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RESEARCH**

APPLICATION NUMBER:

205383Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology NDA Review	
Number	205-383, SDN 18
Type/Category	Resubmission/Class 2 / Original-1 (Type 3- New Dosage Form)
Brand (generic) Name	OralTag (Iohexol (b) (4) Oral solution)
Proposed Indication	Oraltag: <ul style="list-style-type: none"> is indicated for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis. (b) (4)
Dosage Form	(b) (4) Solution
Route of Administration	Intravenous
Dosing Regimen and Strength	Adults: 1 or 2 bottles of prepared solution (4.5 gI or 9 gI). Prepared at a concentration of 9 mgI/mL, the volume is 500 mL (1 bottle) or 1000 mL (2 bottles). Children: 1 or 2 bottles of prepared solution (4.5 gI or 9 gI). Prepared at a concentration of 9 mgI/mL, the recommended volume is (b) (4) mL to 750 mL; for neonates, infants and toddlers a lesser volume, e.g., less than (b) (4) mL up to 300 mL, may be sufficient. The total oral dose in grams of iodine should generally not exceed 1 bottle (children under 3 years of age) or 2 bottles (children 3 to 18 years of age).
Applicant	(b) (4)
OCP Division	DCP V
OND Division	DMIP
Submission Dates	September 26, 2014

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1. EXECUTIVE SUMMARY

The Applicant is seeking approval of NDA 205-383 for OralTag (Iohexol (b) (4) Oral Solution) under the 505(b)(2) regulatory pathway according to 21 CFR 314.54 as agreed to at the pre-NDA meeting held on March 20, 2012. The approved reference listed product is Omnipaque Oral Solution.

No new clinical or clinical pharmacology studies were conducted in support of this NDA submission.

An earlier submission with the same content as the current submission received a Complete Response (CR) letter on January 8, 2014 due to product quality issues. Dr. Safaa Burns reviewed the prior submission (DARRTS date of Dr. Burns' review is October 29, 2013). Dr. Burns performed a review of the package insert, however, edits to the package insert were not finalized by the Medical Division because of the decision to issue a CR letter. This reviewer has made some additions and minor edits over Dr. Burns' edits. Our recommendations for the package insert are shown in Section 3 of this review.

1.1. RECOMMENDATIONS

The application is acceptable from a clinical pharmacology perspective provided that agreement on package insert language can be reached.

1.2 POST-MARKETING COMMITMENTS AND REQUIREMENTS

None.

Signatures:

Christy S. John, Ph.D.
Reviewer
Division of Clinical Pharmacology V

Gene Williams, Ph.D.
Team Leader
Division of Clinical Pharmacology V

1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

There are no clinical pharmacology findings -- no new clinical or clinical pharmacology studies were conducted in support of this NDA submission.

2. QUESTION-BASED REVIEW

Question-based review is not applicable -- no new clinical or clinical pharmacology studies were conducted in support of this NDA submission.

3. DETAILED LABELING RECOMMENDATIONS

The entirety of the applicant's proposed package insert is appended to this review as Appendix 4.1. The changes to the clinical pharmacology related sections of the package insert are given below (**FDA Table 1.**)

FDA Table 1. Detailed Labeling Recommendations		
Approved Labeling for Omnipaque Oral Solution (Most Recent Version: May 2010)	Applicant's Proposed PLR Labeling for Iohexol ^{(b) (4)} Oral Solution	Reviewer's Revisions to Applicant's Proposed PLR Labeling
<p>Drug/Laboratory Test Interaction</p> <p>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 weeks after contrast medium administration.</p> <p>Thyroid function tests which do not depend on iodine estimation, eg, T3 resin uptake or direct thyroxine assays, are not affected.</p> <p>Many radiopaque contrast agents are incompatible <i>in vitro</i> with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.</p>	<p style="text-align: right;">^{(b) (4)}</p>	<p style="text-align: right;">^{(b) (4)}</p> <p>[entirety of section moved to Section 5.2]</p>

	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>(b) (4)</p>	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>[entirety of section deleted, not needed (b) (4)]</p> <p>[entirety of section deleted, not needed (b) (4)]</p>
<p>CLINICAL PHARMACOLOGY</p> <p>For most body cavities, the injected iohexol is absorbed into the surrounding tissue and eliminated by the kidneys and bowel as previously described in SECTION II, CLINICAL PHARMACOLOGY—</p> <p>Intravascular.</p> <p>Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.</p> <p>Orally administered iohexol is very poorly absorbed from the</p>	<p>12 CLINICAL PHARMACOLOGY</p>	<p>12 CLINICAL PHARMACOLOGY</p>

<p>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.</p> <p>Visualization of the joint spaces, uterus, fallopian tubes, peritoneal herniations, pancreatic and bile ducts, and bladder can be accomplished by direct injection of contrast medium into the region to be studied. The use of appropriate iodine concentrations assures diagnostic density.</p> <p>Orally administered OMNIPAQUE produces good visualization of the gastrointestinal tract. OMNIPAQUE is particularly useful when barium sulfate is contraindicated as in patients with suspected bowel perforation or those where aspiration of contrast medium is a possibility.</p>	<p>Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5% of the oral dose (b) (4) excreted by the kidneys. This amount may increase in the presence of bowel perforation (b) (4) bowel obstruction or severe inflammatory bowel disease. (b) (4)</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>12.1 Mechanism of Action Iohexol enhances imaging through attenuation of photons. Different tissues within the body attenuate the beam of X-rays to different degrees. The enhanced visualization is due to the iodine present in the tissue of interest.</p> <p>12.3 Pharmacokinetics 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. This amount may increase in the presence of bowel perforation, bowel obstruction, or severe inflammatory bowel disease.</p>
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	<p style="text-align: center;">(b) (4)</p> <p>IoHexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.</p>	<p>IoHexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.</p>
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4. APPENDICES

4.1 Applicant's Proposed Package Insert

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/s/

CHRISTY S JOHN
02/25/2015

GENE M WILLIAMS
02/25/2015

I concur with the recommendations.

ONDQA BIOPHARMACEUTICS REVIEW

NDA#: 205383/N-000
Submission Date: 03/11/13
Brand Name: Oraltag
Generic Name: Iohexol
Formulation: (b) (4) Oral Solution
Strength: 9.7 grams (4.5 grams of iodine)/bottle
Applicant: Otsuka
Type of submission: Original NDA (under 505(b)(2))
Reviewer: Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Iohexol is an active ingredient in the approved Omnipaque injectable injection for intravenous (IV) administration or non-sterile solution for oral or rectal administration. Omnipaque as a non-sterile oral administration is indicated for imaging procedure prior to CT for the abdomen and pelvis in adults and pediatrics.

Current Submission

Oraltag (Iohexol) (b) (4) Oral Solution was developed by Otsuka. On 03/11/13, Otsuka submitted an original NDA 205383 for Iohexol (b) (4) Oral Solution seeking approval under 505(b)(2) referencing Omnipaque Injectable Injection for oral administration. The Iohexol (b) (4) Oral Solution consists of 100% iohexol without excipients. Each bottle of drug product has a label claim of 9.7 grams of iohexol, equivalent to 4.5 grams of iodine.

No dissolution data were submitted for this is BCS Class3 (high solubility with low permeability) drug substance. The Applicant also submitted in this NDA:

- 1). A biowaiver request for waiving the *in vivo* BE (bioequivalence) or BA (Bioavailability).
- 2). *In vitro* stability testings for Oraltag oral solutions mixed with various beverages/drinks.

On 10/28/13, the FDA sent an information request (IR) letter to the Applicant on CMC issues and on 11/04/13, a teleconference was held to discuss the CMC topics raised in the FDA's 10/28/13 IR letter. On 11/08/13, FDA reviewed and responded to the Applicant's questions regarding CMC issues submitted on 11/06/13.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of the Biowaiver request and the *in vitro* stability data of the oral solution mixed with various beverages/drinks.

The biowaiver request and the *in vitro* stability testings of Oraltag (iohexol) oral solution are reviewed and found acceptable.

Note: No biopharmaceutics related issues were raised in

- 1). FDA’s 10/28/13 IR letter,
- 2). Teleconference dated 11//04/13,
- 3). In the Applicant’s questions submitted on 11/06/13 or
- 4). FDA’s responses on 11/08/13.

Please see the MM of 11/04/13 teleconference and the FDA’s 11/08/13 responses for details.

RECOMMENDATION

Based on overall information available, it is not anticipated that the proposed contrast agent product (Oraltag oral solution) will have different efficacy and safety profiles from the reference product (Omnipaque oral solution) as a single use oral contrast agent. Therefore, from the Biopharmaceutics perspective, this NDA filed under 505(b)(2) is recommended for approval.

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

10/09/13
Date

Tapash Ghosh, Ph.D.
ONDQA Biopharmaceutics Team Leader

10/09/13
Date

CC: DARRTS/NDA No.205383/N000/RLostritto

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Iohexol is an active ingredient in the approved Omnipaque injectable injection for intravenous (IV) administration or solution for oral or rectal administration. Omnipaque as a non-sterile solution for oral administration is indicated for imaging procedure prior to CT for the abdomen and pelvis in adults and pediatrics. Oraltag (Iohexol) (b) (4) Oral Solution (b) (4) Otsuka.

CURRENT SUBMISSION

On 03/11/13, Otsuka submitted an original NDA 205383 for Iohexol (b) (4) Oral Solution seeking approval under 505(b)(2) referencing Omnipaque as a non-sterile oral administration for imaging procedure prior to CT for the abdomen and pelvis in adults and pediatrics. The Iohexol (b) (4) Oral Solution consists of 100% iohexol without excipients. Each bottle of drug product has a label claim of 9.7 grams of iohexol, equivalent to 4.5 grams of iodine. No dissolution development report nor dissolution data were submitted for Iohexol is a BCS Class3 (high solubility with low permeability) drug substance. The Applicant also submitted in this NDA:

- 1). A biowaiver request for waiving the *in vivo* BE (bioequivalence) or BA (Bioavailability).
- 2). *In vitro* stability testings for Oraltag oral solutions mixed with various beverages/drinks.

On 10/28/13, FDA sent an information request (IR) letter to the Applicant on CMC issues and on 11/04/13, a teleconference was held to discuss the CMC topics raised in the FDA's 10/28/13 IR letter. On 11/08/13, FDA reviewed and responded to the Applicant's questions regarding CMC issues submitted on 11/06/13. Please see the MM of 11/04/13 teleconference and the FDA's 11/08/13 responses for details.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the biowaiver request and the *in vitro* stability data/results of the oral solution mixed with various beverages/drinks.

It is the same as the approved product, Omnipaque IV solution for oral administration (the reference product) in terms of the same active drug ingredient in the same concentration and dosage form except that Omnipaque oral solution contains minor inactive ingredients, like EDTA and tromethamine (b) (4)

FORMULATION DEVELOPMENT

Iohexol belongs to the BCS Class3 drug substance, based on its high solubility, namely one unit dose dissolves in a volume of less than one-tenth of 250 mL of water in the pH range tested (pH 1 to 7.5) as shown below.

Table 1. The Solubility of Iohexol (b) (4) Oral Solution

pH of USP Buffer	Volume Required to Dissolve One Dosage Unit ^a
1.2	15.5 mL
2.0	18.5 mL
4.1	24.5 mL
5.5	24.5 mL
7.6 ^b	24.5 mL

^a Volume of buffer required to dissolve 9.7 g (single dose) of iohexol at 37°C ± 1°C.

^b Of the options of standard USP buffers of higher pH (acetate buffers 7.4 or 7.6) that could be used for the high end (pH 7.5) of the pH range proposed in the FDA BCS Guidance noted above, the standard USP acetate buffer pH 7.6 was selected for the study.

Its has low permeability, as reported in the literature for insignificant systemic absorption following oral administration in humans (0.5% or less of the dose based on renal excretion data, as reported in the approved prescribing information for the listed drug.

The drug product is simply the drug substance packaged in a beverage bottle. (b) (4)

(b) (4)
Oral Solution has a label claim of 9.7 grams of iohexol, equivalent to 4.5 grams of iodine/bottle. It can be easily constituted with water or a beverage of choice for oral administration at the prescribed volume or concentration for each patient.

The amount of iohexol, 9.7 g, was selected to allow convenient preparation of the standard concentration of 9 mgI/mL of iodine and volume of 500 mL and also allows other standard concentrations (12, 15, 18 and 21 mgI/mL) to be prepared by filling to the indicated fill line on the bottle.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

No formulation or other modification to the drug substance is required for Iohexol is very soluble in water (BCS Class3). Thus, no dissolution method/data are needed for this is an oral solution product.

In vitro Stability Testing in Various Beverages/Drinks:

The Applicant tested the *in vitro* stability of the Iohexol (b) (4) oral solution when mixed with various beverage/drinks. The results of solution properties all show similar between Oraltag and Ominpaque oral solutions (prepared from Omniague injectable injection). It should be noted that the Oraltag oral solution and its mixing with various beverages is to be prepared (b) (4) prior to performing the CT test in the lab. Please see Appendix for *In vitro* study results for details.

Reviewer's Comments

1. According to CFR 320.22 for Criteria for waiver of evidence of *in vivo* bioavailability or bioequivalence, it is stated if an oral solution contains an active drug ingredient in the same concentration and dosage form as an approved product and contains no inactive ingredient or other change in the formulation that may significantly affect systemic or local availability for products intended to act locally, a biowaiver can be granted for the proposed product.

There were some inactive ingredients, like EDTA or tromethamine, (b) (4)
(b) (4) in the reference product (Omnipaque) (b) (4); however, these minor differences do not seem to have any biological consequence when the product is reconstituted with large volume of aqueous vehicle during ingestion as an oral solution.

2. Similar *in vitro* product quality data, e.g., osmolality, viscosity, stability data after mixing with various sport drinks, etc. were reported by the sponsor as expected based on the similarities in the formulations of the proposed product (Oraltag) with the reference product Omnipaque when both are reconstituted as an oral solution. The *in vitro* stability studies were reviewed and found acceptable.
3. Based on overall information available, it is not anticipated that the proposed contrast agent product (Oraltag oral solution) will have different efficacy and safety profiles from the reference product (Omnipaque oral solution) as a single use oral contrast agent. Therefore, from the Biopharmaceutics perspective, this NDA filed under 505(b)(2) is recommended for approval.
4. No Biopharmaceutics related issues were raised in
 - 1). FDA's 10/28/13 IR letter,
 - 2). Teleconference dated 11//04/13,
 - 3). In the Applicant's questions submitted on 11/06/13 or
 - 4). FDA's responses on 11/08/13.

Please see the MM of 11/04/13 teleconference and the FDA's 11/08/13 responses for details.

NDA 205383 For Oraltag (Iohexol)
Oral Solution

(b) (4)

Appendix

**Summary Data of *In Vitro* Stability
Testing**

Table 6: Solubility of Iohexol Powder DP in diluents

Sample	Diluent	Bottle Id	pH before/after Iohexol addition (-)	Total volume added (mL)	Dissolution time (min)
Iohexol (b) (4) Oral Solution	Tap water ¹	829	7.18/7.36	18.5	4
		841	7.18/7.37	18.5	4
		876	7.18/7.36	18.5	4
	Apple juice	390	3.45/3.45	21.5	5
		534	3.45/3.44	21.5	5
		540	3.45/3.45	21.5	5
	Sprite ²	636	3.34/3.27	24.5	6
		648	3.34/3.25	24.5	6
		660	3.34/3.26	24.5	6
	Gatorade™	870	3.12/3.08	21.5	5
		887	3.12/3.07	21.5	5
		900	3.12/3.08	21.5	5
	Enfamil™	538	6.66/6.69	12.5	4
644		6.66/6.76	12.5	4	
645		6.66/6.75	12.5	4	

Comparisons in Viscosity

Table 7: Viscosity I – Solutions of Iohexol Powder

Sample	Diluent	Viscosity (mm ² /s)		Viscosity (mPa [•] s)	RSD (%)
		Measurement	Mean		
Iohexol (b) (4) Oral Solution	Tap water	0.9893	0.9874	0.989	0.19
		0.9874			
		0.9856			
	Apple juice	1.1829	1.1874	1.231	0.34
		1.1887			
		1.1907			
	Sprite	1.2050	1.2058	1.258	0.10
		1.2052			
		1.2072			
	Gatorade™	1.1302	1.1300	1.163	0.01
		1.1301			
		1.1299			
	Enfamil™	1.6440	1.6449	1.710	0.05
		1.6455			
		1.6452			

Table 8: Viscosity II – Dilutions of Omnipaque

Sample	Diluent	Viscosity (mm ² /s)		Viscosity (mPa [•] s)	RSD (%)
		Measurement	Mean		
Omnipaque™ (iohexol) Injection, 300 mg I/mL	Tap water	0.9884	0.9817	0.984	0.59
		0.9786			
		0.9780			
	Apple juice	1.2252	1.2261	1.271	0.10
		1.2255			
		1.2275			
	Sprite	1.2314	1.2321	1.286	0.05
		1.2324			
		1.2324			
	Gatorade™	1.1477	1.1483	1.182	0.05
		1.1486			
		1.1487			
	Enfamil™	1.6827	1.6830	1.750	0.02
		1.6828			
		1.6834			

Comparisons in Osmolality

Table 9: Osmolality I – Solutions of Iohexol Powder

	Iohexol ^{(b) (4)} Oral Solution				
	Diluent				
Measurement (osmol/kg)	Tap water	Apple juice	Sprite	Gatorade™	Enfamil™
1	0.030	0.766	0.466	0.286	0.391
2	0.029	0.755	0.448	0.230	0.366
Average	0.030	0.761	0.457	0.258	0.379
Rel. difference (%)	2	1	2	11	3

Table 10: Osmolality II – Dilutions of Omnipaque

	Omnipaque™ (iohexol) Injection, 300 mg I/mL				
	Diluent				
Measurement (osmol/kg)	Tap water	Apple juice	Sprite	Gatorade™	Enfamil™
1	0.030	0.729	0.451	0.306	0.378
2	0.030	0.739	0.431	0.283	0.310
Average	0.030	0.734	0.441	0.295	0.344
Rel. difference (%)	0	1	2	4	10

Comparisons in Density

Table 11: Density I – Solutions of Iohexol Powder

	Iohexol ^{(b) (4)} Oral Solution				
	Diluent				
Measurement (g/cm ³)	Tap water	Apple juice	Sprite	Gatorade™	Enfamil™
1	1.00782	1.05420	1.05019	1.03333	1.04102
2	1.00827	1.05340	1.04964	1.03583	1.04083
Average	1.00804	1.05380	1.04992	1.03458	1.04092
Rel. difference (%)	0.02	0.04	0.03	0.12	0.01

Table 12: Density II – Dilutions of Omnipaque

	Omnipaque™ (iohexol) Injection, 300 mg I/mL				
	Diluent				
Measurement (g/cm ³)	Tap water	Apple juice	Sprite	Gatorade™	Enfamil™
1	1.00806	1.04820	1.04772	1.03636	1.03912
2	1.00824	1.05277	1.04629	1.03413	1.04077
Average	1.00815	1.05049	1.04700	1.03525	1.03994
Rel. difference (%)	0.01	0.22	0.07	0.11	0.08

Stability Comparisons in Tap Water mixed with SGF

Table 13: Stability of solutions of Iohexol Powder DP in tap water mixed with SGF

Diluent	Tap water				
Buffer	Simulated gastric fluid				
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.38	19.37	100.0	100.0
	2	19.35		100.0	
30	1	19.47	19.35	100.4	99.9
	2	19.23		99.4	
60	1	19.32	19.20	99.7	99.2
	2	19.09		98.6	
90	1	19.43	19.31	100.3	99.7
	2	19.20		99.2	

Table 23: Stability of solutions of Omnipaque™ (iohexol) Injection in tap water mixed with SGF

Diluent	Tap water				
Buffer	Simulated gastric fluid				
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.40	19.31	100.0	100.0
	2	19.22		100.0	
30	1	19.56	19.53	100.8	101.1
	2	19.49		101.4	
60	1	19.38	19.20	99.9	99.4
	2	19.01		98.9	
90	1	19.20	19.06	99.0	98.7
	2	18.92		98.4	

Stability Comparisons in Apple Juice mixed with SGF

Table 14: Stability of solutions of Iohexol Powder DP in Apple juice mixed with SGF

Diluent	Apple juice				
Buffer	Simulated gastric fluid				
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.15	19.01	100.0	100.0
	2	18.86		100.0	
30	1	19.00	19.07	99.2	100.3
	2	19.13		101.4	
60	1	19.06	18.96	99.6	99.7
	2	18.85		99.9	
90	1	18.88	18.88	98.6	99.3
	2	18.88		100.1	

Table 24: Stability of solutions of Omnipaque™ (iohexol) Injection in Apple juice mixed with SGF

Diluent	Apple juice				
Buffer	Simulated gastric fluid				
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	18.88	18.87	100.0	100.0
	2	18.86		100.0	
30	1	18.86	18.96	99.9	100.5
	2	19.07		101.1	
60	1	18.89	18.92	100.0	100.2
	2	18.95		100.4	
90	1	18.91	18.94	100.1	100.3
	2	18.97		100.6	

Stability Comparisons in Sprite mixed with SGF

Table 15: Stability of solutions of Iohexol Powder DP in Sprite™ mixed with SGF

Diluent		Sprite™			
Buffer		Simulated gastric fluid			
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.29	19.37	100.0	100.0
	2	19.46		100.0	
30	1	19.27	19.26	99.9	99.4
	2	19.24		98.9	
60	1	19.26	19.33	99.8	99.8
	2	19.40		99.7	
90	1	19.16	19.21	99.3	99.2
	2	19.27		99.0	

Table 25: Stability of solutions of Omnipaque™ (iohexol) Injection in Sprite™ mixed with SGF

Diluent		Sprite™			
Buffer		Simulated gastric fluid			
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.23	19.21	100.0	100.0
	2	19.19		100.0	
30	1	19.40	19.41	100.9	101.0
	2	19.41		101.1	
60	1	19.61	19.38	102.0	100.9
	2	19.16		99.8	
90	1	19.33	19.29	100.6	100.4
	2	19.25		100.3	

Stability Comparisons in Gatorade mixed with SGF

Table 16: Stability of solutions of Iohexol Powder DP in Gatorade™ mixed with SGF

Diluent		Gatorade™			
Buffer		Simulated gastric fluid			
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.42	19.42	100.0	100.0
	2	19.43		100.0	
30	1	19.21	19.30	98.9	99.4
	2	19.39		99.8	
60	1	19.22	19.35	99.0	99.6
	2	19.49		100.3	
90	1	19.60	19.53	100.9	100.5
	2	19.46		100.2	

Table 26: Stability of solutions of Omnipaque™ (iohexol) Injection in Gatorade™ mixed with SGF

Diluent		Gatorade™			
Buffer		Simulated gastric fluid			
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.14	19.13	100.0	100.0
	2	19.12		100.0	
30	1	19.09	19.07	99.8	99.7
	2	19.05		99.6	
60	1	19.22	19.15	100.4	100.1
	2	19.08		99.8	
90	1	19.20	19.20	100.3	100.3
	2	19.20		100.4	

Stability Comparisons in Enfamil mixed with SGF

Table 17: Stability of solutions of Iohexol Powder DP in EnfamilTM mixed with SGF

Diluent		Enfamil TM			
Buffer		Simulated gastric fluid			
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.42	19.35	100.0	100.0
	2	19.27		100.0	
30	1	19.34	19.30	99.6	99.8
	2	19.27		100.0	
60	1	19.37	19.21	99.7	99.3
	2	19.04		98.8	
90	1	19.39	19.30	99.8	99.8
	2	19.22		99.7	

Table 27: Stability of solutions of OmnipaqueTM (iohexol) Injection in EnfamilTM mixed with SGF

Diluent		Enfamil TM			
Buffer		Simulated gastric fluid			
Storage time (min)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.48	19.34	100.0	100.0
	2	19.20		100.0	
30	1	19.38	19.23	99.5	99.4
	2	19.07		99.4	
60	1	19.60	19.32	100.6	99.9
	2	19.04		99.2	
90	1	19.65	19.37	100.9	100.1
	2	19.09		99.4	

Stability Comparisons in Tap Water mixed with SIF

Table 18: Stability of solutions of Iohexol Powder DP in tap water mixed with SIF

Diluent		Tap water			
Buffer		Simulated intestinal fluid			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.18	19.36	100.0	100.0
	2	19.55		100.0	
1	1	19.29	19.37	100.6	100.0
	2	19.44		99.4	
2	1	19.33	19.40	100.8	100.2
	2	19.46		99.5	
3	1	19.34	19.43	100.8	100.4
	2	19.53		99.9	

Table 28: Stability of solutions of OmnipaqueTM (iohexol) Injection in tap water mixed with SIF

Diluent		Tap water			
Buffer		Simulated intestinal fluid			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.34	19.41	100.0	100.0
	2	19.47		100.0	
1	1	19.62	19.64	101.5	101.2
	2	19.66		100.9	
2	1	19.64	19.60	101.6	101.0
	2	19.56		100.4	
3	1	19.40	19.46	100.3	100.3
	2	19.52		100.2	

Stability Comparisons in Apple Juice mixed with SIF

Table 19: Stability of solutions of Iohexol Powder DP in Apple juice mixed with SIF

Diluent	Apple juice				
Buffer	Simulated intestinal fluid				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t=0)	Average IOH content (% rel. to t=0)
0	1	19.01	19.95	100.0	100.0
	2	20.88		100.0	
1	1	19.15	19.97	100.8	100.2
	2	20.80		99.6	
2	1	19.23	20.01	101.2	100.3
	2	20.78		99.5	
3	1	19.22	19.97	101.1	100.2
	2	20.73		99.3	

Table 29: Stability of solutions of Omnipaque™ (iohexol) Injection in Apple juice mixed with SIF

Diluent	Apple juice				
Buffer	Simulated intestinal fluid				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t=0)	Average IOH content (% rel. to t=0)
0	1	19.13	19.27	100.0	100.0
	2	19.41		100.0	
1	1	19.28	19.37	100.8	100.5
	2	19.46		100.2	
2	1	19.29	19.31	100.8	100.2
	2	19.33		99.6	
3	1	19.37	19.26	101.3	99.9
	2	19.15		98.6	

Stability Comparisons in Sprite mixed with SIF

Table 20: Stability of solutions of Iohexol Powder DP in Sprite™ mixed with SIF

Diluent	Sprite™				
Buffer	Simulated intestinal fluid				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t=0)	Average IOH content (% rel. to t=0)
0	1	19.05	19.14	100.0	100.0
	2	19.23		100.0	
1	1	18.98	19.11	99.6	99.9
	2	19.25		100.1	
2	1	19.37	19.35	101.7	101.1
	2	19.32		100.5	
3	1	19.15	19.22	100.5	100.4
	2	19.29		100.3	

Table 30: Stability of solutions of Omnipaque™ (iohexol) Injection in Sprite™ mixed with SIF

Diluent	Sprite™				
Buffer	Simulated intestinal fluid				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t=0)	Average IOH content (% rel. to t=0)
0	1	19.43	19.51	100.0	100.0
	2	19.58		100.0	
1	1	19.44	19.55	100.0	100.2
	2	19.65		100.3	
2	1	19.61	19.58	100.9	100.4
	2	19.55		99.8	
3	1	19.69	19.77	101.3	101.3
	2	19.85		101.4	

Stability Comparisons in Gatorade mixed with SIF

Table 21: Stability of solutions of Iohexol Powder DP in Gatorade™ mixed with SIF

Diluent		Gatorade™			
Buffer		Simulated intestinal fluid			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	18.96	19.06	100.0	100.0
	2	19.16		100.0	
1	1	18.87	19.25	99.5	101.0
	2	19.64		102.5	
2	1	19.25	19.30	101.6	101.2
	2	19.35		100.9	
3	1	18.98	19.08	100.1	100.1
	2	19.18		100.1	

Table 31: Stability of solutions of Omnipaque™ (iohexol) Injection in Gatorade™ mixed with SIF

Diluent		Gatorade™			
Buffer		Simulated intestinal fluid			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.07	19.21	100.0	100.0
	2	19.34		100.0	
1	1	19.18	19.08	100.6	99.4
	2	18.98		98.2	
2	1	20.08	20.03	105.3	104.3
	2	19.98		103.3	
3	1	20.72	20.15	108.6	104.9
	2	19.58		101.2	

Comparisons of Stability in Enfamil mixed with SIF

Table 22: Stability of solutions of Iohexol Powder DP in Enfamil™ mixed with SIF

Diluent		Enfamil™			
Buffer		Simulated intestinal fluid			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.35	19.15	100.0	100.0
	2	18.94		100.0	
1	1	19.19	19.17	99.2	100.1
	2	19.16		101.1	
2	1	18.97	19.01	98.1	99.3
	2	19.05		100.5	
3	1	18.85	18.89	97.4	98.7
	2	18.93		99.9	

Table 32: Stability of solutions of Omnipaque™ (iohexol) Injection in Enfamil™ mixed with SIF

Diluent		Enfamil™			
Buffer		Simulated intestinal fluid			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.99	19.61	100.0	100.0
	2	19.24		100.0	
1	1	19.05	19.01	95.3	96.9
	2	18.97		98.6	
2	1	19.80	19.50	99.1	99.4
	2	19.20		99.8	
3	1	19.36	19.86	96.9	101.3
	2	20.35		105.8	

Storage Stability of Solution in Tap Water in Room Temp.

Table 33: Room temperature storage stability of solutions of Iohexol Powder DP in tap water

Diluent	Tap water				
Condition	Room temperature				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.26	19.31	100.0	100.0
	2	19.36		100.0	
24	1	19.29	19.16	100.1	99.3
	2	19.04		98.4	
48	1	19.05	18.98	98.9	98.3
	2	18.91		97.7	
72	1	19.29	19.21	100.1	99.5
	2	19.13		98.8	

Table 39: Room temperature storage stability of solutions of Omnipaque™ (iohexol) Injection in tap water

Diluent	Tap water				
Condition	Room temperature				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.33	19.27	100.0	100.0
	2	19.22		100.0	
24	1	19.26	19.25	99.7	99.9
	2	19.24		100.1	
48	1	19.50	19.46	100.9	101.0
	2	19.43		101.1	
72	1	19.44	19.37	100.6	100.5
	2	19.29		100.4	

Storage Stability of Solution in Tap Water in Refrigerator

Table 34: Refrigerator storage stability of solutions of Iohexol Powder DP in in tap water

Diluent	Tap water				
Condition	Refrigerator				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.26	19.31	100.0	100.0
	2	19.36		100.0	
24	1	19.36	18.66	100.5	96.7
	2	17.97		92.8	
48	1	19.15	19.05	99.4	98.7
	2	18.94		97.9	
72	1	19.38	19.28	100.6	99.9
	2	19.19		99.1	

Table 34: Refrigerator storage stability of solutions of Iohexol Powder DP in in tap water

Diluent	Tap water				
Condition	Refrigerator				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.26	19.31	100.0	100.0
	2	19.36		100.0	
24	1	19.36	18.66	100.5	96.7
	2	17.97		92.8	
48	1	19.15	19.05	99.4	98.7
	2	18.94		97.9	
72	1	19.38	19.28	100.6	99.9
	2	19.19		99.1	

Storage Stability of Solution in Apple Juice in Room Temp.

Table 35: Room temperature storage stability of solutions of Iohexol Powder DP in Apple juice

Diluent	Apple juice				
Condition	Room temperature				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	18.85	18.94	100.0	100.0
	2	19.03		100.0	
24	1	18.99	18.92	100.7	99.9
	2	18.84		99.0	
48	1	19.06	18.96	101.1	100.1
	2	18.85		99.1	
72	1	18.94	18.88	100.4	99.7
	2	18.83		98.9	

Table 41: Room temperature storage stability of solutions of Omnipaque™ (iohexol) Injection in Apple juice

Diluent	Apple juice				
Condition	Room temperature				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.14	19.13	100.0	100.0
	2	19.12		100.0	
24	1	19.27	19.31	100.6	100.9
	2	19.35		101.2	
48	1	19.45	19.33	101.6	101.0
	2	19.21		100.4	
72	1	19.15	19.18	100.0	100.2
	2	19.21		100.4	

Storage Stability of Solution in Apple Juice in Refrigerator

Table 36: Refrigerator storage stability of solutions of Iohexol Powder DP in Apple juice

Diluent	Apple juice				
Condition	Refrigerator				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	18.85	18.94	100.0	100.0
	2	19.03		100.0	
24	1	19.10	18.95	101.3	100.1
	2	18.81		98.9	
48	1	19.34	19.16	102.6	101.1
	2	18.97		99.7	
72	1	19.03	18.90	100.9	99.8
	2	18.77		98.7	

Table 42: Refrigerator storage stability of solutions of Omnipaque™ (iohexol) Injection in Apple juice

Diluent	Apple juice				
Condition	Refrigerator				
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.14	19.13	100.0	100.0
	2	19.12		100.0	
24	1	19.44	19.42	101.6	101.5
	2	19.39		101.4	
48	1	19.15	19.09	100.0	99.8
	2	19.04		99.5	
72	1	19.34	19.30	101.0	100.9
	2	19.26		100.7	

Storage Stability of Solution in Gatorade in Room Temp.

Table 37: Room temperature storage stability of solutions of Iohexol Powder DP in Gatorade™

Diluent		Gatorade™			
Condition		Room temperature			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.51	19.32	100.0	100.0
	2	19.14		100.0	
24	1	19.02	19.05	97.5	98.6
	2	19.08		99.7	
48	1	18.89	18.87	96.8	97.7
	2	18.86		98.5	
72	1	19.19	19.12	98.4	99.0
	2	19.05		99.5	

Table 43: Room temperature storage stability of solutions of Omnipaque™ (iohexol) Injection in Gatorade™

Diluent		Gatorade™			
Condition		Room temperature			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.28	19.31	100.0	100.0
	2	19.34		100.0	
24	1	19.59	19.60	101.6	101.5
	2	19.60		101.4	
48	1	19.37	19.38	100.5	100.4
	2	19.39		100.3	
72	1	19.30	19.31	100.1	100.0
	2	19.32		99.9	

Storage Stability of Solution in Gatorade in Refrigerator

Table 38: Refrigerator storage stability of solutions of Iohexol Powder DP in Gatorade™

Diluent		Gatorade™			
Condition		Refrigerator			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.51	19.32	100.0	100.0
	2	19.14		100.0	
24	1	19.40	19.24	99.4	99.5
	2	19.07		99.6	
48	1	19.20	19.08	98.4	98.7
	2	18.96		99.1	
72	1	19.25	19.14	98.6	99.0
	2	19.03		99.4	

Table 44: Refrigerator storage stability of solutions of Omnipaque™ (iohexol) Injection in Gatorade™

Diluent		Gatorade™			
Condition		Refrigerator			
Storage time (hod)	Measurement	IOH Content (mg/mL)	Average IOH content (mg/mL)	IOH content (% rel. to t = 0)	Average IOH content (% rel. to t = 0)
0	1	19.28	19.31	100.0	100.0
	2	19.34		100.0	
24	1	19.40	19.50	100.6	101.0
	2	19.60		101.3	
48	1	18.88	19.11	98.0	99.0
	2	19.34		100.0	
72	1	19.31	19.31	100.2	100.0
	2	19.31		99.8	

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/s/

TIEN MIEN CHEN
12/05/2013

TAPASH K GHOSH
12/05/2013

CLINICAL PHARMACOLOGY REVIEW

SUBMISSION	NDA 205383/S-000/SDN 1
BRAND NAME	(b) (4)
GENERIC NAME	Iohexol (b) (4) Oral Solution
DOSAGE FORMS	(b) (4) oral solution (9-21 mgI/mL) (mgI = mg Iodine)
INDICATIONS	As an opacification agent during computed tomography of the abdomen and pelvis and adults and children
SUBMISSION DATE	March 11, 2013
SUBMISSION TYPE	Original-1 (Type 5- New Formulation or New Manufacturer)
APPLICANT	Interpharma Praha A S
OND DIVISION	Division of Medical Imaging Drug Products
OCP DIVISION	Division of Clinical Pharmacology 5
OCP REVIEWER	Safaa Burns, Ph.D.
OCP TEAM LEADER	Gene Williams, Ph.D.

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1. EXECUTIVE SUMMARY

The Applicant is seeking approval of NDA 205383/S-000 for (b) (4) (Iohexol (b) (4) Oral Solution) under the 505(b)(2) regulatory pathway according to 21 CFR 314.54 as agreed at the pre-NDA meeting held on March 20, 2012.

No **new clinical** or **clinical pharmacology studies** have been conducted in support of this NDA submission. The NDA relies on published data for the approved product, Omnipaque.is a liquid approved for oral as well as intravenous administration.

The applicant is seeking a waiver (a "biowaiver") of the requirement for measuring *in vivo* bioavailability or demonstrating *in vivo* bioequivalence with the new drug product. The waiver request will be reviewed by the Office of New Drug Product Quality (ONDQA).

1.1 RECOMMENDATIONS

The application is acceptable from a clinical pharmacology perspective provided that the applicant incorporate our revisions to their proposed PLR labeling as detailed in Section 3 **DETAILED CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS** of this review.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

There are no clinical pharmacology findings -- no **clinical** or **clinical pharmacology studies** have been conducted in support of this 505(b)(2) NDA submission.

Omnipaque is marketed as a liquid and with varied formulation strengths. The current NDA submission is for a powder used exclusively to prepare a solution for oral use. The prepared oral solution is used as an opacification agent during computed tomography (CT) for visualization of the abdomen or pelvis. This therapeutic use as an oral contrast agent requires the drug to be present in the gastrointestinal (GI) tract. Hence systemic bioavailability following oral administration is not a prerequisite for the drug's therapeutic indication for CT imaging of the abdomen, GI lumen and surrounding structures.

To support the current NDA submission, the Applicant has submitted published data on the **oral administration** of already 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 has also submitted published data on **intravenously (IV) administered** iohexol including PK studies in healthy volunteers, studies in patients with renal impairment studies and a study in lactating women to estimate the amount of iohexol excreted into breast milk. (b) (4)

These studies were not reviewed because this 505(b)(2) application is for an indication already approved for Omnipaque, and as the studies did not use the applicant's product, they in no way allow for distinguishing differences between the applicant's product and Omnipaque.

2. QUESTION BASED REVIEW

Refer to the original Omnipaque NDA 18-956 submission.

3. DETAILED CLINICAL PHARMACOLOGY LABELING RECOMMENDATIONS

The reviewer's recommendations for edits to portions of Sections **HIGHLIGHTS OF PRESCRIBING INFORMATION -- USE IN SPECIFIC POPULATIONS, 5 WARNINGS AND PRECAUTIONS, 7 DRUG INTERACTIONS, 8 USE IN SPECIFIC POPULATIONS** and **12 CLINICAL PHARMACOLOGY** begin on the next page. The applicant's entire proposed package insert is included as **Appendix 4.1**.

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/s/

SAFAA BURNS
10/29/2013

GENE M WILLIAMS
10/29/2013

**CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST
FOR NDA/BLA or SUPPLEMENT**

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	205383 (SDN 1)		Brand Name	(b) (4)
OCPB Division (I, II, III)	DCP V		Generic Name	Iohexol
Medical Division	DMIP		Drug Class	Mineral
OCP Reviewer	Safaa Burns		Indication(s)	For oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis. (b) (4)
OCP Team Leader	Gene Williams		Dosage Forms	(b) (4) Oral Solution
			Dosing Regimen	Adults: Single dose of 1 or 2 bottles of prepared solution (4.5 g I or 9 g I). Children: Single dose. Total dose for children under 3 years of age should generally not exceed (b) (4)g of I and for children from 3 to 18 years of age should not exceed (b) (4) g I.
Date of Submission	March 11, 2013		Route of Administration	Oral
Estimated Due Date of OCP Review	August 1, 2013		Sponsor	Otsuka
PDUFA Due Date	January 11, 2014		Priority Classification	505(b)2
Division Due Date	November 11, 2013			
<u>Clin. Pharm. and Biopharm. Information</u>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			

Labeling	X			
Reference Bioanalytical and Analytical Methods		0	0	
I. Clinical Pharmacology		0	0	
Mass balance:		0	0	
Isozyme characterization:		0	0	
Blood/plasma ratio:		0	0	
Plasma protein binding:		0	0	
Pharmacokinetics (e.g., Phase I)		0	0	
- <i>Healthy Volunteers-</i>		0	0	
single dose:		0	0	
multiple dose:		0	0	
- <i>Patients-</i>		0	0	
single dose:		0	0	
multiple dose:		0	0	
Dose proportionality -		0	0	
fasting / non-fasting single dose:		0	0	
fasting / non-fasting multiple dose:		0	0	
Drug-drug interaction studies -		0	0	
In-vivo effects on primary drug:		0	0	
In-vivo effects of primary drug:		0	0	
In-vitro:		0	0	
Subpopulation studies -		0	0	
ethnicity:		0	0	
gender:		0	0	
pediatrics:		0	0	
geriatrics:		0	0	
renal impairment:		0	0	
hepatic impairment:		0	0	
PD:		0	0	
Phase 2:		0	0	
Phase 3:		0	0	
PK/PD:		0	0	
Phase 1 and/or 2, proof of concept:		0	0	
Phase 3 clinical trial:		0	0	
Population Analyses -		0	0	
Data rich:		0	0	
Data sparse:		0	0	
II. Biopharmaceutics		0	0	
Absolute bioavailability:		0	0	
Relative bioavailability -		0	0	
solution as reference:		0	0	

alternate formulation as reference:		0	0	
Bioequivalence studies -		0	0	
traditional design; single / multi dose:		0	0	
replicate design; single / multi dose:		0	0	
Food-drug interaction studies:		0	0	
Dissolution:		0	0	
(IVIVC):		0	0	
Bio-wavier request based on BCS		0	0	
BCS class		0	0	
III. Other CPB Studies		0	0	
Genotype/phenotype studies:		0	0	
Chronopharmacokinetics		0	0	
Pediatric development plan		0	0	
Literature References		24	0	
Total Number of Studies		0	0	
Filability and QBR comments				
	“X” if yes	Comments		
Application filable?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable)		
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	None			
Other comments or information not included above	No clinical studies have been conducted in support of this application. The NDA relies on the pharmacokinetic (PK) data supporting the approval of OMNIPAQUE. The applicant has requested a waiver from the requirement to submit evidence measuring the <i>in vivo</i> bioavailability or demonstrating the <i>in vivo</i> bioequivalence of the proposed new drug product, consistent with 21 CFR 320.21. The waiver request will be reviewed by the biopharmaceutics group within the Office of ONDQA.			
Primary reviewer Signature and Date	Safaa Burns			
Secondary reviewer Signature and Date	Gene Williams			

CC: DARRTS (Electronic Entry), DMIP (James Moore), HFD-860 (Williams, Booth, Rahman)

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/s/

SAFAA BURNS
04/24/2013

GENE M WILLIAMS
04/24/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205383
Product name, generic name of the active, and dosage form and strength	(b) (4) Iohexol, (b) (4) Oral Solution, 9.7 grams
Submission date	03/11/13
Applicant	Otsuka
Medical Division	Medical Imaging
Type of Submission	Original, 505(b)(2)
Biopharmaceutics Reviewer	Tien-Mien Chen, Ph.D.
Biopharmaceutics Lead	Angelica Dorantes, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	Iohexol is reportedly dissolved rapidly in water (<250 mL) over the pH 1.2- 7.5 (BCS Class 3).
2.	Is the dissolution test part of the DP specifications?		X	
3.	Does the application contain the dissolution method development report?		X	
4.	Is there a validation package for the analytical method and dissolution methodology?		X	
5.	Does the application include a biowaiver request?	X		Module 1, Section 1.12.15 Request for Waiver of In Vivo Bioavailability and Bioequivalence Studies
6.	Does the application include an IVIVC model?		X	
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

8.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	No PK or clinical studies conducted or submitted.
B. filing conclusion				
	Parameter	Yes	No	Comment
9.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		➤ The NDA is filable from Biopharmaceutics Perspective
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
12.	Are there any potential review issues identified?		X	
13.	The submitted information supporting the biowaiver request needs to be reviewed. The submitted <i>in vitro</i> stability data for Iohexol in other beverages prior to oral administration needs to be reviewed.			

{See appended electronic signature page}

Tien-Mien Chen, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

04/16/13
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader

04/16/13
Date

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

Office of New Drug Quality Assessment

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/s/

TIEN MIEN CHEN
04/16/2013

ANGELICA DORANTES
04/17/2013