mgI/mL; total volumes administered: Oral: 120 – 500 mL Enema: 60 – 120 mL Gastric tube: 60 – 300 mL
Smevik, 1990	Pediatric N = 160	Patients referred for abdominal CT (malignant disease confirmed in 81%)	69M / 91F	Oral / Gastric Tube / Enema: 0 – 1 y: n = 15 / n = 2 / n = 3 1 – 2 y: n = 13 / n = 3 / n = 6 2 – 5 y: n = 35 / n = 0 / n = 4 5 – 10 y: n = 45 / n = 0 / n = 2 10 – 16 y: n = 34 / n = 0 / n = 4	Iohexol 6 mgI/mL Iohexol 7 mgI/mL	Age range: mL (mean)(route) *0 – 1 y:* 50 – 300 mL (176) (oral) 60 – 80 mL (70) (gastric tube) 35 – 40 mL (38) (enema) *1 – 2 y:* 60 – 300 mL (171) (oral) 120 – 150 mL (130) (gastric tube) 30 – 100 mL (62) (enema) *2 – 5 y:* 60 – 800 mL (290) (oral) 100 – 120 mL (115) (enema) *5 – 10 y:* 0 – 1350 mL (397) (oral) 10 – 150 mL (80) (enema) *10 – 16 y:* 20 – 1500 mL (681) (oral) 60 – 300 mL (135) (enema)
Mahmoud, 2010	Pediatric N = 365	Patients referred for abdominal CT; study assessed gastric fluid volume	213M / 152F	Mean 32 mo (0.7 - 211.1 mo)	Iohexol 6 mgI/mL	Diluted from 300 mgI/mL (1 mL in 50 mL of clear liquid); mean volumes administered: < 1 y: 18.4 mL/kg (range: 7.5 - 43.6 mL/kg) 1 - 5 y: 18.4 mL/kg (range: 1.5 - 82.8 mL/kg) 6 - 12 y: 14.8 mL/kg (range: 3.1 - 27.8 ml/kg) > 12 y: 12.6 mL/kg (range: 6.1 - 20.4 mL/kg)
Stake, 1985	Pediatric N = 30	Patients referred for X-ray radiography	NA	Median 35 wk (1 d – 14 y) 18 patients < 1 y	Iohexol 175 mgI/mL Iohexol 350 mgI/mL	Diluted from 350 mgI/mL with equal amounts of water, n = 29 Undiluted 350 mgI/mL, median dose = 40 mL (range: 8 – 225 mL), n = 4 Perorally = 14 Gastric tube = 17 Enema = 2
Ratcliffe, 1986	Pediatric N = 115 examinations Iohexol, n = 28; Ioxaglate, n = 70; Iopamidol, n = 18	Patients referred for X-ray radiography	Esophagogram: 28M / 14F Meal: 30M /16F Enema: 9M / 3F Loopogram: 10M / 6F	Esophagogram/swallow: 1 d – 10 y Meal: 3 d – 14 y Enema: 1 d – 3 y Loopograms: 1 wk – 3 y	Iohexol 180 mgI/mL Ioxaglate 320 mg/mL Iopamidol 200 mg/mL Injection (not approved in US)	NA

First Author, Year	Population				Study Drug	
	Number	Examination	Gender (M / F)	Mean or Median Age (Range or Standard Deviation)	Concentration (mgI/mL)	Volume (mL or mL/kg)
Langer, 1987	Pediatric (newborn and infants) N = 293 Oral, n = 225 Enema, n = 68	Patients referred for X-ray radiography (fluoroscopy)	Oral: 129M / 96F Enema: 40M / 28F	Oral / Enema: 0 – 1 mo: n = 53 / n = 17 1 – 2 mo: n = 34 / n = 7 2 – 3 mo: n = 30 / n = 7 3 – 6 mo: n = 41 / n = 7 6 – 12 mo: n = 30 / n = 15 1 – 2 y: n = 21 / n = 8 > 2 y: n = 16 / n = 7	Iohexol 300 mgI/mL Iopamidol	Diluted with 5% glucose 1:1 for oral and aqua dest 1:1 for rectal administration. Mean volume given was 5 mL/kg body weight for orally and 5 - 10 mg/kg body weight for enemas.
Cohen, 1991	Pediatric Part 1: N = 64 Iohexol 180 mgI/mL, n =21 Iohexol 300 mgI/mL, n = 21 Barium, n = 22 Part 2: Iohexol 180 mgI/mL, N = 18	Patients referred for X-ray radiography	Part1: 11M / 10 12M / 9F 15M / 7F Part 2: 9M / 9F	Part 1: Iohexol 180: 4.7 ± 4.8 y Iohexol 300: 5.4 ± 5.8 y Barium: 3.5 ± 4.5 y Part 2: Iohexol 180: 1.2 ± 3.1 y	Part 1: Iohexol 180 mgI/mL Iohexol 300 mgI/mL Barium 30% or 60% Part 2: Iohexol 180 mgI/mL	Part 1: Iohexol 180 mgI/mL: 5.2 ± 5.9 mL/kg Iohexol 300 mgI/mL: 7.0 ± 7.0 mL/kg Barium: 6.5 ± 3.3 mL/kg Part 2: Iohexol 180 mgI/mL: 9.2 ± 5.6 mL/kg
Wright, 2002	Pediatric N = 152 Iohexol, n = 78 Iodixanol, n = 74	Patients referred for X-ray radiography	48M / 30F 48M / 26F	Iohexol: 6.4 (0 - 15) y Iodixanol: 5.8 (0 - 15) y	Iohexol 140 mgI/mL Iohexol 300 mgI/mL Iodixanol 150 mgI/mL Iodixanol 320 mgI/mL	10 – 400 mL

NA = information not available; F = female; M = male; mo = month; y = year

*Reproduced from NDA 205383, Module 2, Section 2.7.3, Summary of Clinical Efficacy, pages 44-46

5.2 Review Strategy

The submitted efficacy data in the main literature articles were reviewed. All materials submitted with the NDA were reviewed for safety. Table 5 is a summary listing of the efficacy studies that were reviewed in adults by author, title, journal, and year of publication. Table 6 is a similar listing of efficacy studies in children. Studies chosen by the applicant are listed in alphabetical order by first author.

Table 5: Adult Studies Involving Oral Administration of Iohexol

	Authors	Title	Journal	Year

CT Examinations				
1	Diederichs et al	Oral administration of intravenous contrast media: a tasty alternative to conventional oral contrast media in computed tomography	Rofo	2007
2	Lonnemark et al	Oral contrast media in CT of the abdomen. A double-blind randomized study comparing an aqueous solution of amidotrizoate, an aqueous solution of iohexol and a viscous solution of iohexol	Acta Radiol	1993
3	Lonnemark et al	Oral contrast media in CT of the abdomen. Iohexol of different concentrations as a gastrointestinal contrast medium	Acta Radiol	1995
4	McNamara et al	Oral contrast media for body CT: comparison of diatrizoate and iohexol for patient acceptance and bowel opacification	AJR Am J Roentgenol	2010
5	Peterson et al	Prospective randomized trial of iohexol 350 versus meglumine sodium diatrizoate as an oral agent for abdominopelvic computed tomography	J Comput Assist Tomogr	2011
X-Ray (Pass Through) Radiography Examinations				
6	Jobling et al	The use of non-ionic water soluable contrast agents for small bowel follow-through examination	Eur Radiol	1999
7	Kinnunen et al	Omnipaque and Gastrograffin in gastrointestinal follow-through examinations	Rontgenblatter	1989
8	Laerum et al	Intestinal follow-through examinations with iohexol and iopentol. Permeability alterations and efficacy in patients with small bowel obstruction	Invest Radiol	1991

Table 6: Pediatric Studies Involving Oral Administration of Iohexol

	Authors	Title	Journal	Year
CT Examinations				
1	Mahmoud et al	Oral contrast for abdominal computed tomography in children: the effects on gastric fluid volume	Anesth Analg	2010
2	Smevik and Stake	Iohexol as contrast medium for bowel opacification on abdominal CT in infants and children	In: Kaufman,editor. Contrast Media in Pediatric Radiology	1985
3	Smevik and Westvik	Iohexol for contrast enhancement of bowel in pediatric abdominal CT	Acta Radiol	1990
X-Ray Radiography Examinations				
4	Cohen et al	Comparison of iohexol with barium in gastrointestinal studies of infants and children	AJR Am J Roentgenol	1991
5	Langer et al	Nonionic contrast media for gastro-intestinal studies in newborns and infants	J Belge Radiol	1987
6	Ratcliffe	The use of low osmolality water soluable (LOWS) contrast media in the pediatric gastro-intestinal tract. A report of 115 examinations	Pediatr Radiol	1986
7	Stake et al	Iohexol as contrast medium for the gastrointestinal tract in childhood	In: Kaufman,editor. Contrast Media in Pediatric Radiology	1985
8	Wright et al	Iodixanol in paediatric gastrointestinal imaging: safety and efficacy comparison with iohexol	Br J Radiol	2002

5.3 General Discussion of Individual Studies/Clinical Trials

There were no pre-specified criteria for well-controlled studies. The literature reports for both adults and children were chosen based on the oral administration of iohexol, either for CT or radiography exam. For efficacy, the studies performed qualitative and/or quantitative evaluations of the GI tract, excluding the esophagus. The published literature was searched to establish the approximate numbers of publications referable to a comprehensive safety database. The applicant's focus for safety was for

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administration via the oral route based on the lack of access to source data and an inconsistent application of an adverse events dictionary.

The databases searched included MEDLINE® 1950-2012, Biosis Previews® 1969-2012, EMBASE alert 2012, EMBASE 1974-2012, SciSearch® Cited Ref Sci 1990-2012 and SciSearch Cited Ref Sci 1974-1989. The cut off date for the oral route of administration was 28 Aug 2012. The cut off date for injection routes of administration was 29 August 2012. The "Clinical Literature Search-Oral" included clinical trials, case reports, letters, and reviews describing oral administration of iohexol; and clinical trials, studies, and case reports describing use of iohexol in conjunction with GI computed tomography, in the clinical population, published in English. The "Clinical Literature Search-Injection" was conducted to assure that articles associated with other routes of administration that could be pertinent to safety or to PK would not be excluded.

6 Review of Efficacy

Efficacy Summary

The applicant performed an extensive literature search for the administration of iohexol (Omnipaque) to adults and children via an oral or intravascular route.

Qualitative and/or quantitative evaluations of opacification by oral iohexol of the GI segments in adults undergoing abdomino-pelvic CT yielded satisfactory visualization of all regions of the GI tract with the approved dose of Omnipaque, (300 mgI/mL diluted to 6-9 mgI/mL. 500-1000 mL volume). Subjective measures of contrast medium distribution and opacification were conducted either by using a Visual Analog Scale (VAS zero to 100% scale), a 4-point scale, or a 5-point scale and were performed by two or more independent readers. Three studies used quantitative measurements of radiodensity by Hounsfield Units. Four studies compared iohexol to other contrast media. One study evaluated three concentrations of iohexol.

There were no differences in attenuation values between 3 concentrations of iohexol however distribution and transit times varied for the 3 concentrations. In patients where the distribution of iohexol was considered insufficient in the stomach and duodenum (9 patients), it was noted that 6 of these patients received the lowest concentration of iohexol (4.5 mgI/mL). When compared to other contrast media, there were no statistically significant differences in the subjective measures of contrast distribution or opacification although for one study the quantitative measurement of attenuation was statistically different for the ileum and was attributed to the lower osmolality of iohexol compared to meglumine sodium diatrizoate which was also evaluated.

Subjective assessments of taste and patients acceptance were performed using different tools but in all instances noted iohexol as preferred or acceptable. In one study, a viscosity increasing agent was added to the iohexol which decreased transit time to the ascending colon but which did not affect taste.

Data from radiography pass-through (also known as follow through) examinations conducted using higher concentrations and lower volumes of undiluted Omnipaque, (350 mgI/mL, 100-195 mL), were used as supportive efficacy data. The trials assessed efficacy in terms of diagnostic visualization of the bowel, radiographic quality, and transit time. One of the trials assessed suitability in a surgical population and related the studies to final clinical diagnoses. Taste and patient acceptance were evaluated in one of the trials.

Contrast visualization in the bowel was noted to be sufficient to good for two of the studies and slightly less than optimal for the third study but with overall radiographic quality sufficient to make a diagnosis. Transit times, when measured, did not differ from study comparators. The majority of patients rated the taste of iohexol as neutral.

All pediatric age groups (ages 1 day to 16 years) were studied.

Subjective measures of the quality of bowel opacification and visualization were described for 3 studies (1 CT study and 2 GI studies) which used either a 3-point or 4-point scale by one or more readers. Image quality and contribution to diagnosis were also rated for one of these radiographic studies. Another radiographic study compared iohexol to other contrast media. One study selected patients who were considered at risk for use of either barium sulfate or conventional hypertonic water soluable contrast media. Taste acceptance was recorded in 4 studies.

There were three published studies in pediatrics demonstrating the efficacy of iohexol administered orally for use in contrast CT of the abdomen and pelvis. All studies included patients with malignant disease. One of the studies was primarily focused on the effects of administering oral contrast agent on gastric fluid volume prior to anesthesia or sedation. Bowel enhancement was generally reported to be good with inadequate or poor visualization reported for reasons such as insufficient volume of contrast medium (vomiting, large amounts of air filled bowel, refusal to drink reported).

Iohexol was administered either orally or rectally for the x-ray radiography GI studies. Of the 5 published reports of x-ray radiographic studies, the comparative double-blind trial of iohexol and barium by Cohen, 1991 supported the approval of Omnipaque. Visualization was generally reported as good to excellent for the 5 pediatric supportive radiographic studies. Stake and Smevik, 1985 did recommend higher concentrations of iohexol for small structures such as fistulas and Wright, 2002 reported generally higher VAS scores with higher concentrations of iohexol but noted that efficacy was acceptable with lower concentrations. In this same trial, 96.4% of radiographic

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examinations from patients that were administered iohexol contributed to the overall final clinical diagnosis.

Taste acceptance was measured for two CT and two radiography studies and was generally reported as good.

6.1 Indication

The applicant is seeking the following indication:

(b) (4)

6.1.1 Methods

For the efficacy review in adults, 5 published reports demonstrating the efficacy of iohexol administered orally for CT examination of the abdomen and pelvis and 3 published reports for radiography pass through examinations were reviewed. For the efficacy review in children, 3 published reports demonstrating the efficacy of iohexol administered orally for CT examination of the abdomen and pelvis and 5 published reports for radiography GI studies were reviewed.

6.1.2 Demographics

The following Tables 7 and 8 are similar to Tables 3 and 4 in section 5.1 and reflect the demographics of both the adult and pediatric populations in the published literature but are limited to only patients who received iohexol via an oral route, for either CT or radiographic exam.

For the adult population, a wide range of ages, (21-85 years), is again noted with the mean/median about 50-60 years. For CT iohexol administration where gender was noted, the percentage of females undergoing study was similar, (44% versus 41%).

For the pediatric population, the age range is from newborn to 15 years with the majority of patients under age 5. Allowing for 50% in the 1987 Langer study, approximately 900 children received iohexol for oral CT or radiography), 44% of whom were females, (sex not stated for 30 children). This was also similar to the percentage of females in combined CT and radiography studies, (42%).

Table 7: Demographic Data of Adult Patients Administered Oral Iohexol*

First Author, Year	Number of Evaluated Patients[a]	Gender		Age (Range/Mean/Median)	Examination
		Male	Female		
Lonnemark, 1993[b]	20	12	9	30 – 85 years	Abdominal CT
Lonnemark, 1995	30	21	9	21 – 71 years	Abdominal CT
Diederichs, 2007[c]	30	NA	NA	28 – 82 years	Abdominal-pelvic CT for routine tumor staging
McNamara, 2010[d]	149	NA	NA	56.7 years	Abdominal-pelvic CT
Peterson, 2011[e]	49	23	26	51.6 years	Abdominal-pelvic CT
Kinnunen, 1989[f]	35	NA	NA	61.8 years	X-ray radiography GI follow-through examinations
Laerum, 1991[g]	52	24	28	56.8 years	X-ray radiography small bowel obstruction follow-through examinations
Jobling, 1999	42	NA	NA	NA	X-ray radiography small bowel follow-through examinations

NA = information not available.
[a]Only the number of patients administered iohexol are shown.
[b]Study included a total of 30 patients administered amidotrizoate aqueous solution (n = 10), iohexol aqueous solution (n = 10), or iohexol with a viscosity-increasing agent added (n = 10).
[c]Study included a total of 160 patients administered lysine amidotrizoate (n = 160), sodium amidotrizoate (n = 30), ioxithalamate (n = 30), iopromide (n = 30), iohexol (n = 30), or iotrolan (n = 30).
[d]Study included a total of 300 patients administered diatrizoate sodium (n = 151) or iohexol (n = 149).
[e]Study included a total of 100 patients administered diatrizoate (n = 51) or iohexol (n = 49).
[f]Study included a total of 71 examinations; patients were administered meglumine sodium diatrizoate (n = 36 examinations) or iohexol (n = 35 examinations).
[g]Study included a total of 96 patients administered iopentol (n = 44) or iohexol (n = 52).

*Reproduced from NDA Module 2, Section 2.7.3, Summary of Clinical Efficacy, page 28

Table 8: Demographic Data of Pediatric Patients Administered Iohexol*

First Author, Year	Number of Evaluated Patients[a]	Gender		Mean or Median Age (Range or Standard Deviation)	Examination
		Male	Female		
Smevik, 1985	32	13	19	Median 142 wk (31 wk – 13 y); 15 patients < 2 y	Abdominal CT for malignant disease
Smevik, 1990	160	69	91	Oral / Gastric Tube / Enema: 0 – 1 y: n = 15 / n = 2 / n = 3 1 – 2 y: n = 13 / n = 3 / n = 6 2 – 5 y: n = 35 / n = 0 / n = 4 5 – 10 y: n = 45 / n = 0 / n = 2 10 – 16 y: n = 34 / n = 0 / n = 4	Abdominal CT (malignant disease confirmed in 131 patients)
Mahmoud, 2010	365	213	152	Mean 32 mo (0.7 - 211.1 mo)	Abdominal CT to measure gastric fluid volume
Stake, 1985	30	NA	NA	1 d – 14 y; 18 patients < 1 y	X-ray radiography
Ratcliffe, 1986[b]	28	12	16	Esophagogram/swallow: 1 d – 1.5 y Meal: 10 d – 1.5 y Enema: 2 d Loopograms: 4 mo – 2 y	X-ray radiography
Langer, 1987[c]	293 total iohexol and iopentol patients Oral, n = 225 Enema, n = 68	Upper GI: 129 Enema: 40	Upper GI: 96 Enema: 28	Oral: Newborns and infants < 6 mo: n = 158 > 6 mo: n = 67 Enema: Newborns and infants < 6 mo: n = 38 > 6 mo: n = 30	X-ray radiography
Cohen, 1991[d]	Part 1: Iohexol 180 mgI/mL, n = 21 Iohexol 300 mgI/mL, n = 21 Part 2: Iohexol 180 mgI/mL, n = 18	11 12 9	10 9 9	Part 1: Iohexol 180 mgI/mL: 4.7 ± 4.8 y Iohexol 300 mgI/mL: 5.4 ± 5.8 y Part 2 : Iohexol 180 mgI/mL: 1.2 ± 3.1 y	X-ray radiography
Wright, 2002[e]	78	48	30	6.4 y (0 - 15 y)	X-ray radiography

NA = information not available; d = day; mo = month; y = year; wk = week.

[a] Only the number of patients administered iohexol are shown.
[b] Study included a total of 115 examinations; patients were administered ioxaglate (n = 70), iopamidol (n = 18), or iohexol (n = 28).
[c] Study included a total of 293 patients administered iopentol or iohexol; the results were combined.
[d] Study included a total of 82 patients and was conducted in two parts; (1) patients were administered iohexol 180 mgI/mL (n = 20), iohexol 300 mgI/mL (n = 20), or barium (n = 22) and (2) patients were administered iohexol 180 mgI/mL (n = 18).
[e] Study included a total of 152 patients administered ioidixanol (n = 74) or iohexol (n = 78). One hundred forty-seven patients contributed to the efficacy evaluation: 71 iodixanol and 76 iohexol.

*Reproduced from NDA 205383, Module 2, Section 2.7.3, Summary of Clinical Efficacy, pp.30-31

6.1.3 Subject Disposition

The efficacy of iohexol was based on a review of publications describing the use of iohexol as an enteric contrast medium in abdominal CT exams and as a contrast agent for radiography exams of the GI tract in both adult and pediatric populations.
8 published studies describe the use of oral contrast for CT or radiography. Apart from Diederichs, (CT for tumor staging) and Laerum, (small bowel obstruction), specific reasons for patient referral were not noted. 621 patients received CT exams. 196 patients received radiography exams, some multiple for a total of 219 exams. 41% of all patients studied were females. 50 % of all patients, 45% of CT patients, and 60% of radiography patients received iohexol. By gender, there were 41% females receiving iohexol for CT studies with gender and contrast media not matched for 25% of CT patients. Slightly more females than males were in the single radiography study where gender was noted. For CT exams, iohexol diluted from 300 mgI/mL or from 350 mgI/mL to a volume of 800-1000 mL was administered resulting in a concentration of 4.5-9 mgI/mL. The proposed concentration is 9 mgI/mL which is approved for the RLD and which was used for the published studies. Other drugs administered for CT studies were used in similar concentrations. 100-200 mL of undiluted iohexol 350 mgI/mL was administered for radiography exams.

Iohexol was generally well tolerated as an oral contrast medium. For most patients, the distribution of iohexol was satisfactory for evaluation. 2 patients (Diederichs et al) who received iohexol for a CT exam vomited and were not included in the study.

8 published studies describe the use of oral contrast for CT or radiography in children. Apart from Smevik, (CT for malignant disease) and Malmoud, (CT to assess gastric fluid volume), specific reasons for patient referral were not noted. 557 patients received CT exams. 672 patients received radiography exams. 42% of all patients studied were females. 60 % of all patients, 100% of CT patients, and 50% of radiography patients received iohexol. By gender, there were 44% females receiving iohexol for CT studies and 39% undergoing radiography exams, (gender not specified for 30 children). For CT exams, iohexol diluted from 300 mgI/mL or from 350 mgI/mL to various volumes depending on patient age and whether administration was via oral route, gastric tube, or enema. Iodine concentration administered ranged from 6-7 mgI/mL. The proposed concentration is 9-21 mgI/mL with a volume of 180-750 mL which is approved for the RLD. For radiography exams, both diluted and undiluted iohexol or alternate drug were administered in varying volumes depending on patient size and type of study.

Iohexol was generally well tolerated for the majority of pediatric patients. The majority of patients studied for CT exams had malignant disease. Many of the patients receiving radiographic exams had life threatening conditions such as bowel perforations. Some pediatric patients required sedation or anesthesia for exams. Several instances of vomiting, refusal to drink contrast, or large amounts of bowel gas were reported nonetheless, all patients in the studies were able to be evaluated and when there was a reason for a poor evaluation this was noted.

Reference ID: 3394106

6.1.4 Detailed Review of The Studies in Adults

6.1.4.1

Diederichs et al. Oral administration of intravenous contrast media: a tasty alternative to conventional oral contrast media in computed tomography. Rofo. 2007 Oct; 179(10): 1061-7.

The objective of this prospective clinical study was to find a product with better taste and identical opacification properties to the lysine amidotrizoate currently in use. The authors expressed a need to improve taste based on the value of contrast use in CT staging exams that oncology patients undergo, frequently repeatedly, while suffering from nausea associated with chemotherapy.

Prior to the clinical study, density values of iohexol (Omnipaque), iopromide (Ultravist), iotrolan (Isovist), amidotrizoic acid (Gastrografin), and lysine amidotrizoate (Peritrast) were measured at 5 dilutions in a phantom study using study equipment. The phantom study revealed identical density values.

160 patients who were undergoing routine staging within the scope of tumor aftercare were selected for the study based on a prior scan with lysine amidotrizoate within 6 months. Patients were assigned to groups of 30 each. Group allocation proceeded chronologically. 10 additional patients who were assigned to receive Peritrast for the second exam were considered the control group, (group 6). 61 females and 90 males ranging in ages from 28 to 82 years, (mean age: 61 years), were included. There were no significant differences in age and sex among the groups. Patients were excluded for factors such as hyperthyroidism, contrast allergy, renal insufficiency, and inability to remember the taste of the contrast media supplied for the previous exam.

Patients were instructed to drink the contrast medium in regular intervals within a period of one hour prior to CT exam and then to drink the last 100 mL shortly before the onset of examination. Taste was assessed based on subjective impression just prior to CT scan. Assessment was based on a score of 0 (very bad) to 10 (very good) with 5 defined as being equivalent to the neutral taste of water. The taste of Peritrast was assessed retrospectively. Adverse events for the prior contrast administration were also assessed retrospectively based on targeted questioning. Then, taste for the current exam was assessed. Adverse events were recorded immediately and 24 hours after

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exam via telephone surveys. CT scans were standardized to include intravenous injection of 120 mL Ultravist 370 administered at an injection rate of 2.5 mL/sec.

The density of the contrast medium in the bowel lumen was measured in Hounsfield Units, (HU), for all segments in segments that were well distended and continuously opacified. Overall opacification was noted. A qualitative assessment for homogeneity of the distribution and distension was determined using a 5 point scale ranging from 0 (no opacification) to 4 (good opacification with optimal distribution and full distension). Statistical calculations were performed for taste deviations and for comparing adverse events.

Assessment of taste resulted in Omnipaque and Isovist having significantly better taste than Peritrast, Telebrix also significantly better (variable quartiles), and no significant differences for Gastrografin and Ultravist. There were no statistically significant differences in the determined density values of the five contrast media compared to Peritrast in any segments of the small intestine that were examined. Likewise, qualitative evaluation of bowel opacification compared to segmental opacification was similar for all contrast media, all of which revealed no differences between single segments and the whole bowel. In general the quality of duodenal opacification was estimated as rather poor compared to more distal bowel segments.

Adverse event evaluation noted nausea, vomiting, and diarrhea for all contrast media. For Peritrast, these incidences were 7.5%, 1.3%, and 5.6% respectively. Nausea occurred most often in patients who received Ultravist and Isovist (6.7%). Omnipaque caused vomiting in 6.7% of cases.

Conclusions (Diederichs et al):

The use of oral contrast media in CT exams carried out in the scope of tumor aftercare is important to distinguish normal bowel from recurrent disease. A good tasting orally administered contrast media is an important factor as it influences patient compliance and comfort. This study evaluated several contrast media for efficacy (delineation of bowel), safety (adverse events), and taste. Efficacy was similar for all contrast media that was tested. The adverse event profile was similar although there was some variability in the occurrence of nausea and vomiting. Omnipaque, Isovist, and Telebrix were all preferred to Peritrast (the control) for taste.

Low-osmotic (Ultravist, Omnipaque) and iso-osmotic (Isovist) products potentially lead to higher density values in the distal bowel segments due to increased water resorption in distal bowel segments which accounts for high density values for Isovist in the ileum, however in this study there was no negative effect on the qualitative evaluation of opacification. The authors briefly discuss various alternative products that may be used for bowel opacification.

Regarding the range of adverse events, the low-osmotic and iso-osmotic contrast media cause an increased resorption of water and thus account for less laxative effects. The underlying diseases should be noted in the consideration of nausea and vomiting.

6.1.4.2

Lonnemark et al. Oral contrast media in CT of the abdomen. A double-blind randomized study comparing an aqueous solution of amidotrizoate, an aqueous solution of iohexol and a viscous solution of iohexol. Acta Radiol. 1993 Sep;34(5):517-9.

The objective of this study was to compare a 2.5% solution of amidotrizoate (Gastrografin as an aqueous solution of 9 mgI/mL) to aqueous iohexol (9 mgI/mL) and to a similar solution of iohexol to which a viscosity increasing agent had been added. The viscosity increasing agent was based on ordinary food additives, (starch, cellulose). As the rationale for this study, the authors noted that distribution of contrast media in bowel loops on CT exams of the abdomen is often unsatisfactory resulting in various attempts such as the addition of other drugs to the oral contrast agent to solve the problem.

30 patients ranging in age from 28-85 years with a mean age of about 50-60 were included, 10 patients in each group. Exclusion was for GI disease, current GI symptomatology, or recent abdominal surgery. Contrast medium was ingested in four 200 mL portions every 40 minutes for 2 hours prior to CT exam. The viscosity increasing agent was added to the iohexol solution each time and was then vigorously shaken prior to ingestion. Imaging was standardized according to the suspected pathology.

Analysis for contrast distribution in small bowel loops was based on a visual analogue score, (VAS), with the left end at 0% and the right end at 100%. The presence of contrast medium in segments of colon was also noted. Duodenum was evaluated separately.

Patients were interviewed for safety and tolerance. Taste and consistency were recorded on a VAS scale of 0%-100% also, with 0% awful taste or impossible to drink and 100% good taste or no problem to drink. Adverse events were recorded as mild, moderate, or severe and patients were requested to report any delayed adverse events.

Three radiologists evaluated the distribution of contrast material in the small intestine in a blinded read fashion and found no statistical difference in contrast medium distribution. Both aqueous solutions tended to be seen in the ascending colon sooner than the viscous iohexol group. Taste acceptance was best for the aqueous iohexol with a significant difference between aqueous and viscous preparations however there was no significant difference in taste between amidotrizoate and the other two

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preparations. Consistency of the two aqueous solutions was rated as significantly better.

There were no side effects of clinical importance noted either during or following the investigation.

Conclusions (Lonnemark et al):

The addition of a viscosity-increasing agent to an oral CT contrast medium did not improve distribution in the small intestine as has been shown previously for an oral MR contrast medium. This may be explained by the different chemical and physical properties of the contrast media.

For the three contrast media that were tested as oral contrast media for abdominal CT exams, there was no significant difference in the distribution of contrast media in the small bowel. The aqueous contrast media solutions were comparable regarding passage time through the bowel with a longer passage time noted for the viscous solution. Taste was preferred for the aqueous iohexol which may provide a viable alternative when patients are unable to drink the large volumes of the alternate solution or when children are being studied. The viscous solution was significantly different from the aqueous solution as rated on a subjective VAS scale where the consistency of the viscous iohexol solution was rated near to 50 with the aqueous iohexol close to 100.

The authors concluded that this study did not show any reason for exchanging the conventional oral amidotrizoate or iohexol for a viscous solution but that there remained a need for oral CT contrast media with better distribution properties than those currently available.

6.1.4.3

Lonnemark et al. Oral contrast media in CT of the abdomen. Iohexol of different concentrations as a gastrointestinal contrast medium. Acta Radiol. 1995 Jul;36(4):396-8.

The objective of the study was to compare the contrast effect of low (4.5 mgI/mL), medium (6.75 mg I/mL), and high (9 mgI/mL) concentrations of iohexol in an aqueous solution and to evaluate the distribution of the contrast medium in the intestines and the occurrence of adverse events.

30 patients were studied, 10 in each group, ages 21-71 years with a mean age of 50 years. Iohexol 350 mgI/mL was diluted with water to achieve the desired concentration. The total volume used was 800 mL ingested as four 200 mL portions every 40 minutes with the last portion taken immediately prior to examination.

Imaging was standardized. One radiologist assessed the images to try to determine which concentration had been given. Two radiologists evaluated the distribution and contrast effect of the contrast medium in the intestines. A visual analogue scale of 0% to 100% was used for scoring contrast medium in bowel loops. Duodenum and stomach were evaluated separately. The presence of contrast medium in various segments of colon was also noted. Multiple region of interest measurements were made for attenuation values of contrast filled bowel loops. All patients were interviewed about subjective acceptance and adverse effects with taste and consistency of the contrast medium reported on a VAS where 0% was poor acceptance and 100% was good acceptance. Adverse effects were recorded as mild, moderate, or severe.

In all patients, the overall impression of the concentration of contrast medium was satisfactory but it was not possible to determine visually which concentration of contrast was used and attenuation values within stomach and bowel loops did not differ. Generally, contrast medium was more concentrated distally in the bowel. There were no significant differences between the groups regarding distribution and transit time of the contrast medium. Regarding contrast in the stomach and duodenum, there was a tendency for a difference between the lowest concentration group and the other two groups with 6 showing no contrast in stomach and poor filling or no contrast in duodenum versus 3 patients combined from the other two groups showing no contrast in stomach. Taste and consistency were not significantly different for the three groups. No side effects of clinical importance were noted during or after the investigation.

Conclusions (Lonnemark et al):

Several types of contrast media have been used to opacify the GI tract for abdominal CT exams. When diatrizoate (Gastrografin) has been used, it has been used as a solution with 9 mgI/mL. This concentration results in sufficient opacification of the GI tract. Iohexol has been used as an alternative because the taste of Gastrografin may not be acceptable, for example in children. This study showed that it was possible to reduce the concentration of iohexol by 50% with sustained effect of the contrast medium. With the exception of the stomach and duodenum, contrast medium was well distributed in the small intestine in all patients. In 9 patients, 6 of who received the lowest concentration, the distribution was considered insufficient in the stomach and duodenum. The authors concluded that 4.5 mgI/mL iohexol is sufficient for bowel opacification.

6.1.4.4

McNamara et al. Oral contrast media for body CT: comparison of diatrizoate and iohexol for patient acceptance and bowel opacification. AJR Am J Roentgenol.2010 Nov;195(5): 1137-41.

The purpose of the study was to determine whether there is a difference in patient preference between the oral contrast media iohexol (Omnipaque) and diatrizoate sodium (Gastroview) which are used for abdomino-pelvic CT. A secondary objective was to evaluate for differences in bowel opacification and adverse event profile for the two agents.

The authors noted the need to maximize diagnostic accuracy of CT exams and cited previous studies that have evaluated various contrast media for bowel opacification, patient taste preference, and adverse events. They noted further that the administration of positive oral contrast frequently results in patient complaints of noxious taste and occasional nausea and vomiting.

300 patients, ages 19-92 years with a mean age of 56 years, were studied; 39% were females. Patients were excluded for known contrast allergy to either of the agents, loss of sense of smell or taste, and contraindication to oral administration such as aspiration risk. The contrast agents were mixed according to manufacturer's recommendations. Iohexol 350 used was diluted in water for a total of 9 g of iodine; diatrizoate sodium was diluted in water to yield 9.17 grams of iodine. Each patient was instructed to consume 300 mL of oral contrast agent with no specific instructions concerning rate of ingestion or time limit.

CT exams were performed using intravenous contrast, (iopamidol [Isovue 370]), administered at 3.8 mL/sec per a protocol based on body weight. Upon completion of the exam, patients were surveyed rating the taste of the agent they received on a Likert 5-point scale, ranging from -2 as dislike very much to 0 as neutral and neither like or dislike, to +2 like very much. Next, a direct taste test was performed with each patient drinking 30 mL of each diluted agent separated by drinking at least 30 mL of water to clear the taste of the first agent. This was rated on a 3-point scale of -1 preference for A, 0 no preference, and +1 preference for B.

Bowel opacification was rated by two independent reviewers using a 4-point scale of 0 (absent opacification), 1 (less than 25% of the analyzed segment opacified), 2 (25%-75% of the analyzed segment opacified), and 3 (more than 75% of the segment opacified). Each segment of small intestine and colon was separately rated. Stomach and small bowel segments were averaged for an overall opacification. The ratings of the two readers were averaged. Adverse events were assessed on the day of exam and at 24 hours.

On the contrast agent taste response scale, the mean score for iohexol was 0.86 ± 1.09 with -0.21 ± 1.23 for diatrizoate sodium. Direct taste preference results showed 233, (81%) patients preferred iohexol, 54, (19%), preferred diatrizoate sodium, and 10 had no preference. There was no difference for order of contrast tasted or for gender.

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There was no significant difference in bowel opacification between the two agents and there was good inter observer agreement between raters regarding the opacification. Some subjects in both groups had contrast in the colon with no difference in grading of opacification between the agents.

Adverse events consisting of vomiting, nausea, and queasy feeling at the onset were low with equal numbers for each agent, (5). The adverse event rate at 24 hours was more inclusive for terms but was also low with no differences between the agents.

Conclusions (McNamara et al):

Satisfactory bowel opacification is important for accurate abdominal-pelvic CT scan interpretation. Lack of a noxious taste and decreased unpleasant adverse effects from oral contrast administration is expected to improve patient compliance when drinking the contrast agent. This study showed a statistically significant taste preference for dilute iohexol compared to dilute diatrizoate sodium for oral contrast for CT. No significant difference in bowel opacification or adverse events profile was identified. The authors noted that a limitation of the study was that adverse events could be associated with the intravenous contrast and that various CT techniques were used for the study but that the effect of these variables should be limited by the randomization process.

6.1.4.5

Petersen et al. Prospective randomized trial of iohexol 350 versus meglumine sodium diatrizoate as an oral agent for abdominopelvic computed tomography. J Comput Assist Tomogr. 2011 Mar-Apr;35(2):202-5.

The objective of this study was to compare the efficacy and patient tolerance of iohexol (as iohexol 350) and meglumine sodium diatrizoate as oral contrast agents for computed tomography, (CT). The authors noted that positive oral contrast agents, both barium and iodine based, are routinely used to opacify the GI tract for CT examinations of the abdomen and pelvis. While safe and effective, barium-based oral contrast agents are contraindicated when a leak of the GI tract is suspected because barium products can provoke an inflammatory response within the peritoneum, retroperitoneum, and mediastinum. Diazotrizoate (Gastroview) is a high-osmolality iodine-based oral contrast agent that can be safely used in patients with a GI tract leak however it is poorly tolerated by many patients based on an objectionable taste and GI tract upset due to increased peristaltic activity. Iohexol (Omnipaque) is a low osmolar iodinated contrast agent that is FDA approved as an oral contrast agent.

100 patients were randomly assigned to receive either diazotrate (N = 51) or iohexol (N = 49), both of which were prepared to achieve an iodine concentration of 8 mgI/mL. Mean age for both groups of patients was 52 years. 39% of patients in the Gastroview

group were males. 47% in the Omnipaque group were males. Patients drank 1000 mL of contrast total with two thirds of the contrast ingested over a 35 minute period beginning at 45 minutes before the scan and the final third of contrast ingested immediately before scanning.

On completion of the CT exam, patients were asked to rate the taste of the contrast agent on a scale of 1 to 10, were questioned about the occurrence and severity of nausea, vomiting, bloating, abdominal cramping, and diarrhea, and asked whether they had received oral contrast for a CT exam in the past and to compare the previous contrast agent for taste and adverse effects. One to three days after CT exam, patients were contacted for adverse event determination.

Two radiologists assessed the extent and density of contrast opacification of stomach, small bowel segments, and colon which was rated on a scale of 1 to 5 with 5 indicating the most opacification. Attenuation values were measured for all segments.

Patient demographics of the contrast groups were similar. Both contrast agents were well tolerated. Only a few unpleasant reactions were noted with no significant differences between the two groups. Patients reported a small but statistically significant preference for the taste of iohexol. On a 10 point scale with 10 being the best, iohexol was ranked at 7.1 versus diatrizoate at 6.0. Patients who had previously received contrast had a greater tendency to report that they preferred the taste of their current contrast when they were given iohexol than when they were given diatrizoate. Bowel opacification for qualitative rank was similar for the two agents. For the rank of opacification density, only the difference in opacification in the ileum was statistically significant (4.4 for diatrizoate versus 4.7 for iohexol) and that difference was for only one of the two readers. Measured radiodensity was similar for both groups apart from a small but statistically significant difference in the mean attenuation value in the ileum with a higher mean attenuation value in the iohexol group.

Conclusions (Peterson et al):

This study demonstrated patients' preference for the taste of iohexol compared to that of meglumine sodium diatrizoate. There was no statistically significant difference between the two agents in the incidence of adverse reactions. The extent and density of GI tract opacification were similar between the two groups. The low osmolality of iohexol compared to diatrizoate with less osmotic drag may explain the small difference in bowel opacification that occurred in the ileum. Colonic opacification was variable between the two groups but not statistically significant. The authors concluded that since iohexol 350 is a readily available alternative to meglumine sodium diatrizoate with comparable cost and similar adverse events, since it offers a better tolerated taste, it may be helpful for use in ill patients who often have difficulty drinking oral contrast because of its taste.

6.1.4.6

Jobling et al. The use of non-ionic water soluable contrast agents for small bowel follow-through examination. Eur Radiol. 1999;9(4):706-10.

This study retrospectively reviewed a consecutive series of small bowel examinations using non-ionic contrast media in order to determine their efficacy. The author noted that in certain situations such as perforation or obstruction it is preferable to perform small bowel examination using water-soluable contrast agents, generally ionic agents, rather than barium sulfate. Ionic agents result in dilution and loss of contrast in the mid to distal small bowel due to their high osmolality and thus there may be a preference for non-ionic agents in selected patients.

52 small bowel follow through exams were performed in 42 patients. Post operative patients comprised the largest group studied. Clinical indications included post operative evaluations, total parenteral nutrition, barium intolerance, and acute abdomen. Obstruction followed by fistula was the main reason for exam within these groups. Each patient received 100 mL of iohexol contrast and was placed in a right lateral position to improve gastric emptying. Abdominal films were taken frequent intervals early in the study then at follow up intervals depending on the rate of contrast transit through the bowel. Intermittent fluoroscopy and spot films with compression were performed as required. A median of 3 films per patient was taken excluding spot fluoroscopy views with times ranging from 5 to 265 minutes after ingestion of contrast medium..

Two radiologists reviewed the films for radiographic quality and clinical findings. Mucosal detail in small bowel was scored as good, poor, or not visualized. Findings such as obstruction, perforation, fistula, and surgery were noted. Comparison was made with operative findings and clinical outcome.

The procedure was well tolerated by the majority of patients. One patient had a major anaphylactic reaction to iohexol. The entire small bowel was able to be examined in 21 patients who had not had previous small bowel resection. Duodenal contrast was judged as good in 96% of exams with jejunal and ileal contrast good in 92% and 73% respectively. Duodenal and jejunal fold pattern was visualized in all exams with ileal fold pattern visualized in 81% of exams. All patients who were diagnosed with obstruction or fistulae and who were followed up surgically had radiological findings confirmed and 5 patients with a negative radiology exam had negative findings at laparotomy. Water soluable exam did not diagnose an ileo-anal suture line dehiscence in a patient suspected of having a small bowel obstruction, an intermittent ileostomy torsion, or a duodenal fistula that had been seen on a prior exam and that remained patent.

Conclusions (Jobling et al):

The authors concluded that non-ionic water-soluable contrast agents may be used to adequately examine the small bowel and are helpful in patients when barium suspensions are contraindicated. They noted that despite a risk of aspiration pneumonitis and dehydration due to hypertonicity with a progressive loss of radiographic contrast as an agent travels distally, ionic agents such as Gastrografin continue to be used because many surgeons consider these agents as therapeutic for resolution of postoperative ileus or obstruction. They further noted that to counter this advantage, some investigators have studied the use of non-ionic agents in children and some have compared ionic and non-ionic agents, (reviewed as part of this NDA submission). The authors noted that performing the small bowel follow through examination with iohexol is possible by simple modification of the standard barium exam of decreasing the volume of contrast that needs to be ingested, the flavor of the non-ionic iohexol is relatively neutral so it is well tolerated, and the loops of distal ileum are well opacified with this contrast. Lastly it was noted that adverse reactions can occur with any product but were rare. The authors were aware of a single documented reaction to barium attributed to the presence of additives and a single anaphylactic – type reaction to oral iohexol in a 31 year old man.

6.1.4.7

Kinnunen et al. Omnipaque and Gastrografin in gastrointestinal follow-through examinations. Rontgenblatter. 1989 May;42(5):228-31.

The aim of the study was to compare ionic high-osmolar water- soluable Gastrografin with non-ionic low-osmolar water-soluable Omnipaque in gastrointestinal follow-through examinations. The major objectives were to assess patient reactions, taste acceptance, diagnostic visualization of the bowel, and transit time. Omnipaque has been shown to be successful for pediatric gastrointestinal exams, producing satisfactory to excellent diagnostic images. Both agents have been used for CT exams of the abdomen yielding equal image quality.

71 consecutive follow-through exams were performed in 58 patients. The average age of patients was similar for both groups, (63.7 years for Gastrografin and 61.8 years for Omnipaque). 61 exams were performed for suspected ileus, 10 for “anastomosis control.” 60 studies were performed in patients with previous abdominal surgery. There were 36 Gastrografin (meglumine sodium diatrizoate) exams and 35 Omnipaque (iohexol 350 mgI/mL) examinations. Patients having multiple exams were symmetrically distributed with 6 patients receiving both contrast media. Patients ingested 100 mL of contrast medium. A standard series of radiographs was obtained for each patient until the contrast medium had reached either the rectum or the cecum, depending on the indication.

Patients were asked whether the taste was neutral or unpleasant and the day after the exam were questioned about nausea, emesis, and diarrhea. Nausea and emesis were scored as present or not. Diarrhea was scored as 0 for none, 1 for mild, and 2 for severe.

All radiographs from each examination were score independently by three radiologists using a linear analogue scale of 0 (poor) to 100 (excellent) on line of measured length 100 mm. Contrast medium density and diagnostic visualization of stomach, small bowel, and colon was scored and transit time to the cecum was noted.

The occurrence of nausea and emesis was small and was similar for both groups. There was slightly more diarrhea after Gastrografin (14/36 with severe diarrhea) than after Omnipaque (6/35 with severe diarrhea) but the difference was not significant

Contrast medium density and diagnostic visualization were significantly better for Omnipaque in the small bowel with a trend for better visualization in colon and better visualization of anastomoses with Omnipaque also, although not significant. Mean transit to cecum was similar for both agents (about 3 hours).

Conclusions (Kinnunen et al):

Gastrografin passes through the GI tract more quickly than barium and does not cause chronic inflammatory reactions if leaked outside the GI tract and because of its hypertonicity it may be used therapeutically to relieve meconium ileus and may facilitate peristalsis in postoperative ileus or reduce edema at a bowel anastomosis. However, it may cause dehydration due to fluid shift into the bowel and it may cause pulmonary edema and inflammation if aspirated. Low-osmolar contrast agents such as iohexol have less side effects than Gastrografin. This study showed that there was better diagnostic visualization with Omnipaque with dilution of Gastrografin noted in the small bowel. The osmotic effect was not rapid enough to impair visualization in the stomach and Gastrografin regained density in the colon where fluids are absorbed from the bowel .Transit time and the occurrence of diarrhea were similar for both contrast agents so the authors felt that whether a therapeutic effect exists it is equal for both. Adverse events and taste acceptance were similar for both. The overall conclusion of the authors was that Omnipaque is favored for use in cases where visualization of detailed small bowel pathology is desired and the use of barium is contraindicated.

6.1.4.8

Laerum et al. Intestinal follow-through examinations with iohexol and iopentol. Permeability alterations and efficacy in patients with small bowel obstruction. Invest Radiol. 1991 Nov;26 Suppl 1:S177-81.

There were two main objectives of this study. The first was to study intestinal suitability of iopentol 350 mgI/mL compared to iohexol 350 mgI.mL for intestinal follow-through examinations in adult patients suspected of having intestinal obstruction. The second was to observe increased permeability for water-soluable contrast media in a surgical patient population and relate it to final patient diagnosis.

Both contrast media are water-soluable, nonionic, and monomeric with an iodine concentration of 350 mgI/mL. Both have an osmolality that is twice body fluids. The resulting increased water influx through the semipermeable bowel walls may affect the intestines by increasing mobility and resolving subtotal obstructions.

130 patients were enrolled in the study. Entry into the study was based on an acute abdominal condition such as suspected small bowel obstruction that required an enteric follow up exam. Patients were excluded for known or suspected iodine or contrast media hypersensitivity, recent injection of intravascular contrast media, and prior study participation. The mean patient age was 60 years and was similar for both agents. There were slightly more females than males in the study. Patients received hematology and blood chemistry tests prior to study and at 2-4 hours after contrast medium ingestion.

A mean of 186 mL of iopentol and 195 mL of iohexol was given orally or via a gastric tube. Mean time from start until end of intake was 5 minutes. Patients were instructed to lie in the right decubitus position. Sequential films were obtained up to 24 hours, longer if indicated. Films were interpreted when contrast material had reached the colon/rectum or if there was a decision for the patient to undergo acute surgery. Patients were requested to record taste acceptance on a visual analogue scale (VAS) of 11.9 cm marked bad through neutral through good, using a 1-2 mL aliquot in the patient's mouth if the contrast was administered via a gastric tube. Adverse events such as nausea, vomiting, and diarrhea were assessed during and after contrast intake and were recorded for time of onset, duration, intensity, and relationship to contrast media, procedure, or patient disease. Patients were followed to determine clinical signs of improvement, medication use, surgical treatment, referral, and final diagnosis.

Two radiologists evaluated the radiographs with initial evaluation by a single radiologist followed by a consensus read of two radiologists. Times were recorded for progression of contrast medium in the bowel and VAS scales were used to evaluate contrast medium density with 0 as too lucent and anatomical details not well defined, 5 as optimal with anatomic details well defined, and 10 as too dense with anatomic details obscured. Diagnosis was scored on a 0 to 10 scale with 0 as insufficient information to make a radiologic diagnosis and 10 as more than sufficient information. Increased radiopaque density in the urinary bladder during the course of the exam was also noted.

Urine was sampled periodically during the examination period for determination of urinary contrast medium concentration using high performance liquid chromatography with determined values corrected for time and urinary volume.

96 patients were included for analysis. There were a small number of adverse events (nausea, vomiting, or diarrhea) noted for each group, (5 for iopental and 4 for iohexol). There was no statistically significant difference in blood tests between the two groups. Taste acceptance was not significantly different for the two contrast media although numerically iohexol was considered somewhat better.

There was no statistically significant difference between the two contrast media for radiographic density in the small bowel or colon or overall radiographic exam with contrast media density slightly below optimal for both although the quality of the exams was sufficient to make a radiologic diagnosis. Transit time to reach the cecum after ingestion was higher for iopentol but this was not statistically significant. Clinical improvement was noted for 53% of patients who received iopentol and for 61% of patients who received iohexol. The remaining patients underwent surgery within 24 hours following the exam. An arbitrary cut off of 100 mg contrast medium/hour was chosen for urinary excretion. 70 out of 91 patients were below this. Contrast medium was seen in the urinary bladder in 15 out of 91 patients. This patient group was noted to have intestinal cancers, bowel perforations, obstructions, or inflammation/irritation.

Conclusions (Laerum et al):

Iohexol and iopentol are both suitable for and have similar properties for intestinal follow-up examination. Physico-chemical characteristics of both substances are similar and both have an osmolality about twice body fluids resulting in increased water influx through the bowel walls which may affect the intestine. Taste acceptance is probably influenced by the state of the patients which, for this study, was acutely ill, with the mean value for taste rated as less than neutral for both groups although slightly better for iohexol. Adverse events were few and were mild for both groups. Radiographic appearance was similar for both groups. Urinary excretion that was noted for 15 of 91 patients has been previously reported with intestinal ischemia, obstruction, and inflammation with mucosal damage affecting intestinal permeability even when there is no bowel obstruction. The authors concluded by recommending further investigations to explore the diagnostic potential of water-soluable contrast media as a membrane marker in conditions implying permeability alterations of the gut.

6.1.5 Detailed Review of the Studies in Children

6.1.5.1

Mahmoud et al. Oral contrast for abdominal computed tomography in children: the effects on gastric fluid volume. Anesth Analg. 2010 Nov;111(5):1252-8.

The purpose of this retrospective study was to measure gastric residual volume after administration of oral enteric contrast medium (ECM) when ECM is administered for abdominal CT study for up to one hour before anesthesia/deep sedation and to review records for all complications that occurred with the different sedative/anesthetic techniques used. The rationale for this study was based on the rapid transit time of ECM through the stomach and small bowel which is associated with a one hour window prior to study for optimal image evaluation which is at odds with guidelines for sedation/anesthesia nothing-by-mouth (NPO) guidelines of 2 hours prior to sedation/anesthesia in order to decrease risks for aspiration pneumonia. The authors hypothesized that patients receiving ECM 1 hour before anesthesia would have residual gastric fluid volume (GFV) >0.4 mL/kg.

Anesthesia and radiology reports, CT images, and department incident reports were reviewed between January 2005 and June 2009 for all children who required sedation/anesthesia for abdominal CT. The study evaluated 365 patients ranging in age from 0.66 to 211.1 months (mean age 32 months) who received oral/IV contrast material before anesthesia/sedation and 47 patients, (age range 0.63 to 215.8 months, mean age 52 months), who received only IV contrast and were fasting for the study. 91% of children were under age 5. Older patients were developmentally delayed necessitating the use of general anesthesia (GA) or deep sedation. The M/F ratio was 58%/42% for the group that received oral contrast and 45%/55% for the group that received only IV contrast. The abdominal CT scans were performed for various clinical indications, (tumors and miscellaneous). Patients with trauma and possible appendicitis were not included since these patients do not receive ECM for studies. Most patients in both groups were ASA (American Society of Anesthesiology) classification 2 or 3 (mild or severe systemic disease). Anesthesia/sedation reports were reviewed for airway protection and showed 260 patients had unprotected airways such as native airways or laryngeal masks and 105 patients had protected airways with either a tracheostomy or endotracheal tube. Among patients who received oral contrast, 207 patients had general anesthesia and 158 patients had deep sedation. Complications potentially related to ECM such as coughing and aspiration were noted.

Diluted iohexol 300 mgI/mL (diluted to 6 mg/mL) was used for enteric contrast. The contrast was diluted in a clear liquid with volume administered dependent on the age of the patient. Whenever possible, contrast was administered by mouth. Drinking started 2 hours before and ended 1 hour before anesthesia. Ioversal 320 mg/mL (Optiray 320) was used for IV contrast. The volume of IV contrast was based on the weight of the patient. 2 mL/kg up to a maximum volume of 100 mL was used and was injected into a peripheral IV access by means of a power injector at a rate of 2 mL/sec or by hand injection, depending upon the size of the peripheral IV access catheter. CT imaging was standardized. Regions of interest were drawn on images to demonstrate contrast in the stomach with volumes created by adding areas together based on slice thickness.

In patients who did not receive ECM, the volume of fluid in the stomach was calculated by use of a region of interest measuring the area of fluid density within the stomach on each image with fluid in the stomach and converting areas to volumes and adding the volumes together as was done for the ECM group.

The primary outcome variable was GFV measured in milliliters per kilogram. Patients were placed in dichotomous groups on the basis of GFV—those having a zero volume and those with more than zero volume. A chi-squared test was applied to determine whether there was any difference in the proportion of fasted patients with zero GFV in comparison with those who had ECM one hour before. A chi-squared test was performed to compare the same two groups with respect to percentage of patients who had residual GFV exceeding 0.4 mL/kg. The Wilcoxon Mann-Whitney test was used to examine whether there was a difference in GFV between groups with and without a protected airway. The presence or absence of ascites was observed and the chi-squared test (or Fisher's exact test, when appropriate) was used to see whether the incidence of ascites was associated with protected/unprotected airway or with outlier/nonoutlier values of GFV. All tests were two-sided with statistical significance as p values ≤0.05.

Distribution of contrast within the GI tract of the 365 children who received ECM was not uniform. 90% had contrast in the small intestine, 78% had contrast in the large intestine, and 74% had opacification of both small and large intestine.

The median GFV was significantly higher for patients who received ECM than for those who received IV contrast only with 0.38 mL/kg for those who received oral contrast compared to 0.15 mL/ kg for those who did not receive oral contrast. The mean GFV 1 hour after completing the oral contrast was 2.10 mL/kg versus 0.73 mL/kg for patients who received only IV contrast. There was no difference in GFV between groups with a protected airway and those without a protected airway. When GFV was examined by age groups, the GFV was significantly lower for those who did not receive oral contrast in the 1 to 5 year old group and in the 13 years and older group with no significant differences noted among the less than 1 year olds and the 6 to 12 year olds.

Of the 365 patients who received oral contrast, 91(25%) had zero GFV in comparison with 15 (32%) of the 47 who did not receive oral contrast which was not statistically significant. 189 patients had a GFV that exceeded 0.4 mL/kg. 178 (49%) of the 365 who had received oral contrast were in this group compared with 11 (23%) of the 47 in the group that received IV contrast only. The incidence of ascites and specific presenting pathology did not correlate with large residual GFV (outliers).

The relationship between volume of ECM administered and residual volume 1 hour after ingestion was examined and the authors then generated a table to enable one to estimate the GFV in mL/kg 1 hour after contrast administration if the volume of contrast given in mL/kg is known.

Among those who received oral contrast, 207 patients had general anesthesia and 158 patients had deep sedation. There was no evidence of pulmonary aspiration in any patient. Among the patients who had GA there were two cases of vomiting. None of the patients who had IV contrast had a complication related to contrast administration.

Conclusions (Mahmoud et al):

For children receiving an abdominal CT, the residual GFV exceeded 0.4 mL/kg in 49% (178/365) of those who received oral ECM up to one hour before anesthesia/sedation in comparison with 23% (11/47) of those who received IV-only contrast. The data in this study show that the timing of ECM administration is appropriate from a diagnostic imaging standpoint. 74% of patients in whom this protocol was used had opacification of the small and large intestines. According to literature cited, small intestine transit time averages 1 hour and 24 minutes and is <2 hours in 83% of cases. Inadequate opacification of the intestine can lead to diagnostic confusion between loops of bowel and masses or fluid collections. The authors cite 0.4 mL/kg as the maximum acid aspirate that does not produce significant changes in the lungs based on caesarean delivery and note that GFV has been used as a surrogate marker for pulmonary aspiration risk but that there is no known GFV that places a particular patient at clinically relevant risk or that eliminates all the risk. This study used CT region of interest measurements to compute GFV and noted a large difference between mean and median values which suggested that distribution was non normal and which was confirmed by a Shapiro-Wilk test. The authors noted that based on this study, it is not possible to formulate conclusion relating age to GFV as the volume of enteric contrast administered was based on age rather than weight and patients at both the upper and lower ends of size for a given age range all received the same volume of contrast.

The authors were unable to compare results with previous studies because the measurement was made after one hour of fasting in patients who had no premedication, the approach to measurement (CT regions of interest) differed from previous protocols, and the patient population differed in that patients were not presenting for elective surgery which required intubation (i.e. ASA I or II versus ASA II or III for this study).

There is great variation of sedation practices and ECM administration in children contributing to differences in safety reports. For this study, ECM was administered one hour prior to anesthesia/sedation with no evidence of increased complications in this study group. Aspiration of contrast material leading to adverse events in children has been reported to occur with a low incidence in the literature but was not seen in this study. Vomiting also has been reported, also at a low incidence but slightly higher than for aspiration. Two incidences of vomiting were reported in this study. Nonetheless, based on residual GFV exceeding 0.4 mL/kg in a significantly greater percentage of patients who received ECM one hour prior to CT study (49%) versus those who did not receive ECM (23%) the authors concluded that no firm recommendations could be

made on the safety of a technique for anesthesia/sedations for patients who receive ECM 1 hour before their CT exams.

6.1.5.2

Smevik B. and Stake G. Iohexol as contrast medium for bowel opacification on abdominal CT in infants and children. In: Kaufman,editor. Contrast Media in Pediatric Radiology; 1985 Aug 22-24; Berlin, Germany. Karger; 1986. p. 79-80.

The aim of the study was to evaluate the suitability and tolerability of iohexol in CT of the abdomen in infants and children by monitoring patient reactions, taste acceptance, and image quality. Good identification of the intestinal loops is important for diagnosis which will promoted if there is patient acceptance of a contrast medium with a good or neutral taste.

13 males and 19 females ages 31 weeks to 13 years (median 142 weeks) receiving consecutive CT exams of the abdomen were studied. All patients had a histologically confirmed diagnosis of malignancy. CT scan parameters were standardized. All patients received iohexol 350 mgI/mL diluted to a concentration of 7 mgI/mL before administration into the gastrointestinal tract. The volumes of contrast media administered ranged from 120 to 500 mL given orally, from 60 to 120 mL given rectally, and from 60 to 300 mL given via a gastric tube. 25 patients received intravenous iohexol 350 mgI/mL as 3 mL/kg body weight. 13 patients were sedated with pentobarbital rectally, 6 mg/kg body weight.

Patients were followed in the hospital for at least 24 hours. 2 patients in the group fed with the gastric tube vomited, one of whom was undergoing chemotherapy with vomiting, the other whom had inadvertently ingested copious amount of fluid on the day of the exam. These patients also received penta barbital immediately prior to administration of the contrast. No nausea or vomiting was otherwise noted. Taste acceptance was registered for 20 patients with 6 judged as good, 13 judged as neutral, and 1 judged as less good. The patient who reported the taste as less good had a recent study where the amount of contrast ingested was greater and where taste was reported as good which suggested that there might be taste perversion from ongoing cytotoxic treatment. Diagnostic quality of exams was very satisfactory for 26 one satisfactory for 6 with bowel enhancement adequate for 27 and inadequate for 5. In this latter group, 2 patients had vomited and 3 had a preponderance of distended air filled bowel in the abdomen which would have required greater amounts of contrast to fill.

Conclusions (Smevik and Stake):

The authors' impression was that iohexol taste acceptance was improved compared to the commonly used Gastrografin® (diatrizoate) and they cite two studies that support an

unpleasant taste for Gastrografin. In addition to good acceptance and tolerability of the contrast medium, visualization of the bowel was good when the amount of contrast retained was adequate and when the amount of air in the bowel wasn't excessive.

6.1.5.3

Smevik B and Westvik J. Iohexol for contrast enhancement of bowel in pediatric abdominal CT. Acta Radiol. 1990 Nov;31(6):601-4.

Adequate opacification of the intestinal loops is important for a reliable diagnosis in abdominal CT. Different methods to achieve this have been proposed include diluted or undiluted Gastrografin, flavored corn oil emulsion, and barium suspension. Visualization ultimately depends on the amount of iodine that the patient drinks. A bitter taste and unpleasant smell makes the ionic agents unpalatable to children, particularly those who are receiving chemotherapy. Historically, when diluted with a beverage of the child's choice, iohexol has a neutral taste. This study reports the results of pediatric abdominal CT using iohexol in concentrations of 6 to 7 mgI/mL to enhance the bowel.

This was a retrospective study of CT scans from 160 examinations performed on pediatric patients using iohexol 2 percent as contrast medium for bowel enhancement. There were 91 girls and 69 boys aged between 8 days and 16 years. 79 patients were under age 5. 81% of patients had malignant disease confirmed histologically. Iohexol 350 or iohexol 300 mgI/mL was diluted to yield 6-7 mgI/mL. The volumes of contrast medium given prior to the abdominal CT study were chosen individually and the timing and duration of contrast medium intake were tailored in an attempt to coat the bowel loops in the area of interest. CT parameters were standardized. Scans were reviewed by the authors and graded for bowel loop opacification, (good, reasonable, or poor).

Contrast volumes varied from 0-1500 mL orally by cup or bottle (N = 142), 60-150 mL via feeding tube (N = 5), and 10-300 mL rectally (N = 19) with 6 patients receiving both oral and rectal contrast medium. 139 out of 142 patients drank the full amount of dilute contrast offered. 2 patients took no contrast due to nausea and vomiting and one 10-year old child refused after taking 20 mL. Taste acceptance was assessed in 20 patients that received 7 mgI/mL solution and was recorded as good in 6 patients, neutral in 13 patients, and less good in one patient. In the second group of 128 patients who received 6 mgI/mL diluted from iohexol 300 mgI./mL, 4 patients (2.8%) vomited. There were no refusals to drink contrast. The usefulness of contrast medium was evaluated as good in 58.1% of patients, reasonable in 22.5% of patients, and poor in 19.4% of patients.

Conclusions (Smevik and Westvik):

There is a definite need for a more acceptable oral contrast agent in pediatric abdominal CT. The advantages of using a contrast medium formula with a good or neutral taste

are more obvious in children who may not be persuaded to cooperate as would be the case with adults. The additional benefit of improved taste is noted when patients experience nausea and vomiting associated with treatments. In this study, 49.4% of patients were under age 5. The percentage of refusals was only 2.1% which compares favorably to that reported for adults. Four patients vomited and 2 of them did not retain any contrast. Bowel opacification is essential to abdominal CT to rule out pseudotumors and tailoring the amount of contrast medium and timing of the scans is recommended to optimize results. Even so, poor visualization may still occur, for example when ingested volume is too small or vomiting occurs. Cost of contrast media is a factor. For a portion of this study, the authors successfully used contrast media that was leftover from angiocardiography studies (checking sterility first). In conclusion, the authors noted that a concentration of 6-7 mgI/mL diluted in a beverage of preference is well suited for bowel opacification in abdominal CT in infants and children with a low incidence of refusals and good taste acceptance and that this formula could also be used in selected adult patients when nausea is pronounced.

6.1.5.4

Cohen et al. Comparison of iohexol with barium in gastrointestinal studies of infants and children. AJR Am J Roentgenol. 1991 Feb;156(2):345-50.

This study is was a two part study to evaluate iohexol as a contrast agent in the gastrointestinal tract in children. The purpose of the study was to evaluate the usefulness of low-osmolality contrast agents to study the GI tract by comparison of iohexol to barium (part 1) and then to evaluate iohexol use in the GI tract in patients in whom barium was contraindicated (part 2). The objectives were to assess safety of, tolerance of patients to, and quality of radiologic visualization and to compare these for the two agents and then to evaluate these same factors in a subgroup of children in whom barium was contraindicated.

Three groups of contrast agents can be used to study the GI tract: barium, high-osmolality water-soluable contrast agents, and low- osmolality water-soluable contrast agents. Barium is widely used, safe, and effective but is contraindicated in suspected bowel perforation. High-osmolality agents are undesirable in preterm infants or patients with inflammatory bowel disease. Metrizamide, a low-osmolality agent had been widely studied but based on expense the authors noted a need to study the efficacy of the newer less expensive low-osmolality agents. Iohexol is similar to metrizamide but is less costly.

Patients under age 18 were eligible for this study if they had signs or symptoms that necessitated contrast-enhanced examination of the gastrointestinal tract. Patients were studied for the iohexol only part if they had a contraindication to barium such as pneumoperitoneum. Patients were excluded if they had had an enhanced examination,

were scheduled for an enhanced exam within 48 hours, or had received another investigational drug. Patients' allergies or previous contrast sensitivity were noted but were not a reason for exclusion. Patients were prepared for the studies according to routine hospital procedures. All images were acquired according to clinical need and routine departmental procedure. Barium, iohexol 180 mgI/mL or iohexol 300 mgI/mL was used for the study. Barium concentration used for single-contrast upper gastrointestinal exams was 60% weight per volume. Barium concentration was 30% weight per volume for the lower intestinal single-contrast barium studies. The amount of contrast used was determined individually for each patient. Patients were monitored with vital signs and were followed up for 24 hours for the occurrence of adverse events.

Image quality was evaluated for the overall exam and for each segment of the GI tract with poor (nondiagnostic), good, or excellent visualization. Density of opacification was assessed on a three point scale of dense enough, optimal, and too dense. Mucosal coating was assessed as poor, good, or excellent. Radiologic diagnosis was made at the end of each study in order to facilitate patient care.

64 patients were included in the first part of the study in which iohexol in concentrations of 180 and 300 mgI/mL was compared with barium. The second part was an evaluation of iohexol 180 mgI/mL in 18 patients in whom barium was contraindicated. There were approximately equal numbers in each of the four groups with male/female ratio close to equal for the iohexol groups but with a ratio of 2:1 for the barium group. Most patients in part 1 of the study were White. One third of patients in the iohexol alone study were Black. Mean patient age of about 4-5 years and weight of about 19 kg were similar for part 1 of the study although slightly less for the barium study. Mean age for the iohexol alone study was only 1.2 years with corresponding mean weight of only 4.7 kg. 60% of all patients coexisting risk factors, most frequently allergy and age less than one year. There was no significant difference in volume of contrast administered to the three groups in part 1 however for the iohexol 180 mgI/mL, the dose per kilogram was significantly difference between patients in part 1 and patients in part 2 (5.2 mL/kg versus 9.2 mL/kg). Vital sign changes were noted in several patients, mostly transient, with no patients requiring treatment on the basis of vital sign changes. The most common adverse event was mild to moderate diarrhea. This was reported in a similar number of patients for both iohexol concentrations with no reports in the barium group. The number of adverse events between the iohexol and barium groups was statistically significant with only a single adverse event (vomiting) reported for the barium group.

For part 1 image quality evaluation for radiologic visualization, mucosal coating, and contrast density yielded 90-100% of segments as good or excellent diagnostic quality for all three parameters with only 3 of the barium exams assessed as nondiagnostic on the radiologic visualization parameter.. For the iohexol 300 mgI/mL group, there was a similar range of assessments apart from the small bowel where percent diagnostic for all three parameters ranged from 60-67% and for mucosal coating in the large bowel which was rated as good or excellent for only 80% of studies. Seven of these exams

were considered nondiagnostic for the radiologic visualization parameter. Radiologic visualization, mucosal coating, and contrast density for iohexol 180 mgI/mL in part 1 mostly ranged from 88 to 100% apart from the small bowel (63-75%) and mucosal coating noted in the duodenum as 69%. Six exams were rated as nondiagnostic. For part 2 where iohexol 180 mgI/mL was administered as the contrast agent, all parameters in all segments were rated as good or excellent for 82%. There were three instances where visualization was nondiagnostic. The overall radiologic efficacy for each contrast agent was good or excellent for 100% of the barium studies and the part 2 iohexol studies and 90 percent for both part 1 iohexol studies.

Conclusions (Cohen et al):

Low-osmolality water-soluable contrast agents have advantages over other contrast agents for examination of the GI tract in children in selected clinical situations. Metrizamide has been used for these studies but is costly. Based on properties of stability in bowel secretions and lack of absorption from normal bowel, this study evaluated iohexol for clinical usefulness by comparing iohexol 180 mgI/mL and iohexol 300 mgI/mL to barium. The first part of the study which assessed and compared both concentrations of iohexol and barium, the results indicated that radiologic visualization with iohexol was good but that if barium was not contraindicated, barium was the preferred agent. For the second part of the study which assessed only studies performed with iohexol 180 mgI/mL, there were no instances of poor visualization compared to the part 1 study where three cases were rated as poor. The authors suggested that this may have related to a significantly greater volume of contrast material per kg (9.2 versus 52. mL/kg) or to the lower median age of patients (1.2 years versus 4.7 years) with lower body weights accounting for less scatter of the x-ray beam and thus less loss of contrast on the images.

Both agents were assessed as safe although there was a higher frequency of minor side effects with iohexol, most commonly diarrhea, which did not correlate with the presence of high risk factors in the patients' histories. The difference in the frequency of diarrhea in patients receiving iohexol compared to barium was significant however the authors' review of the literature was not helpful in determining the reason for this.

In summary, the authors noted that iohexol could be effectively used as a contrast agent in the GI tract as an excellent substitute when barium is contraindicated and that although the frequency of side effects was greater than for barium, the side effects were mild. This study was used as supportive data submitted to the FDA for approval to label iohexol "for oral use in the gastrointestinal tract in children."

6.1.5.5

Langer and Kaufmann. Nonionic contrast media for gastro-intestinal studies in newborns and infants. J Belge Radiol. 1987;70(3):211-6.

This publication is a review of the use of non-ionic contrast media (Iohexol 300 and Iopamidol Gastro) in 293 patients who received contrast medium for gastrointestinal studies. This is a review of the authors' experience from January 1983 until October 1986. The study is a follow up to their earlier use of Metrizamide to ascertain adequate tolerance and contrast quality with nonionic contrast media.

Indications for use of nonionic contrast media for upper gastrointestinal studies included diagnoses such as clinical suspicion of aspiration, GI tract obstruction, tracheo-esophageal fistula,congenital malformation, and postoperative evaluation. Indications for enemas included suspicion of colonic perforation or disease associated with perforation, large bowel obstruction post NEC, suspicion of intestinal fistula, and post colon surgery among other diagnoses. 293 patients were examined by oral or rectal administration of nonionic contrast medium for gastrointestinal studies. There were 225 patients in the upper gastrointestinal studies, 129 boys and 96 girls, ranging in age from newborn to over age 2. 24% were 0-1 month in age. 7% were over age 2. There were 68 patients, 40 boys and 28 girls, in the group that received enemas with about 25% 0-1 month and 10% over age 2. Older children received the nonionic contrast only under special circumstances such as severe conditions which required subsequent surgery. Contrast medium was diluted with 5% glucose 1:1 for oral administration and with aqua dest. 1:1 for rectal instillation. The mean volume given was 5 mL/kg body weight orally and 5-10 mg/kg body weight for enemas. All studies were documented fluoroscopically.

Image quality for all studies was assessed as satisfactory. In some cases was possible to evaluate the colon after oral administration. Diarrhea was not observed. There were several cases of aspiration which did not result in either pulmonary edema or infiltrate. The renal pelvis was not seen to enhance as an expression of resorption of the nonionic contrast medium from the intestine.

Conclusions (Langer and Kauffman):

Nonionic contrast media has been used for gastrointestinal studies in pediatric radiology since the beginning of the 1980's in patients where severe illness precludes oral or rectal administration of barium or Gastrografin®. Barium is contraindicated when perforation is suspected because it is not resorbed by the peritoneum and granulomas develop. When used for oral studies, it may flocculate in the distal small bowel poorly outlining the bowel. If aspirated, it cannot be coughed up and may result in death. Hyperosmolar water-soluable contrast media are contraindicated in infants with dehydration because they induce an influx of water into the bowel lumen followed by a total body fluid shift. This also contributes to poor image quality. However, it is noted that because of this fluid shift, Gastrografin may be used in a 1:4 dilution to relieve inspissated meconium and chronic constipation. If aspirated Gastrografin is toxic and

Reference ID: 3394106

results in pneumonia or lung edema. When there is bowel perforation, hyperosmolar contrast media may also cause inflammation of the peritoneum. Nonionic water-soluable contrast media in this study were shown to be tolerable and x-ray studies were fully diagnostic. Based on the successful use of the nonionic contrast media in the pediatric population and because of the limitations discussed, the authors noted that barium should only be used if the mucosa must be visualized and hyperosmolar water-soluable contrast media are only indicated for use as a dilute solution to relieve constipation.

6.1.5.6

Ratcliffe. The use of low osmolality water soluable (LOWS) contrast media in the pediatric gastro-intestinal tract. A report of 115 examinations. Pediatr. Radiol. 1986:16(1):47-52.

This paper reports the use of three low osmolality water soluable (LOWS) contrast media in 115 examinations of the gastrointestinal tracts of 89 babies and children. Dilute barium sulfate suspensions have traditionally been used to demonstrate the intact GI tract in children. Deaths have been reported as a result of inhalation of barium into the lungs of babies. For certain indications such as suspected perforation a water soluable contrast medium such as Gastrografin or Hypaque has been advocated however these agents are hypertonic and have their own dangers. The pediatric GI tract has been investigated in small numbers using metrizamide (Amnipaque) and ioxaglate (Hexabrix). Metrizamide is expensive and requires preparation before use. Less costly non-ionic compounds , (iopamidol [Niopam], iohexol [Omnipaque], and sodium/meglumine ioxaglate [Hexabrix]) are now available. All of these are low osmolality water soluable iodinated contrast media.

For the period between December 1981-December 1984 911 barium examinations and 115 LOWS contrast examinations of the GI tract were performed in children ages 1 day to 15 years. The LOWS examinations were performed on 89 selected babies and children, 23 of whom were premature infants. 95% of the patients were followed for a prolonged interval. Four types of examinations were performed: esophageal by swallowing or tube esophagogram, meal, enema via a rectal tube, or enema as a “loopogram” which is an enema via a stoma in either an antegrade or retrograde direction. Patients were selected based on risk of spill into the respiratory tract, mediastinum, pleura, peritoneum, or retroperitoneal tissues which was based on clinical conditions such as laryngo-pharyngeal incoordination or clinical suspicions such as ruptured viscus.

For all four exam types, most children were under age 5. The age range for patients receiving Hexabrix for esphagogram and meal was higher, (10 years and 14 years respectively) however there were larger numbers in these groups compared to other contrast media groups and other types of exams. The numbers of males and females

Reference ID: 3394106

for each contrast medium in each group were similar apart from the two Hexabrix groups as noted above, each of which had slightly greater than three times the number of males as females.

Hexabrix 320 was diluted with an equal volume of water apart from two early cases where it was diluted to quarter strength. In one case only, Niopam 200 was diluted with an equal quantity of water. Omnipaque 180 was not diluted. All examinations were performed with low kVp for both radiography and screening.

The radiographic density of Niopam 200, Omnipaque 180, and half strength Hexabrix was excellent. Quarter strength Hexabrix and half strength Niopam 200 was adequate for esophageal imaging but poor in the abdomen of older children. 53 examinations were positive.

20 complications occurred which the author notes could have had serious consequences if a high osmolality medium or barium had been used. 7 of these were children where large volumes of contrast medium entered the lung parenchyma, 6 of whom were noted to have “bubbling respiration which lasted up to ten minutes.” The children were treated by sucking out the oropharynx without the addition of oxygen and all seven made a prompt and uneventful recovery. Six babies experienced small amounts of LOWS media spillage into the trachea or major bronchi with three responding by coughing. All six recovered with no adverse sequelae. 3 patients had free leak from the GI tube into the peritoneum without ill effect with contrast absorption from the peritoneum and excretion by the kidneys. Leak of contrast occurred into loculated spaces or fistulae in 2 cases in the chest and 2 in the abdomen. Structures were well shown and the LOWS media was either drained or absorbed completely.

Conclusions (Ratcliffe):

Spillage of contrast media into the respiratory is expected in babies and children with certain conditions such as laryngo-pharyngeal incoordination with the risk enhanced by factors such as prematurity, cerebral palsy, and severe gastroesophageal reflux. For this reason, aspiration of contrast from the stomach may be performed after examination. When hyperosmolar iodinated contrast material is used for studies, it is diluted and is associated with poor radiographic density and it may exacerbate dehydration and cause inflammation. For intact GI tracts, barium is preferred but it is also associated with serious consequences if it is inhaled or if there is a GI tract perforation. LOWS media offer an alternative to hyperosmolar contrast media since they are not diluted in the gut by the extraction of water. LOWS may even be used in cases where an enema is indicated for meconium ileus or equivalent by the addition of 0.1% polysorbate 80 to the LOWS agent. LOWS were used in this study based on a risk of inhalation in 63 cases and a risk of contrast leak in 41 cases. This study showed that the radiographic density of LOWS media was excellent for single contrast examination of the GI tract in all cases in this series apart from the two cases where

quarter strength Hexabrix was used for esophageal imaging and half strength Niopam was used for abdominal imaging. In addition to decreasing patient morbidity and mortality, LOWS have an advantage of allowing endoscopy to be performed immediately after an exam. In summary, the author presented numerous clinical indications for LOWS contrast media us in pediatric GI tract exams.

6.1.5.7

Stake and Smevik. Iohexol as contrast medium for the gastrointestinal tract in childhood. In: Kaufman,editor. Contrast Media in Pediatric Radiology; 1985 Aug 22-24; Berlin, Germany. Karger; 1987. p. 107-9.

Barium is the contrast medium of choice in x-ray examinations of the GI tract. In some cases, especially in infants,where there is suspected leakage outside the gut or high risk for aspiration, water-soluable contrast media are needed. Diatrizoate has the disadvantages of a strong taste of anise oil and high osmolality which draws fluid from the plasma and interstitium into the bowel thereby decreasing contrast density, causing fluid and electrolyte disturbances, and possibly causing inflammatory changes in the colonic mucosa and lungs. Metrizamide and Ioxaglate which are nearly isotonic to plasma and iopamidol also have been found to be well suited to study of the GI tract. This study tested iohexol 350 mgI/mL to study the GI tract.

30 patients ranging in age from 1 day to 14 year with a median age of 35 weeks were studied. Patients weighed between 3 and 40 kg with a median weight of 6 kg. 16 patients weighed less than 6 kg. In 29 of the examinations, iohexol was diluted with equal amounts of water. In 4 cases, undiluted contrast medium was used. Administration was orally for 14, by feeding tube for 17, and rectally for 2 studies. The dose ranged between 8 and 225 mL with a median of 40 mL. Taste acceptance was recorded in 11 examinations and reported as neutral in 7. One patient, an 11-year old boy, swallowed only 15 mL which however was sufficient to visualize the stomach and small bowel. No adverse reactions and no cases of diarrhea were reported. Radiographic quality was judged as excellent for 31 and less than good for 2 but the authors noted that to visualize small structures such as fistulas a higher concentration solution may be needed. Good coating of the mucosa was noted and there was even and continuous filling of the small and large bowel. Contrast material reached the small bowel between 30 and 270 minutes after intake.

Conclusions (Stake and Smevik):

Iohexol was well suited for gastrointestinal use in infants and children. It had an acceptable taste, gave excellent images, and caused no adverse effects. The authors anticipated that it would be useful in selected cases where barium or diatrizoate are contraindicated.

6.1.5.8

Wright et al. Iodixanol in paediatric gastrointestinal imaging: safety and efficacy comparison with iohexol. Br J Radiol. 2002 Feb;75(890)127-35.

Barium sulfate suspensions are most commonly used for these studies but are either relatively or absolutely contraindicated in some circumstances such as suspected perforation of the gut or where the risk of aspiration into the lungs is high. Hypertonic contrast media are also used but cause fluid balance disturbances, especially in infants. While these may occasionally be used therapeutically, for example in the treatment of meconium ileus, the influx of fluid into the intestine results in dilution of the contrast medium and deterioration of image quality within the distal bowel and these contrast agents are generally considered inferior to barium for the evaluation of mucosal disease because of poor mucosal coating. This study compared iodixanol (Visipaque®) to two concentrations of iohexol (Omnipaque®) at two concentrations, assessing safety, tolerability, and efficacy during contrast enhanced GI radiography studies in children.

Pediatric (<16 years old) patients referred for upper or lower GI contrast enhanced radiographic examinations were eligible for inclusion into the study. Exclusions were for previous serious reaction to iodinated contrast media, clinical instability, and prior inclusion in a clinical trial with an unregistered investigational drug. 154 patients were entered into the trial, 74 who received iodixanol and 78 who received iohexol. The age range for both groups was 0-15 years with a mean age of about 6 years. The female/male ratio was approximately the same (38% female) and there were similar weight and height ranges and means for the two groups. For both contrast media there were some differences in demographics between the high and low concentration groups but the differences were balanced between the treatment groups. The majority of patients had no known risk factors with the risk factors fairly evenly distributed between the two groups.

The broad indications for exam included abdominal pain, vomiting, tracheo-esophageal fistula, constipation, and other. Some patients had more than one indication. Some children had more than one examination type performed. Prior to the examination, patients followed the instructions regarding restrictions to food and fluid intake in accordance with the hospital's routine for a particular exam. Examinations were performed using standard equipment and standard procedures for the institution. Visipaque was administered as either 150 or 320 mgI/mL. Omnipaque was administered as either 140 or 300 mgI/mL. Fruit juice was added to the trial drug in 91 patients.

Contrast medium efficacy was assessed by individually assessing the component parts of the GI tract. The quality of radiographic evaluation was scored by one of four

categories ranging from no visualization to excellent which was superior radiographic visualization with detailed radiographic delineation. An overall evaluation of the radiographic visualization and diagnostic information was obtained based on a 100 mm visual analogue scale (VAS). The degree of contrast density was evaluated ranging from none to too high. The clinical diagnosis was compared to the radiologic diagnosis and it was noted how much the radiographic exam contributed in making the final diagnosis.

Patients were evaluated for adverse events up to at least 48 hours after examination. Adverse event evaluation included details of the event such as time of occurrence, intensity, and relationship to contrast. Taste acceptance was evaluated ranging from good to bad.

147 patients were included in the efficacy population. One child drank an insufficient amount and 3 children had too high concentration added to the contrast.

VAS values for overall quality of radiographic visualization ranged from 78 to 92. The mean VAS score was higher for iodixanol in both the low and high dose subgroups but was not statistically significantly different from the iohexol. The lowest VAS values were noted in the youngest patients regardless of the contrast medium used. The quality of radiographic visualization evaluated for each anatomical area demonstrated no major differences between the two contrast medium groups. Most evaluations in both groups were excellent or good for those areas applicable to the examination. More patients with a poor rating were observed in the iohexol group, particularly for the esophagus. The reasons for poor visualization included inadequate contrast opacification but more frequently were related to other causes such as patient motion. As far as contrast opacification as a reason for poor visualization, there were more instances reported for iohexol than for iodixanol. In general, the stomach followed by the esophagus and duodenum were best visualized.

Most areas scored showed optimal densities for the areas under examination. Density was scored as too high for a few exams in the distal small bowel. Too low density was scored for several areas. No enhancement was recorded on eight occasions across the iohexol groups.

Assessment of mucosal coating was not applicable in many areas. Most areas scores were good or excellent and nearly equally distributed between the treatment groups. Less poor evaluations were noted for the iodixanol groups especially in the low concentrations. In general, the higher concentration groups had more scores in the excellent category.

On the VAS scale, the overall quality of diagnostic information was scored 92 for both contrast media. Four examinations were non-diagnostic-- 3 from the lower concentration iohexol group and one from the lower concentration iodixanol group.

Radiological examinations were generally consistent with and contributory to final diagnoses.

The overall frequency of adverse events was lower for iodixanol than for iohexol and was statistically significant with the number of adverse events related to contrast medium similar for both but less for iodixanol in the uncertain group and less for the numbers of patients with adverse events. There were no adverse events resulting in dose, procedural change, or withdrawal from the trial and none were considered serious. The most common adverse event was diarrhea followed by nausea, vomiting, and abdominal pain. Three patients in the iodixanol group experienced skin reactions, one of 72 hours duration, another commencing 26 hours after exam and lasting for 4 hours, and one appearing 20 hours after examination and lasting for 48 hours. The first patient in this group was treated medically for the reaction. The other two patients recovered without treatment.

Taste acceptance was scored by 104 children. 33 scored taste as good, 36 as acceptable, 19 as unpleasant, and 16 as bad. There was no statistically significant difference between the two groups and the addition of fruit juice did not improve taste acceptance. None of the patients rated the taste of the contrast media without the fruit juice as bad.

Conclusions (Wright et al):

The authors noted that the ideal contrast medium for diagnostic pediatric examinations should be physiological in composition, represent no risk to the child, give perfect opacification of the part of the GI tract under investigation, and have pleasant or acceptable taste. The aim of this trial was to evaluate iodixanol for these characteristics and to compare iodixanol to iohexol which is a commonly used contrast medium in pediatric practice. This study showed that overall quality of radiographic visualization as measured on a 100 mm VAS scale was not statistically different. There were higher scores for the higher concentration groups but both products also gave acceptable efficacy at the lower concentrations. When individual areas of the GI tract were evaluated, there was also no statistically significant difference between the contrast media for the good and excellent ratings although more patients in the iohexol group had a poor or no visualization score. Iodixanol produced slightly better results for areas assessed for contrast density, apart fro the ileum. The studies suggested that adequate mucosal coating could be obtained with water soluable agents although patient numbers were too small to optimally assess this. There was no significant difference between the two agents in the overall quality of the diagnostic examination and radiological diagnoses supported final/clinical diagnoses. Adverse events, namely diarrhea, were more common with iohexol. Three cases of skin hypersensitivity were reported in the iodixanol group, only one of which required treatment. One patient in each group aspirated contrast medium, with no harm to either patient. Taste acceptance was similar for both contrast media.

6.1.6 Other Endpoints

There were no additional endpoints as this is a 505(b)(2) submission. The applicant conducted a literature review to demonstrate efficacy and safety of the reference listed drug.

6.1.7 Subpopulations

This is not a relevant consideration for a diagnostic imaging drug. This drug is not administered for diagnostic purposes and it has no therapeutic effects. It is administered orally to patients undergoing abdomino-pelvic CT exams to assist in the delineation of loops of bowel.

Only one study in adults reported on race: 88% were Caucasian and 12% were African-American. One study in the pediatric population reported on race: 85% were Caucasian and 15% were African-American.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The reference listed drug, (RLD), Omnipaque is approved as a sterile solution for injection, (NDAs 18,956 and 20,608). The proposed drug product is a non sterile (b) (4) reconstitution with water or a beverage which is highly soluble, contains the same active ingredient as the RLD and may be reconstituted to contain iodine in concentrations similar to the RLD. The proposed drug formulated as a powder contains 9.7 grams of iohexol per bottle which is equivalent to 4.5 grams of iodine. When reconstituted for oral use, the concentration ranges from 9 to 21 mgI/mL, with standard concentrations being 9, 12, 15, 18, and 21 mgI/mL, compared to 6 to 21 mgI/mL for the RLD. The literature review of the RLD for oral use demonstrated efficacy (acceptable opacification on CT scans) at 4.5 mgI/mL to 9 mgI/mL which is the recommended dosage of Iohexol (b) (4) Oral Solution in adults.

In the studies reviewed, patients ages 19-92 years were administered concentrations of iohexol between 4.5 mgI/mL to 9 mgI/mL in volumes ranging from 800 to1500 mL and acceptable levels of opacification, taste, and patient acceptance were demonstrated. Clinical use of the RLD and usage guidelines (ACR, 2012) support this dose.

For children, the proposed oral concentration of iohexol powder is the same as for the approved product Omnipaque, i.e 9 mgI/mL to 21 mgI/mL with total oral dose in grams

of iodine not to exceed (b) (4) grams of iodine in children under age 3 or a total of (b) (4) grams of iodine for children from 3 to 18 years of age.

Table 9 provides the iohexol concentrations and volumes reported in the published literature as tabulated for abdominal CT in children.

Table 9: Concentrations and Volumes of Iohexol Administered to Pediatric Patients in Abdominal CT Studies*

Reference	Concentration	Number of Patients	Age Groups	Volume[a]
Smevik, 1985	7 mgI/mL	32	31 weeks – 13 years	120 - 500 mL
Smevik, 1990	6 or 7 mgI/mL	15	0 – 1 year	50 – 300 mL (176)
		13	1 – 2 years	60 – 300 mL (171)
		35	2 – 5 years	60 – 800 mL (290)
		45	5 – 10 years	0 – 1350 mL (397)
		34	10 – 16 years	20 – 1500 mL (681)
Mahmoud, 2010	6 mgI/mL	365 (numbers administered iohexol by age group not specified)	< 1 year	150 mL; 18.4 mL/kg (7.5 – 43.6)
			1 – 5 years	300 mL; 18.4 mL/kg (1.5 – 82.8)
			6 – 12 years	450 mL; 14.8 mL/kg (3.1 – 27.8)
			> 13 years	600 mL; 12.63 mL/kg (6.1 – 20.4)

[a]Mean values (mL, Smevik) or ranges (mL/kg, Mahmoud) are presented parenthetically.
*Table reproduced from NDA 205383, Module 2, Clinical Overview, Section 2.5, page 31

The approved labeling for the pediatric CT indication for the RLD was approved based on these studies and support the recommended volume of 180 mL to 750 mL. The volumes and dosages used in clinical practice are in line with the publications and are the basis for the proposed label for Iohexol (b) (4) Oral Solution.

Additional published papers. (Kaufman RA. Technical aspects of abdominal CT in infants and children. AJR Am J Roentgenol. 1989 Sep;153(3): 549-54. and Ziegler MA et al. Is administration of enteric contrast material safe before abdominal CT in children who require sedation? Experience with chloral hydrate and pentobarbital. AJR Am J Roentgenol. 2003 Jan;180(1):13-5.), are compatible with similar volumes for the contrast medium Hypaque™ used orally for CT scan of the abdomen.

Smaller administered volumes of a more concentrated solution are recommended when a child has difficulty consuming a large volume of contrast medium. The use of higher concentrations is supported by safety studies with the approved dose range for use of

the Omnipaque 180 to 300 mgI/mL for radiography examinations ranging from 1.1 to 18.5 times the approved pediatric dose for CT.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects are not expected and have not been reported based on single study use via an oral route of administration with elimination via the GI tract and minimal drug absorption. Renal excretion via glomerular filtration rapidly clears the minimal absorption that occurs or the increased absorption that has been demonstrated with bowel inflammation.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy analyses/analyses were noted.

7 Review of Safety

Safety Summary

In adults, adverse events were generally seen on the day of contrast administration with information collected 1-3 days after CT examinations. Adverse events were collected up to 48 hours after examinations in the pediatric studies. No adverse events were reported that persisted beyond the follow up windows.

Table 10 summarizes the adverse events reported in the literature after oral administration of iohexol for CT studies. As can be seen in the table, no clinically important side effects were reported in two studies published by Lonnemark, (1993, 1995). Diederichs, (2007), reported a 6.7% incidence of vomiting. In the trial by McNamara et al, 5/149 patients were noted to have immediate vomiting, nausea, or a queasy feeling (results for iohexol and diatrizoate sodium combined). McNamara, (2010), also noted on 24 hour follow up for iohexol that there were adverse events for 34 of 148 which included diarrhea, nausea, constipation, abdominal cramping, vomiting, and other undefined events. Adverse events in abdominal CT trials were reported by Peterson, (2011), as diarrhea (2%) and nausea (2%).

Table 10: Adverse Events After Oral Administration of Iohexol (CT Studies)*

First Author, Year[a]	Nausea n/N (%)	Vomiting n/N (%)	Abdominal Cramping n/N (%)	Diarrhea n/N (%)	Constipation n/N (%)	Other n/N (%)
Lonnemark, 1993	No clinically important side effects reported					
Lonnemark, 1995	No clinically important side effects reported					
Diederichs, 2007[b]	0	2 / 30 (6.7%)	0	0	0	0
McNamara, 2010[c]	19	5	15	40	11	17[d]
Peterson, 2011	1 / 49 (2%)	0	0	1 / 49 (2%)	0	0

[a]Adverse events as reported by the authors, for iohexol only; n/N = number of events/No. of subjects per group.

[b]The authors identified the dose of CM diluted for use during CT as 300 mg/dL prepared as a 5% aqueous solution but this is considered a self-evident error since osmolalities reported elsewhere in the publication indicate that the concentration of stock solution was 0.69 Osmol/kg, indicative of 300 mgI/mL, and the diluted solution was 0.051 Osmol/kg. All patients were administered IV CM (ULTRAVIST 370).

[c]Oral iohexol dose was 9 gI; adverse events/effects collected by patient survey; pooled rates of events for iohexol and diatrizoate sodium at 24 hour follow-up (adverse effect rates were 34 of 148 (iohexol) and 41 of 149 for diatrizoate sodium)); all but two subjects were also administered IV iopamidol.

[d]Adverse events categorized as mild, moderate and severe; no description of these 'other' events were specified by the authors.

*Reproduced from NDA 205383, Module 2, Section 2.5, Clinical Overview, page 34

Adverse events (AEs) for x-ray radiography follow-through exams were similar. Kinnunen, (1989), noted a greater frequency of AEs which were attributed to patients' illnesses, (diarrhea [31%], nausea [22%], and vomiting [17%]). Laerum et al, (1991), attributed adverse events to contrast medium and noted nausea (5%), vomiting (2%), and diarrhea (2%). Jobling et al, (1999), noted that the procedure was well tolerated but had one report of a severe anaphylactic reaction where iohexol was administered for a follow through study to exclude subacute obstruction, (Glover JR, Thomas BM. Hypersensitivity reaction to oral iohexol. AJR Am J Roentgenol. 1991a Jan:156(1): 197 and Glover JR, Thomas BM. Case report: severe adverse reaction to oral Iohexol. Clin Radiol. 1991b Aug;44(2): 137-8).

It is noteworthy to mention that case reports of rare, anaphylactoid contrast reactions have been reported with orally administered contrast media, typically within the same time frame as reactions with IV contrast. Such reactions are rare and are treated in the same manner as those that occur after intravascular injection. The NDA references published reports by Ridley, (Ridley LJ. Allergic reactions to oral contrast. Australas Radiol. 1998 May;42(2): 114-7) who discussed three cases of rashes that were considered allergic/idiosyncratic reactions to oral iodinated contrast (none of which was

for iohexol) and Seymour, (Seymour CW et al. Anaphylactoid reaction to oral contrast for computed tomography. J Trauma. 2004 Nov:57(5): 1105-7), who reported a similar reaction where respiratory failure occured, also not for iohexol.

Pasternak, 2012, (Pasternak JJ, Williamson EE. Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: A primer for the non-radiologist. Mayo Clin Proc. 2012 Apr; 87(4): 390-402), discussed enteric contrast administration and noted the rare potential for anaphylactoid-type reactions which typically occur in the same time frame as reactions to intravascular contrast. He also noted that potentially deleterious effects of iodinated contrast media on the kidneys are not believed to occur in a clinically significant manner for nonvascular routes of administration,

All of the publications provided by the applicant as support for the efficacy of oral iohexol in the pediatric population also assessed safety in this group. Mahmoud, (2010), performed a retrospective review of 365 charts of children ages 0.7 to 211.1 months who required sedation or general anesthesia for CT exam and who had received oral plus IV or IV contrast for the exam. For those who received oral contrast, there was no evidence of pulmonary aspiration in any patient. Two cases of vomiting were reported in the general anesthesia group, one incident after awake extubation and one after the laryngeal mask airway was removed during anesthesia. None of the 47 patients who received IV contrast medium had any complications related to contrast administration. Smevik, (1985), studied 32 children ages 31 weeks to 31 years with malignancies who received iohexol orally, rectally, or via gastric tube. Overall, the contrast medium was well tolerated with no late reactions over the 24 hour period and no serious adverse reactions. Two patients vomited after being dosed using a gastric tube, one who had ingested considerable amounts of fluid and one who had a history of repeated vomiting prior to dosing. Smevik, (1990), also published a retrospective review of abdominal CT scans in 160 pediatric patients ages 8 days to 16 years, also patients dosed orally, rectally, or by gastric tube. All patients were followed for 24 hours with no late reactions attributed to contrast medium. 4 patients (2.8%) vomited which may have related to treatment for malignancies.

In general, iohexol was reported to be well tolerated for pediatric radiography exams with mild GI symptoms of diarrhea, nausea, and vomiting reported as adverse events. Cohen, (1991) noted mild to moderate diarrhea as the most common adverse event in patients who received iohexol for GI studies. An observational study of children who received iodinated contrast media for GI studies or rectally by enema reported on by Langer and Kauffman, (1987) reported that the contrast agents were well tolerated and that no local reactions or diarrhea were observed. Additionally, although there were several cases of aspiration no pulmonary edema or infiltrates were noted. Ratcliffe, (1986), performed GI radiography exams in 115 “at risk” (for aspiration, contrast leak for example) children and reported that morbidity from the inhalation or extravasation of contrast medium was negligible. This included contrast medium spillage into the lung parenchyma and free leak from the GI tract. Stake and Smevik, (1985), administered

iohexol orally, by gastric tube, or rectally to 30 children with no adverse effects reported. Wright, (2002), assessed the safety of iohexol and iodixanol for GI imaging in children. 35.9% of patients who received iohexol experienced adverse events, mainly GI disorders and mainly diarrhea (23 of 28 patients).

No deaths related to oral administration of iohexol were reported in the published studies reviewed. Serious or life-threatening reactions have rarely been reported with an incidence of approximately 4 in 10,000 examinations with mortality rate reported as approximately 1 in 170,000 examinations via the IV route, (Katzberg RW, Lamba R. Contrast-induced nephropathy after intravenous administration: fact or fiction? Radiol Clin North Am. 2009 Sep:47(5): 789-900). A meta-analysis of 41 studies that included 333,693 parenteral administrations of both high and low osmolality contrast media (HOCM/LOCM) reported the estimated risk of severe reactions with LOCM as 31 per 100,000, (Caro JJ et al. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. AJR Am J Roentgenol 1991 Apr; 156(4):825-32). The NDA application contains 6 detailed reports of SAEs associated with intravascular administration of iohexol to include fatal acute vasculitis, fatal Lyell's syndrome, disseminated intravascular coagulation, sialadenitis (4 cases), toxic epidermal necrolysis, and cardiac arrest with renal failure.

7.1 Methods

No clinical studies have been conducted in support of this application. The literature reports for both adults and children were chosen based on the oral administration of iohexol, either for CT or radiography exam. X-ray radiography exams which were considered supportive were conducted at higher doses than the CT exams. The published literature was searched to establish the approximate numbers of publications referable to a comprehensive safety database. The applicant's focus for safety was for administration via the oral route based on the lack of access to source data and an inconsistent application of an adverse events dictionary.

Based on the known pharmacokinetics of iohexol after oral ingestion, (passage through the GI tract with minimal, if any, resorption in normal patients and minimal resorption with glomerular filtration in patients with inflammatory bowel disease or bowel obstruction), this reviewer concentrated on literature reports of iohexol safety via the oral route.

The databases searched by the applicant included MEDLINE® 1950-2012, Biosis Previews® 1969-2012, EMBASE alert 2012, EMBASE 1974-2012, SciSearch® Cited Ref Sci 1990-2012 and SciSearch Cited Ref Sci 1974-1989. The cut off date for the oral route of administration was 28 Aug 2012. The cut off date for injection routes of administration was 29 August 2012. The "Clinical Literature Search-Oral" included clinical trials, case reports, letters, and reviews describing oral administration of iohexol; and clinical trials, studies, and case reports describing use of iohexol in conjunction with

GI computed tomography, in the clinical population, published in English. The "Clinical Literature Search-Injection" was conducted to assure that articles associated with other routes of administration that could be pertinent to safety or to PK would not be excluded.

The overall safety profile for iohexol (b) (4) oral solution was based on Omnipaque which was approved by the FDA in 1985. Approximately (b) (4) bottles of Omnipaque 140 and 180, (b) (4) bottles of Omnipaque 240, (b) (4) bottles of Omnipaque 300, and (b) (4) bottles of Omnipaque 350 were sold to hospitals between 1 July 2011 and 30 June 2012. Using patient numbers from dosing with Pharmacy Bulk Packaging and volumes used in diagnostic imaging centers, an adjusted estimate of the number of patients exposed for the one year period (all routes of administration, all strengths, all clinical settings, and all indications) is (b) (4) per year in the US (IMS, 2012).

Table 11 summarizes the extent of clinical exposure reviewed and summarized by the applicant in the Integrated Summary of Safety in the NDA.

Table 11: Published Articles Summarized inThe Integrated Summary of Safety*

Study Grouping	Size of Safety Database Described in Published Literature
CT in Adults (Oral)	278
X-ray Radiography in Adults (Oral)	152
CT in Pediatrics (Oral)	557
X-ray Radiography in Pediatrics (Oral or Rectal)	493
IV Healthy Volunteers	36
Intravascular Adults and Pediatrics (focus on IV)	>49,000[a]

*Reproduced from NDA 205383, Module 2, Section 2.5, Clinical Overview, page 33

a: an approximation based on studies described in the ISS literature review for safety of intravenous injection since some literature articles have essentially the same study and do not include definitive disposition data, are observational or retrospective reviews, are meta-analyses of high and low osmolality contrast material or do not detail how patients received iohexol

For the safety review in adults, 5 published reports demonstrating oral administration of iohexol for CT examination of the abdomen and pelvis and 3 published reports for radiography pass through examinations were reviewed. For the safety review in children, 3 published reports demonstrating iohexol administered orally for CT examination of the abdomen and pelvis and 5 published reports for radiography GI studies were reviewed. In addition, the single published case report of an adult who had a major anaphylactic reaction (noted in Jobling 1999 publication, published by Glover, 1991a; Glover 1991b) was reviewed.

Multiple articles on the safety of intravascular injection that were included in the submission were reviewed but this reviewer did not render in depth comments apart from specific sections which reviewed significant AEs, drug-drug and drug-disease interaction, immunogenicity, and reproduction-pregnancy data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical trials listed below in Table 12 by author in alphabetical order that were the basis for the efficacy summary in adults were also analyzed for the safety summary. The report of a hypersensitivity reaction to oral iohexol in Jobling's article reported on by Glover is summarized in section 7.3.4.

Table 12: Adult Studies Involving Oral Administration of Iohexol

Authors	Population M/F; Age	Study Drug(s)	Adverse Events
CT Examinations			
Diederichs et al, 2007	N = 160 (30 each, 5 groups; 10, lysine amidotrizoate) 90/61; 61y	Amidotrizoate 300 mgI/mL Diatrizoate 360 mgI/mL Ioxithalamate 300 mgI/mL Iopromide 300 mgI/mL Iohexol 300 mgI/mL Iotralan 300 mgI/mL	Reported immediately and at 24 hours. Incidence of nausea, vomiting, diarrhea low, were 7.5%, 1.3%, 5.6% for amidotrizoate. Nausea 6.7% with iopromide and iotrolan. Nausea and vomiting with iohexol 3.3% and 6.7%.
Lonnemark et al, 1993	N = 30 (10 per group) Diatrizoate: 7/3;50y Aqueous iohexol: 6/4; 53y Viscous iohexol; 6/5; 62y	Diatrizoate 9 mgI/mL Aqueous iohexol 9 mgI/mL Viscous iohexol 9 mgI/mL	No immediate or delayed adverse events
Lonnemark et al, 1995	N = 30 (10 per group) Iohexol 4.5 mgI: 6/4; 49 y Iohexol 6.75 mgI: 7/3; 50 y Iohexol 9 mgI: 8/2; 49 y	Iohexol 4.5 mgI/mL Iohexol 6.75 mgI/mL Iohexol 9 mgI/mL	No immediate or delayed adverse events

McNamara et al, 2010	N = 300 Iohexol = 149 Diatrizoate = 151 184/116; 56y (both)	Iohexol 9 mgI/mL Diatrizoate 9.17 mgI/mL	Immediate and 24 hour follow up. 5 patients in each group with immediate vomiting, nausea, or queasy feeling. At 24 hours, 34/148 had AE with iohexol and 41/149 had AE with diatrizoate sodium. AEs at 24 hours also included diarrhea, cramping, constipation, and other.
Peterson et al, 2011	N = 100 Iohexol 49 (23/26); 51y Diatrizoate 51 (20/31); 52y	Iohexol 8 mgI/mL Diatrizoate 8 mgI/mL	Adverse events immediately and up to 3 days. Mild nausea (4 diatrizoate, 1 iohexol), 1 cramping (diatrizoate), 1 cramping (diatrizoate), 1 diarrhea (iohexol).
X-Ray Radiography Examinations			
Jobling et al, 1999	N = 42 (52 exams) Gender and age not stated	Iohexol 350 mgI/mL	Noted that the procedure is generally well tolerated. Single anaphylactoid reaction reported.
Kinnunen et al, 1989	N = 58 (71 exams) Iohexol 35; 62y Diatrizoate 36; 64y	Iohexol 350 mgI/mL Diatrizoate 370 mgI/mL	Small occurrence of nausea and emesis for both groups. 14/36 with severe diarrhea after diatrizoate; 6/35 with severe diarrhea after iohexol, no statistical significance
Laerum et al, 1991	N = 96 Iohexol 52 (24/28); 57y Iopentol 44 (20/24); 64y	Iohexol 350 mgI/mL Iopentol 350 mgI/mL	Nausea, vomiting, diarrhea similar (5 iopentol, 4 iohexol). Blood tests similar for both.

For CT exams, the volumes of study drug (iohexol and other contrast media) was diluted and ranged from 800-1000 mL. For radiography exams, study drug was not diluted and ranged from 100-200 mL for both iohexol and comparators. Table 13

summarizes for CT iohexol only the number of adults exposed to iohexol for CT exams, the concentration, and the volume administered.

Table 13: Oral Administration of Iohexol for Abdominal or Abdominal Pelvic CT Examinations in Adults*

First Author, Year	Number of Patients Exposed[a]	Concentration	Volume
Lonnemark, 1993[b]	20	350 mgI/mL diluted to: 9 mgI/mL	800 mL
Lonnemark, 1995	30	350 mgI/mL diluted to: 4.5 mgI/mL 6.75 mgI/mL 9 mgI/mL	800 mL
Diederichs, 2007[c]	30	300 mgI/mL in 5% aqueous solution	1500 mL
McNamara, 2010[d]	149	350 mgI/mL diluted to: 9 mgI/mL	900 mL
Peterson, 2011[e]	49	350 mgI/mL diluted to: 8 mgI/mL	1000 mL

[a]Only the number of patients administered iohexol are shown.

[b]Study included a total of 30 patients administered amidotrizoate aqueous solution (n = 10), iohexol aqueous solution (n = 10), or iohexol with a viscosity-increasing agent added (n = 10).

[c]Study included a total of 160 patients administered lysine amidotrizoate (n = 160), sodium amidotrizoate (n = 30), ioxithalamate (n = 30), iopromide (n = 30), iohexol (n = 30), or iotrolan (n = 30). The authors identified the dose of iohexol that was diluted as 300 mg/dL but this is considered a self-evident error since osmolalities reported elsewhere in the publication indicate that the concentration of stock solution was 0.69 Osm/kg, indicative of 300 mgI/mL, and the diluted solution was 0.051 Osm/kg.

[d]Study included a total of 300 patients administered diatrizoate sodium (n = 151) or iohexol (n = 149).

[e]Study included a total of 100 patients administered diatrizoate (n = 51) or iohexol (n = 49).

* Reproduced from NDA 205383, Module 2, Section 2.7.4, Summary of Clinical Safety, page19

The three x-ray radiography exams in 129 adults were conducted using 100 or 200 mL of iohexol 350 mgI/mL.

The clinical trials listed below in Table 14 by author in alphabetical order that were the basis for the efficacy summary in children were also analyzed for the safety summary.

Table 14: Pediatric Studies Involving Oral Administration of Iohexol

Authors	Population M/F; Age*	Study Drug(s)**	Adverse Events
CT Examinations			
Mahmoud et al, 2010	N = 365 213/152; 32m	Iohexol 6 mgI/mL Volumes by weight	No cases of aspiration. 2 cases of vomiting in

		0-5y 18.4 mL/kg 6-12y 14.8 mL/kg >13y 12.6 mL/kg	genl. Anesthesia group. No complications in IV contrast group.
Smevik and Stake, 1985	N = 32 13/19; 142w	Iohexol 7 mgI/mL Oral: 120-500 mL Rectal: 60-120 mL G tube: 60-300 mL	In hospital follow up for at least 24 hours. 2 cases of vomiting relating to patient clinical history.
Smevik and Westvik, 1990	N = 166 69/91;8d-16y	Iohexol 7 mgI/mL Iohexol 6 mgI/mL Volumes by age Oral: 0-1500 mL Rectal: 10-300 mL G tube: 60-150 mL	4 patients vomited.
X-Ray Radiography Examinations			
Cohen et al***	Part 1, N = 64 Iohexol 180 11/10; 4.7y Iohexol 300 12/9; 5.4y Barium 15/7; 3.5y Part 2 N = 18 Iohexol 180 9/9; 1.2y	Part 1: Iohexol 180 mgI/mL, 5 mL/kg Iohexol 300 mgI/mL, 7 mL/kg Barium 30% or 60%, 6.5 mL/kg Part 2: Iohexol 180 mgI/mL, 9.2 mL/kg	Vital sign monitoring during exams. Adverse event follow up for 24 hours. Transient vital sign changes noted. Mild to moderate diarrhea reported for both iohexol groups. One incident of vomiting in barium group. Studies used to support approval of Omnipaque for oral use in children.
Langer and Kaufman, 1987	N = 293 total Upper GI 129/96; <6m (158); ≥6m(67) Enema 40/28; <6m(38);≥6m (30)	Iohexol 300 mgI/mL Iopamidol, diluted with 5% glucose 1:1 for oral and aqua dest 1:1 for rectal, mean oral volume 5 mL/kg BW, mean rectal 5-10 mL/kg BW	Several cases of aspiration without pulmonary edema or infiltrate. No diarrhea.
Ratcliffe, 1986	N = 115 total Iohexol only: Esophagogram 4/6; 1d-1.5y Meal 5/8; 10d-1.5y	Iohexol 180 mgI/mL Ioxaglate 320 mg/mL Injection Iopamidol 200 Injection	95% of patients followed for a prolonged interval, reported for all 3 contrast media used. 7 cases of aspiration with prompt recovery. 6

	Enema 1/0; 2d Loopogram 2/2; 4m-2y		cases of contrast spill into trachea or major bronchi with no adverse sequelae. Leak into peritoneum (3), loculated spaces or fistulae (4) which was drained or absorbed with free leak excreted by kidneys
Stake and Smevik, 1985	N = 30 35wk	Iohexol 175 mgI/mL 8-225 mL, 29 diluted with equal amount water, 4 undiluted 14 oral, 2 rectal, 17 G tube	No adverse reactions.
Wright et al, 2002	N = 154 Iodixanol 48/26; 5.8y Iohexol 48/30; 6.4y	Iohexol 140 mgI/mL Iohexol 300 mgI/mL Iodixanol 150 mgI/mL Iodixanol 320 mgI/mL	48 hour follow up for adverse events. No serious adverse events. Most common adverse event was diarrhea followed by nausea, vomiting, abdominal pain. Three patients in iodixanol group with skin reactions, one requiring medical treatment. Fewer adverse events with iodixanol than iohexol.

***** d, w, m, y: days, weeks, months, years
** Some ages were reported as mean, some as median with either an age range or standard deviation. Some volumes were reported with standard deviations. These were not included in the table.
*** Study was used to support approval of oral iohexol in the pediatric population. More detailed review of this study is provided below.

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Cohen, 1991, conducted a randomized, double-blind study that compared iohexol 180 mgI/mL and iohexol 300 mgI/mL to barium and an open label study using only iohexol 180 mgI/mL and found no significant differences in the adverse events between the two doses of iohexol. In the randomized comparative portion of the trial 11 patients from the iohexol 180 mgI/mL group experienced 17 adverse events and 9 patients from the iohexol 300 mgI/mL group experienced 12 adverse events. The most common adverse event was mild to moderate diarrhea, (10 for iohexol 180 mgI/mL and 8 for iohexol 300 mgI/mL). Blood pressure was monitored before and after contrast administration. 9 patients had systolic BP changes of 30 mm Hg or greater and 3 patients had diastolic

BP changes of 30 mm Hg or greater. 21 patients had pulse rate changes of 30 beats per minute or greater. Changes were transient and attributed to the clinical status of the patient when vital sign measurements were taken. No clinical adverse events were attributed to vital sign changes and no treatment was required due to changes in vital signs.

In children, for CT exams, iohexol was diluted and administered by volume depending on patient age/weight/route of administration. Volumes ranged from 0-1500 mL. For radiography exams, contrast media were used as either dilute or undiluted solutions with variable volumes depending on patient age/weight/route of administration. Table 15 displays exposure for the CT exams by age, dose, and volume. There was generally a diverse range of age groups however only one of the studies, (approximately 26% of the total patients studied), presented doses based on patient age. Table 15 displays exposure for the x-ray radiography exams. Patient ages and exam doses are not specified for these studies however it can be concluded that are large number of pediatric patients ranging in age from newborn to 15 years received either undiluted or diluted iohexol for radiography exams and were evaluated for safety at the time of exam.

Table 15: Oral Administration of Iohexol to Pediatric Patients (Abdominal CT)*

First Author, Year	Number of Patients Exposed	Dose	Age Groups	Volume[a]
Smevik, 1985	32	7 mgI/mL	31 weeks – 13 years	120 mL - 500 mL
Smevik, 1990	15	6 or 7 mgI/mL	0 – 1 year	50 – 300 mL (176)
	13		1 – 2 years	60 – 300 mL (171)
	35		2 – 5 years	60 – 800 mL (290)
	45		5 – 10 years	0 – 1350 mL (397)
	34		10 – 16 years	20 – 1500 mL (681)
Mahmoud, 2010	365 (number administered iohexol by age group was not specified)	6 mgI/mL	< 1 year	150 mL, 18.4 mL/kg (7.5 – 43.6)
			1 – 5 years	300 mL, 18.4 mL/kg (1.5 – 82.8)
			6 – 12 years	450 mL, 14.8 mL/kg (3.1 – 27.8)
			> 13 years	600 mL, 12.63 mL/kg (6.1 – 20.4)

[a]Mean values (mL, Smevik) or ranges (mL/kg, Mahmoud) are presented parenthetically.
* Reproduced from NDA 205383, Module 2, Section 2.7.4, Summary of Clinical Safety, page 20

Table 16: Oral/Rectal Administration of Iohexol to Pediatric Patients (X-Ray)*

First Author, Year	Number of Patients Exposed[a]	Iohexol Concentration	Age Groups	Volume
Stake, 1985	30	350 mgI/mL	Median 35 wk (1 d – 14 y)	Diluted from 350 mgI/mL with equal amounts of water, n = 29 Undiluted 350 mgI/mL, median dose = 40 mL (range 8 - 225 mL), n = 4 Perorally = 14 Gastric tube = 17 Enema = 2
Ratcliffe, 1985[b]	28	180 mgI/mL	1 d - 2y	Undiluted 180 mgI/mL, volume not specified
Langer, 1987[c]	293 total iohexol and iopentol patients combined	300 mgI/mL	0 - > 2 y	Diluted with 5% glucose 1:1 Oral: 5 mL/kg body weight Enema: 5 – 10 mg/kg body weight
Cohen, 1991[d]	180 mgI/mL: 39 300 mgI/mL: 21	Part 1: 180 mgI/mL 300 mgI/mL Part 2: 180 mgI/mL	Part 1: 4.7 ± 4.8 y 5.4 ± 5.8 y Part 2: 1.2 ± 3.1 y	Part 1: 5.2 ± 5.9 mL/kg 7.0 ± 7.0 mL/kg Part 2: 9.2 ± 5.6 mL/kg
Wright, 2002[e]	78	140 mgI/mL 300 mgI/mL	0 – 15 y	Undiluted (1 mL fruit juice per 50 mL CM could be added) 93.5 ± 67.1 mL (range 10 - 400 mL)

d = day; wk = week; y = year.

[a] Only the number of patients administered iohexol are shown unless specified otherwise.

[b] Study included a total of 115 examinations; patients were administered ioxaglate (n = 70), iopamidol (n = 18), or iohexol (n = 28).

[c] Study included a total of 293 patients administered iopentol or iohexol; the results were combined.

[d] Study included a total of 82 patients and was conducted in two parts; (1) patients were administered iohexol 180 mgI/mL (n = 20), iohexol 300 mgI/mL (n = 20), or barium (n = 22) and (2) patients were administered iohexol 180 mgI/mL (n = 18).

[e] Study included a total of 152 patients administered iodixanol (n = 74) or iohexol (n = 78) that contributed to the safety evaluation.

* Reproduced from NDA 208353, Module 2, Section 2.7.4, Summary of Clinical Safety, page 21

Six additional published reports that described the utility of iohexol for other indications in pediatrics were included in the literature review. They include both oral and IV use of iohexol in an acute care setting. These are summarized below:

- Nordshus et al. The use of iohexol in meconium obstruction in the newborn. Fortschur.Rontgenstr. 1986;144(3):358-9: This report describes the successful

use of 5 mL of iohexol 240 mgI/mL administered via g-tube to successfully relieve meconeum ileus in two premature infants.

- Patton et al. Worsening enterocolitis in neonates: diagnosis by CT examination of urine after enteral administration of iohexol. Pediatr Radiol. 1999;29(2):95-9: This report describes three cases of neonates with necrotizing enterocolitis who received 5 mL Omnipaque 300 mgI/mL via g-tube with urine collection up to 24 hours that was measured for CT attenuation coefficient which was suggested to be a sensitive indicator of disease severity and progression than standard radiography.
- Rencken et al. Necrotizing enterocolitis: diagnosis with CT examination of urine after enteral administration of iodinated water-soluable contrast material. Radiology. 1997 Oct; 205(1):87-90: This report describes the methodology used in 22 neonates to assess for necrotizing enterocolitis by determination of attenuation coefficient by CT exam of the urine after infants were administered 5 mL of Omnipaque 300 and concludes that the CT attenuation coefficient is dependent on the extent of bowel ischemia.
- Hara et al. Significance of bowel wall enhancement on CT following blunt abdominal trauma in childhood. J Compute Assist Tomogr. 1992 Jan-Feb; 16(1): 94-8: This report describes 12 children who experienced blunt trauma and who received iohexol 300 mgI/mL either orally plus IV or IV only for CT exam and who were noted to have intense bowel wall enhancement with bowel wall thickening reported in association with hypovolemic complex and that suggested perforation and thus was recommended to lead to strong consideration for surgical intervention.
- Sivit et al. Posttraumatic shock in children: CT findings associated with hemodynamic instability. Radiology. 1992 Mar; 182(3): 723-6: This report describes 27 children who were evaluated by contrast-enhanced CT (6 who received IV Omnipaque 240) that were diagnosed with hypoperfusion complex based on CT findings but noted that 25% of children that did survive for 24 hours developed renal insufficiency felt to relate to hypoperfusion complex.
- Taylor et al. Hypovolemic shock in children: abdominal CT manifestations. Radiology 1987; 164(2): 479-81: This report describes three of the cases noted in the above publication.
- Kauffman et al. Imaging features of ovarian metastases from colonic adenocarcinoma in adolescents. Pediatr Radiol. 1995; 25(4): 286-88: This report describes the imaging features of ovarian metastases from adenocarcinoma of the colon in 6 adolescent females of which two received IV iohexol 300mgI/mL and all of who received oral contrast media, type not specified.

7.1.2 Categorization of Adverse Events

The applicant's focus for safety was for administration via the oral route based on the lack of access to source data and an inconsistent application of an adverse events dictionary and lack of access to source data. The SOC and PT terminology used in the

literature reports for the oral administration of iohexol was the same as the current Medical Dictionary for Regulatory Activities (MedDRA) that is used for categorization (coding) of adverse events. The literature articles demonstrate a reasonable level of consistency in terms of the nature and severity of adverse reactions reported following administration of iohexol via the oral route.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No integrated analysis of the adverse events was performed due to inconsistency in reporting and lack of information about the medical dictionary used across the studies.

7.2 Adequacy of Safety Assessments

For both adults and children, all published studies which reported on oral administration of iohexol as a contrast agent included safety evaluations of patients. Data from oral x-ray examinations conducted using higher concentrations of solutions was provided as supportive to CT exams. The applicant conducted a separate clinical literature search for iohexol injection to assure that articles associated with the IV route of administration pertinent to clinical safety or pharmacokinetics were included in the review. In this regard, the literature search evaluated the safety of iohexol administered orally as a contrast agent during CT of the abdomen and pelvis and the currently approved prescribing information for Omnipaque against the current literature to identify relevant articles in support of clinical safety with CT for oral administration contrast enhanced CT with oral and intravascular routes of administration; oral x-ray radiographic examinations; and intravascular routes of administration focused on more clinically relevant IV data but not excluding other routes such as intra-arterial or intrathecal administration.

All adult and pediatric patients who received oral iohexol for either CT or radiography study received safety evaluations.

The studies were adequately designed and conducted. The safety assessments conducted and analyzed were appropriate for this diagnostic agent.

For some studies, the data was stratified by age. For some studies, the data was evaluated for predictive factors such as allergies and medications.

Most subjects received a single exposure of study drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For the adult population who received iohexol, a wide range of ages, (21-85 years), was noted with the mean/median about 50-60 years. For CT iohexol administration where gender was noted, the percentage of females undergoing study was similar, (44% versus 41%).

For the pediatric population, the age range was from newborn to 15 years with the majority of patients under age 5. Allowing for 50% in the 1987 Langer study, approximately 900 children received iohexol for oral CT or radiography), 44% of whom were females, (sex not stated for 30 children). This was also similar to the percentage of females in combined CT and radiography studies, (42%).

In the adult population, approximately 74% of patients were studied by CT exam. 50% of all adult patients and 45% of adults who were studied by CT exam received oral iohexol. In the pediatric population, about 44% were studied by CT exam. 65% of all children and 100% of children who were studied by CT exam received iohexol.

Iohexol, a diagnostic agent for oral administration, is administered as a single dose. There were a few adult patients in the published literature who received more than one radiography study based on clinical condition. These repeat studies were performed as interval follow up studies.

Age and gender demographics were appropriate for the studies. The age range for adults who received oral iohexol was 21-85 years. The age range for children who received iohexol was newborn to 15 years. Gender was not available for all studies. For the total adult population who received iohexol, slightly greater than 50% were males; for children, 55%.

In adults, the administered dose of iohexol was diluted from 300 or 350 mgI/mL to a concentration ranging from 4.5 mgI/mL to 9 mgI/mL for CT exams with the volumes of iohexol ranging from 800-1000 mL. Comparator drugs were diluted to similar concentrations and volumes. For radiography exams, Iohexol 350 mg/mL was used. Study drugs were not diluted with volumes ranging from 100-200 mL for both iohexol and comparators.

In children, for CT exams, iohexol was diluted and administered by volume depending on patient age/weight/route of administration. Volumes ranged from 0-1500 mL. For radiography exams, contrast media were used as either dilute or undiluted solutions with variable volumes depending on patient age/weight/route of administration. Due to variable methodology for administration and reporting, there were no means to determine absolute volumes used however, Wright reported on oral iohexol use in 78 children and oral iodixanol use in 74 children ages 0-15 years using volumes of 10-400

mL. In adults, for CT exams, the volumes of study drug (iohexol and other contrast media) were diluted and ranged from 800-1000 mL. For radiography exams, study drug was not diluted and ranged from 100-200 mL for both iohexol and comparators.

In children, for CT exams, iohexol was diluted and administered by volume depending on patient age/weight/route of administration. Volumes ranged from 0-1500 mL. For radiography exams, contrast media were used as either dilute or undiluted solutions with variable volumes depending on patient age/weight/route of administration. Volumes administered for enemas were unable to be determined.

7.2.2 Explorations for Dose Response

Information relevant for dosing recommendations of iohexol (b) (4) oral solution originates from CT studies presented in support of efficacy and safety and from the package insert of Omnipaque (iohexol), the reference listed drug. The applicant did not conduct any formal studies to determine dose response. The approved adult dose range of Omnipaque for use during CT exams is 9 mgI/mL in 500-1000 mL volume, totaling 4.5-9 gI. Oral x-ray radiography exams were supportive of CT for safety and dose response with 1.9-7.8 times greater dose range. The approved adult dose range of Omnipaque for use during oral x-ray radiography exams is 350 mgI/mL as 50-100 mL volume, totaling 17.5-35 gI.

7.2.3 Special Animal and/or In Vitro Testing

The results of the non-clinical studies have been described for approval of the RLD, (NDAs 18,956 and 20,608) with summaries of non clinical studies in this submission. Please see complete P/T reviews.

7.2.4 Routine Clinical Testing

The routine clinical testing of subjects as described in the literature was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Iohexol powder will be reconstituted with a beverage and administered as a single dose via an oral route. In patients with an intact bowel, it is eliminated via the GI tract. In instances of bowel obstruction or inflammatory bowel disease, minimal renal excretion via glomerular filtration may occur. In instances of bowel perforation, iohexol is resorbed by the peritoneum. There is no metabolic or interaction potential.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The potential for hypovolemia exists for all HOCM and LOCM.

There were no reports of hypovolemia associated with the oral administration of iohexol in the published literature. This would not be anticipated based on the dilute and hypotonic and hypo-osmolar (osmolality of 30 mOsmol/kg) nature of the aqueous solutions that are used for CT exams (9 mgI/mL). Undiluted CM (i.e. Omnipaque 350 mgI/mL) which are administered for x-ray radiography exams are hypertonic (osmolality of 844 mOsmol/kg water and osmolarity of 541 mOsmol/L) and have the potential to draw fluid into the intestines which, if severe enough, could result in hypovolemia.

Aspiration is a theoretical concern for administration of oral CM in the elderly population. No literature reports relating to aspiration of iohexol in the adult population were identified.

In children, there are several case reports and retrospective trials in the literature that refer to aspiration following administration of oral CM. Following oral administration of iohexol to the pediatric population, several cases of aspiration/coughing were noted in the published reports of the oral use of iohexol. None resulted in pulmonary edema or infiltration. These cases are noted in Table 13, section 7.1.1. The applicant presented several case reports and retrospective trials in the literature that refer to aspiration or vomiting following administration of *other* oral contrast media to include:

- 3 reports in infants who received contrast-enhanced CT scans during gastroesphageal studies resulting in fatal aspirations, two with barium and one with Hypaque 40%, deaths possibly relating to large volumes of aspiration as versus the material that was aspirated, with discussion of preventative measures for this event, (McAlister and Siegel. Fatal aspirations in infancy during gastrointestinal series. Pediatr Radiol. 1984;14(2):81-3)
- A case report of a 12 year old trauma patient who received oral Gastrografin 2% for CT and IV Isovue 300 who vomited, experienced respiratory distress, and required intubation, with CT scan infiltrates compatible with aspiration which radiologists should be aware of in an acute care clinical setting, (Donnelly et al. Aspirated contrast material contributing to respiratory arrest in a pediatric trauma patient. AJR Am J Roentgenol. 1998 Aug;171(2):471-3)
- A retrospective study of 50 children who underwent abdominal CT scans after blunt force trauma and received oral Gastroview or Gastrografin and IV Iohexol with one of the patients suggested as having clinically silent aspiration of oral contrast but no evidence that administration of oral contrast material was harmful, (Lim-Dunham et al. Aspiration after administration of oral contrast material in children undergoing abdominal CT for trauma. AJR Am J Roentgenol. 1997 Oct;169(4):1015-8)
- Retrospective evaluation of 367 pediatric patients who received oral Hypaque and required sedation for an abdominal CT study with 4 cases of vomiting but no other associated events reported while the patients were awake which suggests that this is a safe practice, (Ziegler et al. Is administration of enteric contrast

material safe before abdominal CT in children who require sedation? Experience with chloral hydrate and pentobarbital. Am J Roentgenol. 2003 Jan;180(1): 13-5)

7.3 Major Safety Results

7.3.1 Deaths

No deaths related to the oral administration of iohexol were reported in the published studies reviewed.

Caro et al, (1991-section 7.3.2 below), in a meta-analysis consisting of 333,692 parenteral administrations of high osmolar CM in 41 studies reported 3 deaths attributed to the CM with the risk of death associated with parenteral use of high osmolar CM estimated to be 0.9 per 100,000. There was no difference in mortality reported for the comparative use of low osmolar CM in 37 studies.

7.3.2 Nonfatal Serious Adverse Events

Severe or life-threatening reactions have rarely been reported via the IV route. Katzberg and Lamba, 2009, (Katzberg and Lamba. Contrast-induced nephropathy after intravenous administration: fact or fiction? Radiol Clin North Am. 2009 Sep;47(5):521-3), reviewed the safety of intravenous contrast media (CM) and noted reactions in association with nonionic monomeric CM in approximately 4 in 10,000 examinations with a mortality rate estimated to be approximately 1 in 170,000 examinations. Based on a meta-analysis of 41 published studies that included 333,692 parenteral administrations of HOCM/LOCM as 31 per 100,000. Caro,1991, (Caro et al. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. AJR Am J Roentgenol 1991 Apr;156(4):825-32), estimated the risk of severe reactions with LOCM administered parenterally to be 31 per 100,000.

7.3.3 Dropouts and/or Discontinuations

The literature reports for the oral use of iohexol for CT in children include 3 cases reported by Smevik and Westvik (1990) or 2.1% of patients studied who refused to drink contrast. Two of the three children were experiencing nausea and vomiting; one 10 year old child refused to continue drinking after drinking 20 mL, reason not specified although 81% of patients in the study had confirmed malignant disease.

7.3.4 Significant Adverse Events

The applicant described several case reports of severe adverse events associated with the i*ntravascular* administration of iohexol, summarized below with references to the publications:

- Goodfellow et al. Fatal acute vasculitis after high-dose urography with iohexol. Br J Radiol. 1986 Jun;59(702):620-1: Case report of the death of a 69 year old female with a 20 year history of hypertension and associated mild chronic renal failure who was considered to have "acute iodism" with the development of rash and edema at 48 hours post exam and then pulmonary edema, ultimately with involvement of all organs and death.
- Sadi et al. An autopsy case of malignant lymphoma with Lyell's syndrome [toxic epidermal necrolysis]. J Dermatol. 1995 Aug;22(8):594-9: Case report of the death a 59 year old male who received an intravenous injection of Omnipaque for a CT exam then developed a skin rash with progression to death.
- Shigyo et al. A rare case of disseminated intravascular coagulation caused by the nonionic contrast medium iohexol. J Urol. 1995 Jun;153(6):1901-3: Case report of a 53 year old female with a left ureteral stone who experienced disseminated intravascular coagulation with multiple organ failure following intravenous administration of 100 mL iohexol 300 mgI/mL over 10 minutes who then gradually recovered with treatment over two weeks.
- Rivera et al. Iodine-induced sialadenitis: report of 4 cases and review of the lioterature. Nephron. 1993;63(4):466-7: Case reports of 4 patients who were undergoing hemodialysis and who experienced sialadenitis after oral and IV administration of iodine compounds, case considered as a rare infrequent reaction to iodine (iodism).
- Rosado et al. Toxic epidermal necrolysis after repeated injections of iohexol. AJR Am J Roentgenol. 2001 Jan;176(1):262-3: Case report of a 33 year old male who underwent contrast enhanced body CT and developed toxic epidermal necrolysis (skin rash) after 4 exams that required treatment in the intensive care unit, considered a delayed reaction to iohexol.
- Jain et al. Metformin-associated lactic acidosis following contrast-media induced nephropathy. Eur J Anaesthesiol. 2007 Feb;25(2):166-7: Case report of a 47 year old male who experienced severe headaches and transient loss of consciousness who received CT and was operated on for aneurysm but then developed renal failure, became hypotensive, suffered a cardiac arrest and could not be resuscitated with post-operative renal failure attributed to the use of iohexol for CT scan and for DSA.

Glover, (1991 a, 1991 b), reported a case of a severe adverse reaction following the oral administration of iohexol. The patient was a 31 year old male with complaints of abdominal bloating and distension who underwent an x-ray radiography exam to rule out a subacute obstruction and late anastomotic dehiscence. He drank 100 mL of oral iohexol 350 mgI/mL. Approximately one hour later he collapsed and complained of abdominal pains and vomited. He was noted to be hypotensive and tachycardic. Concurrently, he complained of mild tightness of the throat but did not experience dyspnea. He was treated symptomatically and recovered. The GI study did not

demonstrate any abnormalities. This reaction is considered a possible idiosyncratic reaction to iodinated CM.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events of nausea, vomiting, and mild diarrhea after oral iohexol for CT have a reported incidence of <2%. Table 17 taken from the 2010 Omnipaque label displays the approved prescribing information for oral use in adults and children.

Table 17: Approved Labeling for Oral Omnipaque Adverse Reactions*

Adverse Reactions
Oral administration of OMNIPAQUE is most often associated with mild, transient diarrhea especially when high concentrations and large volumes are administered. Nausea, vomiting, and moderate diarrhea have also been reported following orally administered OMNIPAQUE, but much less frequently. For CT examinations using dilute oral plus intravenous contrast medium, adverse events are more likely to be associated with the intravenous injection than the hypotonic oral solution. It should be noted that serious or anaphylactoid reactions that may occur with intravascular iodinated media are possible following administration by other routes.
Adults: In controlled clinical trials involving 54 adult patients for oral pass-thru examination of the gastrointestinal tract using OMNIPAQUE 350, the following adverse reactions were reported: diarrhea (42%), nausea (15%), vomiting (11%), abdominal pain (7%), flatulence (2%), and headache (2%). In controlled clinical studies involving 44 adult patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (2%).
Children In controlled clinical studies involving 58 pediatric patients for examination of the gastrointestinal tract at concentrations of 180 and 300 mgI/mL, the following adverse reactions were reported: diarrhea (36%), vomiting (9%), nausea (5%), fever (5%), hypotension (2%), abdominal pain (2%), and urticaria (2%). In clinical studies an increased frequency and severity of diarrhea was noted with an increase in the administered concentration and dose of the radiocontrast agent. In controlled clinical studies involving 69 pediatric patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 240 and OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (1.4%).

* Reproduced from NDA 205383, Module 2, Section 2.7.4, Summary of Clinical Safety, p.26-7

The safety profile of IV iohexol (Omnipaque) is well established with adverse events following IV administration described in the Full Prescribing Information. There were several phase 1 trials in healthy volunteers that assessed the distribution in the body,

renal excretion, and possible metabolism after intravenous injection. There were several published trials comparing IV iohexol to other iodinated contrast media for abdominal and chest CT examinations assessing image quality, bowel opacification, and adverse reactions.

A large prospective study was conducted in Japan, (Katayama et al. Adverse reactions to ionic and nonionic contrast media. Radiology. 1990 Jun;175(3): 621-8), that compared the overall prevalence of adverse drug reactions of ionic CM to the lower osmolar, nonionic CM, (iopamidol and iohexol). 337,647 cases were included in the study, (169,284 cases or 50.1% ionic CM and 168,383 cases or 49.9% nonionic CM). The overall prevalence of ADRs was 12.66% in the ionic CM group and 3.13% in the nonionic CM group. The five most frequent symptoms were the same for both groups with incidences as follows: nausea 4.58% versus 1.04%, heat sensation 2.29% versus 0.92%, vomiting 1.84% versus 0.36%, itching 2.97% versus 0.45%, and urticaria 3.16% versus 0.47%. Severe ADRs occurred in 0.22% of the ionic CM group and 0.04% of the nonionic CM group. Of the severe ADRs, dyspnea accounted for more than 66% of cases for both the ionic and nonionic CM. One death occurred in each group but a causal relationship was not established. The authors concluded that nonionic CM significantly reduce the frequency of severe and potentially life-threatening ADRs to contrast media. Approximately 70% of ADRs due to either type of CM occurred during or within 5 minutes of intravascular injection with 16% noted to occur more than 5 minutes after injection. Similar time frames were noted for the onset of severe ADRs.

Cohen, (Cohen et al. Comparison of intravenous contrast agents for CT studies in children. Acta Radiol. 1992 Nov;133(6): 592-5), reported than similar types of adverse reactions were seen in children administered IV iohexol. The authors conducted a study of 180 children undergoing CT examination randomly allocated to receive either Hypaque or Omnipaque or Isovue with half also receiving a dilute solution of oral Omnipaque 60 to 90 minutes prior to CT. For iohexol, there was one each of the following minor reactions: nausea, vomiting, local discomfort, and additional movement. There were miscellaneous symptoms of warmth, flushing, abnormal taste, and dizziness noted in 11 instances. 49 (82%) of the iohexol patients had no reactions. The authors concluded that there was a lower incidence of minor reactions with nonionic CM than with the ionic CM and that adverse reactions were less common with iohexol as versus iopamidol (Isovue).

7.4.2 Laboratory Findings

Not systematically reported on/reviewed.

7.4.3 Vital Signs

Not systematically reported on/reviewed.

7.4.4 Electrocardiograms (ECGs)

Not systematically reported on/reviewed.

7.4.5 Special Safety Studies/Clinical Trials

Based on the published studies that were reviewed, the differences in adult subpopulations were unable to be assessed by the applicant. The applicant provided published reports on the use of orally administered iohexol to measure bowel permeability in patients with inflammatory bowel disease (IBD) to assess disease activity, literature reports describing the use of IV administered iohexol as a biomarker of renal function, and studies that assessed the effect of IV iohexol in patients with impaired renal function.

Section 4.4.3 (Pharmacokinetics) of this review summarizes three publications, (Halme 1993, Halme 1997, and Gerova 2011) that report on the use of iohexol to measure bowel permeability and disease activity in patients with inflammatory bowel disease. Urinary iohexol is noted to be significantly higher in patients with active disease and excretion is increased with more severe disease.

This same section also discusses the use of iohexol as a biomarker for glomerular filtration rate used to assess the impact of pharmaceuticals on renal function.

The literature search also included 18 published studies assessing the effect of iohexol on renal function and contrast induced nephropathy. Summaries of these studies are contained in the NDA module 2, section 2.7.4 as Table 2.7.4-17. This review does not contain a detailed review of these intravascular studies as the potential for acute kidney injury (AKI) and contrast induced nephropathy (CIN) exists for all iodinated contrast media. Based on the studies provided, the reported incidence varied from no incidence or no cases of clinically important CIN to a low incidence trending to a higher incidence in patients with underlying diabetes or mild renal impairment. The effects were considered transient and were similar to those reported for other iodinated contrast media. The applicants Table 2.7.4-17 follows as Table 18.

Table 18: Published Studies Assessing Effect of Iohexol on Renal Function and Contrast Induced Nephropathy*

Author, year	Number of Patients	CM (Concentration or Volume)	Examination	Definition of CIN	Incidence of CIN Number/Total (%)	Results[a]
Dillman, 2012	N = 389 Iohexol n = 190; Iopamidol n = 199	Iohexol 300 mgI/mL (mean volume: 123.4 ± 8.8 mL)	IV CT	Increase in sCR ≥ 25%, an absolute increase in sCR of ≥ 0.5 mg/dL, and an absolute increase in sCR of ≥ 0.3 mg/dL.	21/190 (11%) ≥ 25% increase in sCR and 8/190 (4%) had a ≥ 0.3 mg/dL increase in sCR and 2/190 (1%) had a ≥ 0.5 mg/dL increase in sCR	The CIN rates between the two CM were not statistically different using any definition
Chuang, 2009	N = 50 Iohexol, n = 25; Iodixanol, n = 25	Mean volume:60.1 ± 10.7 mL	IVP	Increase in sCR ≥ 25%	1 of 25 (4%) for both iohexol and iodixanol (> 10% increase in sCR was 6/25 (24%) and 8/25 (32%) for iohexol and iodixanol)	Both CM were safe and have a low nephrotoxicity profile in high-risk patients.
Siegel, 1996	N = 150 Iohexol 300 mgI/mL n = 50; Iodixanol 270 mgI/mL n = 50; Iodixanol 320 mgI/mL n = 50	Iohexol 300 mgI/mL (1 mL/kg body weight)	IV excretory urography	sCR level > 1.6 mg/mL; Increase in sCR > 40% of the span of the reference ranges	sCR level > 1.6 mg/mL = 3 of 50 (6%); Increase in sCR > 40% of the span of the reference ranges = 3 of 50 (6%)	No difference between the 3 CM (p = 0.517)
Lee, 1996	N = 126 Iohexol 300 mgI/mL; Iodixanol 270 mgI/mL; Iodixanol 320 mgI/mL	300 mgI/mL (volume range 90 to 152 mL)	Body CT	Clinically relevant threshold was a ≥ 4 mg/dL increase or decrease in sCR	1 patient in iohexol group had increase in sCR (unable to void; reversed with catheterization)	Assessment of sCR levels showed no significant differences between iohexol and iodixanol
Jakobsen, 1991	N = 61 Iohexol 350 mgI/mL, n = 31; Iopentol 350 mgI/mL, n = 30	350 mgI/mL, 700 mgI/kg body weight	Abdominal CT	Increase in sCR > 50% or > 88 µmol/L Decrease in CL_{cr} > 50%	1 iohexol patient of 61 total iohexol and iopentol patients (1.6%)	CT study: Minor reductions in CrCL. Mean sCR remain unchanged at 3 h, 24 h and 48 h after CM administration (mean sCR values: iohexol 88 ± 24 µmol/L, range 42 to 180 µmol/L. One iohexol patient had a > 50% increase in sCR with a concomitant decrease in creatinine clearance from 39 mL/min to 29 mL/min. Two iohexol patients in had > 50% decrease in creatinine clearance
Jakobsen, 1990a; Jakobsen, 1990b	N = 33 iohexol N = 25 iohexol	Cardioangiography: Iopentol 350 mgI/mL Iohexol 350 mgI/mL, 700 mgI/kg body weight Peripheral arteriography: Iopentol 150 mgI/mL Iohexol 140 mgI/mL (publication also includes CT study reported in Jakobsen, 1991)	Cardioangiography Peripheral arteriography	sCR <124 µmol/L sCR <150 µmol/L	No incidence of kidney failure reported	Cardioangiography: sCR increased from 87 to 98 µmol/L. The effect on CrCL was a small increase from 90 to 96 mL/minute. Peripheral arteriorography: a significant increase in sCR from 92 to 102 µmol/L. Transient increases in urinary albumin excretion noted for both CM.

Author, year	Number of Patients	CM (Concentration or Volume)	Examination	Definition of CIN	Incidence of CIN Number/Total (%)	Results[a]
Barrett, 1992	N = 249 (HOCM and LOCM)	LOCM (100 mL)	Angiocardiography; IV pyelography; CT	Increase in sCR ≥ 25%	3/24 (12%) 5/32 (3.8%) in the LOCM group	A rise in sCR after CM was significantly associated with the severity of the pre-contrast renal impairment and the presence of diabetes mellitus, but not with type of contrast. Diabetics with a sCR > 2.25 mg/dL pre-contrast had a highest risk of deterioration in renal function after contrast.
Harris, 1991	N = 51	300 mg/dL (OMNIPAQUE 300 mgI/mL); 150 mL	CT	Increase in sCR ≥ 25% within 48 hours	(n = 1 of 51or 2%); subset of 16 diabetic patients no increases ≥25% of sCR in the iohexol group	No cases of clinically important CIN in the study
Weisbord, 2008	N = 421 (IV iodinated CM) 367 with sCR measurements		Nonemergent CT (IV)	Six definitions of CI-AKI: relative increases of sCR from baseline of ≥ 25%, ≥ 50%, and ≥ 100% and absolute increment changes in sCR from baseline of ≥ 0.25 mg/dL, ≥ 0.5 mg/dL, and ≥ 1.0 mg/dL	0% to 6.5% (100% to ≥ 25%); 0.3% to 10.9% (≥ 1.0 mg/dL to ≥ 0.25 mg/dL)	CI-AKI of a ≥ 25% increase in sCR and an increase of sCR ≥ 0.5 mg/dL, congestive heart failure, baseline sCR > 1.5 mg/dL, and inpatient status were the most common patient and procedural factors associated with CI-AKI (p < 0.05) CI-AKI occurred infrequently among outpatients with mild baseline kidney disease.
Trivedi, 2010	N = 28 Iohexol 370 mgI/mL; Iopamidol 370 mgI/mL	Iohexol 350 mgI/mL	IV or IA CT for routine care (eg, abdominal CT or angiogram of the neck); patients received 2 CT scans a mean 20 days ± 13 days apart	Increase in sCR ≥ 25% or ≥ 88.4 µmol/	Four subjects (14.3%) who received iohexol (3 received 165 mL and one received 65 mL)	In patients with relatively preserved renal function, there is a risk of CIN after repeated exposure of CM within a short period of time.
Nossen, 1995	N = 16 Iohexol 350 mgI/mL, n = 8; Iodixanol 320 mgI/mL, n = 8	Iohexol 350 mgI/mL	Pre-operative angiography (kidney transplant patients)	Not defined but patient population was severely renally impaired	None reported; focus of study was renal clearance and PK of CM	Of the dose of iohexol given, 6.1% was recovered in feces and 74.8% was recovered in urine. The authors concluded that, in patients with severely impaired renal function, glomerular filtration of unmetabolized CM is the main excretory pathway, however, the elimination rate is markedly reduced and a larger fraction of the CM is recovered in feces
Apelqvist, 1996	N = 46 diabetic patients received iohexol	Iohexol 300 mgI/mL	Arteriography	Increase in sCR ≥ 25%	26% (did not remain elevated by 30 days after the procedure)	Serum creatinine levels increased in 41 of 46 patients (89%) but did not remain elevated by 30 days after the procedure; a significant decrease in CLcr was also observed 2 days after the procedure

Author, year	Number of Patients	CM (Concentration or Volume)	Examination	Definition of CIN	Incidence of CIN Number/Total (%)	Results[a]
McCullough, 2011	Meta-analysis (25 studies-IA and IV) iodixanol and LOCM including iohexol	LOCM (6 IV studies total with 1 including iohexol)	IA and IV	Increase in sCR of either ≥ 0.5 mg/dL or ≥ 25%.	CI-AKI: 1.4% Iodixanol versus 3.5% LOCM	CI-AKI significantly lower incidence for iodixanol versus LOCM for IA administration but not but not IV administration Incidence of CI-AKI with IV administration (1 study with comparison to iohexol [Chuang, 2009 see above])
Heinrich, 2009	Meta-analysis of 25 studies of IA or IV LOCM versus iodixanol	Various	Two studies included the use of IV administration of iohexol (Siegle and Lee; see above)	Increase in sCR ≥ 25% or increase ≥ 0.5 mg/dL		A subgroup analysis (IA and IV iohexol combined) revealed a significantly lower risk of CIN with the use of iodixanol compared with iohexol (RR: 0.45, 95% CI, 0.26, 0.76, p < 0.01).
Barrett, 1993	Meta-analysis of 31 studies between 1982 and 1991, 18 included comparisons with iohexol; (N > 4286)	CM was administered by the IV route, with cardiac injection and with noncardiac IA injections	Various	Mean changes in GFR or an increase in sCR > 0.5 mg/dL (44 µmol/L)		Among 25 trials (n = 4286), the pooled OR of a rise in sCR level of > 44 µmol/L with LOCM was 0.61 (95% CI, 0.48, - 0.77) times that of HOCM. A statistically significant effect of LOCM in subgroup of patients with renal failure (defined as sCR > 120 µmol/L or GFR < 70 mL/min); OR was 0.50 (95% CI, 0.36, - 0.68) while it was 0.75 (95% CI, 0.52, - 1.1) in patients without prior renal failure. The pooled OR for 4 studies that reported the prevalence of severe changes in renal function (> 90 µmol/L or 50% above baseline) after CM administration showed greater changes in sCR only in those with existing renal failure and less common with LOCM (OR: 0.44; 95% CI, 0.26, - 0.73).
Hipp, 2008	Retrospective review of N = 235 iohexol	Iohexol (concentration not specified), 150 mL	CT of the abdomen (trauma)	Increase in sCR ≥ 25% or ≥ 0.5 mg/dL from baseline 48 hours after CM administration	5.1% (95% CI, 2.9% to 8.8%)	CIN patients were significantly older (≥ 75 years RR for CIN was 7.7 (95% CI, 3.9 to 14.0); renal insufficency (elevated sCR > 1.5 mg/dL) was significantly associated with CIN (p = 0.007) as was GFR < 60 mL/min/1.73 m^2 (P = 0.02)

Author, year	Number of Patients	CM (Concentration or Volume)	Examination	Definition of CIN	Incidence of CIN Number/Total (%)	Results[a]
Lodhia, 2009	Retrospective review of N = 216 cirrhotic patients (MELD score = 17)	Iohexol (concentration not stated) 150 mL	IV CT	25% decrease in CrCL	53 of 216 (25%)	Of the 53 with CIN, 39 (74%) patients had ascites (compared to 46% without CIN). Six (11%) patients developed chronic renal insufficiency (CRI; CrCL less than baseline for six weeks); none required dialysis Ascites was a significant risk factor for the development of CIN (OR 3.38, 95% CI, 1.55 to 7.34, p = 0.0009)
Bruce, 2009	Retrospective comparison of N = 11,588 patients (13,274 patient encounters) Iohexol, n = 5328; Iodixanol, n = 462; Unenhanced CT, n = 7484	NA	IV CT	0.5 mg/dL increase in sCR or ≥ 25% decrease in eGFR	Iohexol cohort paralleled that of the control cohort up to a creatinine level of 1.8 mg/dL; 8 of 30 (26.7%) with a baseline sCR of 1.9 to 2.0 mg/dL; 11 of 27 (40.7%) for sCR > 2.0 mg/dL	Iohexol patients had a significantly higher incidence of acute kidney injury when underlying diabetes was present (p < 0.004). A higher incidence of acute kidney injury was identified among control subjects undergoing unenhanced CT. . The incidence of acute kidney injury in all three subgroups (IV iohexol, IV iodixanol, un-enhanced CT) was similar for patients with baseline CrCL 1.8 mg/dL, above this value IV iohexol presented an increased risk for patients. CIN may be overstated and the elevations in patients may be attributed to background fluctuation, underlying disease or treatment

NA = not available
[a]Iohexol results only
* Reproduced from NDA 205383, Module 2, Section 2.4.7, Summary of Clinical Safety, pp. 87-93.

Lastly, the applicant's literature search included a study to assess the effects of increasing osmolarity of different oral CM on bowel distension and the level of related adverse events, (Borthne et al. Osmolarity: a decisive parameter of bowel agents in intestinal magnetic resonance imaging. Eur Radiol. 2006 Feb;16: 1331-6). Omnipaque 350 mgI/mL was among the contrast agents that were administered. Bowel distension, total discomfort, and adverse events were assessed. The authors concluded that bowel distension was similar for CM with similar osmolarities. Side effects like diarrhea, distaste, nausea, vomiting, flatulence, and abdominal spasm were similar and noted to increase when the ingested dose increased. The authors also noted some more moderate or severe reactions such as profuse diarrhea. The conclusion was that the optimal osmolarity of oral contrast agents is guided by the patient's tolerance of adverse events.

7.4.6 Immunogenicity

Anaphylactic type reactions to oral iodinated contrast media have been reported in the literature. Glover, (1991 a and b), reported a case of a severe adverse reaction following the oral administration of iohexol described in section 7.3.4 above. The patient drank 100 mL of oral iohexol 350 mgI/mL and collapsed and complained of abdominal pains and vomited approximately one hour later. He was noted to be hypotensive and tachycardic. Concurrently, he complained of mild tightness of the throat but did not experience dyspnea. He was treated symptomatically and recovered. This reaction is considered a possible idiosyncratic reaction to iodinated CM and is classified as a hypersensitivity reaction.

Several studies have been conducted to evaluate the frequency and outcomes of hypersensitivity/anaphylactic reactions following IV administration of iohexol. The NDA contains the complete publications which this reviewer has summarized. Siegel, 1991, (Siegel et al. The use of iohexol in patients with previous reactions to ionic contrast material. A multicenter clinical trial. Invest Radiol. 1991 May;26(5):411-6) conducted a multicenter study to determine repeat reaction rate in 291 patients who had previous anaphylactoid symptoms/signs to hyperosmolar ionic CM and found that 5.5% experienced repeat anaphylactoid reactions but that none were severe. There was a relationship between the severity of previous reactions and to other sensitivities. Wang, 2008, (Wang et al. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. AJR Am J Roentgenol. 2008 Aug;191(2):409-15) noted that allergic type reactions occurred in 0.6% of patients injected with nonionic CM and noted that 77% of these reactions were mild. Moderate reactions did not last beyond 24 hours. Patients usually did well after experiencing a reaction. A retrospective review by Pedersen, 1998, (Pedersen et al. Late allergy-like reactions following vascular administration of radiography contrast media. Acta Radiol 1998 Jul;39(4):344-8) compared IV iohexol, iopental, and other CM and focused on late reactions. These were reported in 0.44% of patients who received iohexol and were reported in the same incidence as immediate reactions. Skin reactions, nausea, and itching/pruritis were the most common reactions. There is a single case report by Hauggaard, 1996, (Hauggaard A. Non-cardiogenic pulmonary edema after intravenous administration of non-ionic contrast media. Acta Radiol. 1996 Sep;37(5):823-5) of an adverse reaction to IV administration of iohexol for CT in a 66 year old female who experienced slight dyspnea associated with infiltrates considered non-cardiogenic pulmonary edema with hospitalization and clearing of the pulmonary infiltrates in 24 hours. Park, 2011, (Park et al. Small-bowel angioedema during screening computed tomography due to intravenous contrast material. J Compute Assist Tomogr. 2011 Sep-Oct;35(5):549-52), described 4 case reports of isolated small bowel angioedema caused by allergic reaction to IV CM, 3 of who received iohexol for abdominal CT. All cases showed resolution on follow up exams. Hu, 2012, (Hu et al. Transient small bowel angioedema due to intravenous iodinated contrast media. World J Gastroenterol. 2012 Mar 7; 18(9):999-1002), also reported 3 cases of transient anaphylactic small bowel angioedema from IV administration of nonionic contrast media with a description of CT findings, clinical findings, and outcomes.

No conclusions can be drawn about the relevance of case reports of anaphylactic or hypersensitivity reaction after IV injection to oral administration.

7.5 Other Safety Explorations

Adverse reactions to oral iohexol used for x-ray radiography exams are similar to those reported for CT exams but occur with a greater incidence. In controlled clinical trials with adult patients these were reported as diarrhea (42%), nausea (15%), vomiting (11%), abdominal pain (7%), and flatulence and headache 2% each. In controlled clinical trials involving pediatric patients, diarrhea, vomiting, and nausea were reported with incidences of 36%, 9%, and 5% with fever at 5% and hypotension, abdominal pain, and urticaria at 2% each.

7.5.1 Dose Dependency for Adverse Events

Not assessed. None anticipated as this drug is administered orally and passes through the GI tract without any metabolic interactions. A minimal amount only may be excreted by glomerular filtration in cases of bowel perforation or obstruction or severe inflammatory disease.

7.5.2 Time Dependency for Adverse Events

For the major safety studies for *oral* contrast administration, most adverse events were reported at the time of exam and were of short duration. There were three reports of adverse events (skin rash) in children that were administered a comparator iodinated contrast medium for a radiography exam. One of these reactions started at the time of exam and lasted 72 hours. The other two reactions were delayed in onset (26 hours and 20 hours post exam) with the former reaction reported as lasting 4 hours and the latter reported as lasting for 48 hours.

For *intravascular* administration of iodinated CM, there is a potential for delayed adverse reactions to occur, most commonly allergic-like and cutaneous reactions. The majority of cutaneous reactions occur between 3 hours and 2 days post contrast administration with time frames reported as between 30-60 minutes and 2 days. The reported incidence of cutaneous reactions ranges from 0.5% to 14%. There are other non cutaneous signs and symptoms of delayed reactions to include nausea, vomiting, fever, drowsiness, and headache. These delayed reactions are usual self limiting and do not require therapy. The potential for delayed reactions is recognized by the American College of Radiology in their practice guidelines, (ACR Manual on Contrast Media Vs 8, American College of Radiology, 2012).

7.5.3 Drug-Demographic Interactions

None anticipated. Drug will be used as a diagnostic agent.

7.5.4 Drug-Disease Interactions

Although systemic exposure to iohexol following oral administration is low, following intravenous injection patients with untreated hyperthyroidism have been reported to develop iodine-provoked delayed hyperthyroidism 4-6 weeks after IV contrast administration. The effect is usually self limited.

Nygaard, 1998, (Nygaard et al. Iohexol: effects on uptake of radioactive iodine in the thyroid and on thyroid function. Acta Radiol. 1998 Jun;5(6): 409-14), evaluated 28 patients including 22 with thyroid disease to assess thyroid function after intravenous injection of 100 mL of Omnipaque 300 mgI/mL for CT scanning of the thyroid. Some patients were followed for up to 3 months. There were various temporary changes in thyroid function and I-131 uptake after the CT exams to include self limiting hyperthyroidism. The authors concluded that iohexol could be used in patients with underlying thyroid disease but should be carefully monitored "for months afterward." Bourjeily, 2010, (Bourjeily et al. Neonatal thyroid function: effect of a single exposure to iodinated contrast medium in utero. Radiology. 2010 Sep;256(3):744-50), performed a retrospective review of 344 maternal and 343 newborn thyroid function records to assess the effects of in utero exposure to a single dose of water-soluable IV iodinated CM on thyroid function at birth. Either iohexol 300 mgI/mL or 350 mgI/mL was administered for purposes of pulmonary angiography. Total iodine administered was 45 g/L ± 7.3 grams. Volume administered averaged 128 mL for the iohexol 300 and 148 for the iohexol 350. Mean gestational age at the time of administration was 28 weeks. All newborns had a normal T4 level at birth. Of 85 newborns that were tested for TSH, only one had a transiently abnormal level which normalized at day 6. By history, the iodine exposure was at 26 weeks and the mother had concomitant opiate and cocaine exposure. The authors concluded that a single high dose in utero exposure to low osmolar iodinated intravenous products is not likely to have clinically important effects on neonatal thyroid function at birth. Rhee et al, 2012, (Rhee et al. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med. 2012 Jan 23;172(2):153-9), performed a nested case control study using data from a patient registry to determine if sudden exposure to high iodide levels (i.e iodinated CM) caused thyroid dysfunction. The authors determined that iodinated CM exposure was significantly associated with incident hyperthyroidism and incident overt hypothyroidism. Padovani, 2012, (Padovani et al. One month is sufficient for urinary iodine to return to its baseline value after the use of water-soluable iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy. Thyroid. 2012 Sep;22(9):926-30), studied patients with thyroid carcinoma who received iodinated contrast agents to perform chest or neck CT. She evaluated urine samples to quantify urinary iodine and noted one month as sufficient time for urinary iodine to return to baseline after the use of iodinated CM in patients who have had a total thyroidectomy and received radioiodine therapy. The ACR Manual on Contrast Media, (ACR Manual on Contrast Media vs.8, American College of Radiology, Committee on Drugs and Contrast Media.2012), notes that in certain instances, iodine-provoked delayed

hyperthyroidism may develop 4-6 weeks after IV contrast administration but that this is usually self-limited. The approved label for Omnipaque reflects this and the proposed label for iohexol powder will be an adaptation and update of the current label according to the applicant. This is reflected in Table 19, section 7.5.5 below.

7.5.5 Drug-Drug Interactions

Prospective clinical drug-drug interaction studies have not been conducted with oral iohexol. The clinical literature search did not yield any information related to drug interactions in humans. Based on animal studies which showed that iohexol is not metabolized in the body and is eliminated in the urine as the parent molecule, the risk of significant drug interactions is very low.

The approved labeling for the RLD contains information about drug/laboratory test interactions related to administration of isotopes containing iodine. If iodine containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine binding capacity of thyroid tissue may be reduced up to two weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation such as T3 resin uptake are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many drugs therefore no other pharmaceuticals should be admixed with contrast agents. The approved labeling for Omnipaque intravascular is reproduced as Table 19 below. As noted, the proposed labeling for iohexol (b) (4) oral solution will state effects may last 4 weeks which reflects the above noted publication by Padovani and the ACR Manual on Contrast Media.

Table 19: Approved Labeling for Omnipaque-Intravascular-Drug/Laboratory Interactions*

Drug/Laboratory Test Interaction:
If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2[a] weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, e.g., T3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Source: {OMNIPAQUE, 2010}

[a]Proposed labeling for Iohexol Powder for Oral Solution in Section 1.14.1.2 states 4 weeks to reflect current literature and Chapter 3 of the current ACR Manual on Contrast Media (see also Section 2.5.5.5.2){Padovani, 2012; ACR, 2012}.

* Reproduced from NDA 205383, Module 2, Section 2.5 Clinical Overview, page 21

7.6 Additional Safety Evaluations

None.

7.6.1 Human Carcinogenicity

None anticipated based on low systemic absorption after oral administration with absorption noted only in cases of bowel perforation or obstruction or severe inflammatory disease. When administered orally, all unabsorbed iohexol is eliminated in the feces and any absorbed fraction is not metabolized and is eliminated via renal excretion as iohexol.

7.6.2 Human Reproduction and Pregnancy Data

Animal studies revealed no evidence of impaired fertility or harm to the fetus. I-125 iohexol was used to study placental transfer and mammary excretion following IV administration to rats. Placental transfer in mid and late gestation was minimal. Absorption from the GI tract of suckling animals was low with concentrations of about 0.9 µg/mL measured in the blood. Iohexol was not genotoxic in a battery of genotoxicity assays. Iohexol did not show any mutagenic potential in either mice or guinea pigs. IV administration of iohexol in reproductive and developmental toxicity studies in rats and rabbits demonstrated no effect on male fertility and no embryotoxic or teratogenic potential at doses up to 4.0 gI/kg/day.

Well-controlled studies in pregnant women have not been conducted. It is not known to what extent oral iohexol is excreted in human milk after oral administration. In a published report by Nielsen 1987, (Nielsen et al. Excretion of iohexol and metrizoate in human breast milk. Acta Radiol. 1987 Sep-Oct;28(5):523-6), small amounts of iohexol were found excreted into breast milk of 6 lactating women following an IV dose of iohexol. The maximum concentration in milk was noted between 3 and 6 hours. Based on intravenous administration of 0.755 g/kg to a mother, the amount of iohexol transferred to an infant during the first 24 hours was 3.7 mg/kg or 1.7 mgI/kg, (0.5% of the maternal dose that was given). Based on low lipid soluability, the ACR estimates that less than one percent of IV administered dose of iodinated CM is excreted into breast milk in the first 24 hours with less than 0.91% absorbed by the infant. Langer 1985, (Langer et al. Absorption of nonionic contrast media after oral administration. Book Chapter in Contrast Media in Pediatric Radiology. Kaufmann, HJ. [Ed.]. 1985 p.105-6) also found less than one percent of iohexol was absorbed from the GI tract of neonates and infants.

There is one case in the published literature, (Kato et al. Apparition of iodinated contrast agents in twin neonatal gastrointestinal tracts after maternal contrast-enhanced computed tomography. Jpn J Radiol. 2011 Aug;29(7):521-3), that describes the appearance of iodinated CM in the GI tracts of twin neonates. At 36 weeks gestation,

IV iohexol 300 mgI/mL was administered as a bolus for CT examination. Radiographs of the twins were obtained to evaluate transient tachypnea. TSH hormone levels were normal for both twins at birth. Radiographs taken at 3 weeks did not show any evidence of CM in the GI tract.

7.6.3 Pediatrics and Assessment of Effects on Growth

There is no potential to affect growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

None anticipated. The dilute drug is administered as a single dose for a diagnostic radiology (CT) exam and passes unchanged through the GI tract with only minimal resorption of drug noted in instances of bowel perforation or obstruction.

The approved label for oral Omnipaque 350 references a phase 1 study in which 11 healthy male subjects were administered 150 mL of the drug. 91% (10 out of 11) experienced diarrhea and 27% (3 out of 11) experience abdominal cramping with these events noted as mild and transient but more than double that seen at the recommended doses. The rationale for this occurrence relates to larger volumes of hypertonic contrast media increasing the osmotic load in the bowel and possibly resulting in greater fluid shifts.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

8.1 120 Day Safety Update

The applicant is relying on the FDA's previous findings of safety and efficacy from approval of the reference listed drug, (RLD), Omnipaque™. It is approved in a variety of strengths for indications to include intrathecal myelography and contrast enhanced CT, intravascular administration for CT scanning of the head and body, angiocardiography, aortography, arthrography, hysterosalpingography, and voiding cystourethrography. For oral use, undiluted Omnipaque 180 to 350 mgI/mL is indicated for x-ray (pass-through) radiography exams of the GI tract and diluted solution, (6 to 21 mgI/mL), is indicated for CT of the abdomen. Generic formulations of the RLD are available in some countries. Iohexol (b) (4) oral solution is not marketed in any country.

Post marketing data and data for the 120 day safety update was derived from a literature review of published trials of orally administered iohexol in the adult and

pediatric population. The cut off date for the update was 30 April 2013. Recently published studies involving oral and intravascular administration to include studies related to contrast induced nephropathy were included in the review. The submission was also updated to include studies in which IV iohexol was used as a biomarker to measure glomerular filtration rate and animal studies. The biomarker study in healthy subjects included 35 subjects. Several GFR biomarker studies in special patient groups such as the elderly population included 2467 subjects. IMS data (IMS, 2013) estimated (b) (4) doses of Omnipaque.

No new safety concerns were identified in the review. In the interim since submission of the NDA, the applicant identified two additional studies in adults of orally administered CM with or without co-administration of IV CM. There were no new pediatric studies addressing the oral use of iohexol. Brief descriptions of these studies follow.

Kepner et al. Intravenous contrast alone vs intravenous and oral contrast computed tomography for the diagnosis of appendicitis in adult ED patients. Am J Emerg Med. 2012;30(9): 1765-73, conducted a single center study that studied adults presenting to an emergency department with suspected appendicitis. All patients received IV Omnipaque 350. 113 patients also received 1000 mL of oral Omnipague (concentration not specified). The authors concluded that CT with IV contrast alone has comparable diagnostic performance for the diagnosis of acute appendicitis to CT with oral and IV contrast. Additional value was noted for the diagnosis of acute abdomen. Adverse events were not described in the publication.

The publication by Cabarrus et al. The prevalence and patterns of intraluminal air in acute appendicitis at CT. Emerg Radiol. 2013; 20(1): 51-6, described a retrospective study to examine whether the presence or pattern of air could be used as a diagnostic or exclusion aid in the diagnosis or exclusion of acute appendicitis. 91 of 100 patients studied received oral contrast, type not specified. 92 received IV Omnipague 350. Of 100 patients in a control group, 62 received oral contrast and 95 received Omnipague 350. The authors concluded that no particular pattern or distribution of intraluminal air was helpful in differentiating a normal appendix from appendicitis. Adverse events were not assessed.

There were no new reports that described the use of oral iohexol for radiography. Several recently published studies relating to the intravascular injection of iohexol that were included which provided no new safety information.

9 Appendices

9.1 Literature Review/References

This is a 505(b)(2) submission supported by literature review of the safety and efficacy for the RLD Omnipaque. The applicant reviewed efficacy of oral use for CT and radiography exams in the adult and pediatric populations. Safety review included other routes of administration, namely intravascular (intravenous). The applicant provided a literature review of the pre clinical and clinical pharmacology studies that were used to support approval of the RLD. This reviewer referenced the articles in appropriate sections of the submission.

9.2 Labeling Recommendations

The proposed (b) (4)

9.3 Advisory Committee Meeting

None planned. .

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A STINSON
10/22/2013

ALEXANDER GOROVETS
10/22/2013

This primary clinical review is complete. Of note, (b) (4) has been rejected as this drug's trade name. The currently approved name is OralTag.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205,383 **Applicant:** Interpharma Praha, a.s. **Stamp Date:** 3-11-13

Drug Name: (b) (4) ® (iohexol) (b) (4) Oral Solution **NDA/BLA Type:** 505(b)(2); standard review

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				E CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			Abstracts only in English
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2); iohexol (Omnipaque™)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			x	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3295961

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Diagnostic imaging agent
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3295961

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	Single use for diagnostic imaging
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?			x	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _yes**_____**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Reference ID: 3295961

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Barbara A Stinson, DO	4-8-13
Reviewing Medical Officer	Date
Clinical Team Leader	Date

Reference ID: 3295961

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A STINSON
04/19/2013