

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205383Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 205383**

**Reviewer: Sally Hargus, PhD; DMIP**

**Supervisor: Adebayo Lanionu, PhD; DMIP**

**NDA Number: 205383**

**Applicant: Otsuka, US Agent for  
Interpharma Praha**

**Stamp Date:**

**11 March 2013**

**Trade (generic) Name: Iohexol NDA Type: 505(b)(2)**  
**(b)(4) Oral Solution**

**Meeting Date: 18**

**April 2013**

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?		X	ROA is oral for the DP; other routes have been evaluated for RLD, and are supportive of worst-case parenteral/ intrathecal /intracerebral administration. Sponsor provided rationale during PreNDA for 114359; FDA agreed that available studies would probably be supportive, but no guarantees.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 205383**

**Reviewer: Sally Hargus, PhD; DMIP**

**Supervisor: Adebayo Lanionu, PhD; DMIP**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		X	The submission is a 505(b)(2); the sponsor did not conduct any original studies.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			None were requested.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?		X	No comparative statements were made. This is acceptable at this time for this product; Labeling will be address during the review phase.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	Probably not necessary for the proposed oral formulation of Iohexol, based on FDA's previous finding of safety for Omnipaque (Iohexol) Injection.
11	Has the applicant addressed any abuse potential issues in the submission?		X	Probably not necessary for this product.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES**

The NDA is for "Iohexol <sup>(b)(4)</sup> Oral Solution"; the sought indication is for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis.

The sponsor submitted 117 literature-based references to P/T information on Omnipaque™ [the Reference Listed Drug (RLD)], the Omnipaque™ Label, and some GE study reports that were publically available from the Canadian Health Authority. All sections of Pharmacology and Toxicology within the FDA 21<sup>st</sup> Century Review paradigm appear to have been addressed. The information is organized well, with summaries containing links to referenced materials.

The sponsor also included referenced studies that examined local toxicity of the drug substance to the GI lumen, and potential toxicity to peritoneal tissue, which would be important if perforation of the GI tract resulted in exposure of oral contrast agent to peritoneal tissues.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA 205383**

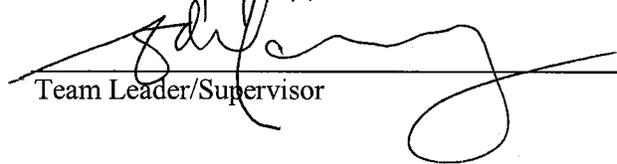
**Reviewer: Sally Hargus, PhD; DMIP  
Supervisor: Adebayo Lanionu, PhD; DMIP**

NDA 20583 is Fileable from the Pharmacology and Toxicology perspectives.

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

No Filing issues identified.

  
\_\_\_\_\_  
Reviewing Pharmacologist 4/17/2013  
Date

  
\_\_\_\_\_  
Team Leader/Supervisor 4/17/2013  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SALLY J HARGUS  
04/18/2013

ADEBAYO A LANIYONU  
04/18/2013

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 205383  
Supporting document/s: 0000 (ORIG-1)  
Applicant's letter date: 11 March 2013  
CDER stamp date: 11 March 2013  
Product: OralTag® (Iohexol) (b) (4) Oral Solution  
Indication: Opacification agent for computed tomography of the abdomen and pelvis in adults and children  
Applicant/Patent Holder: Interpharma Praha, LLC  
Modrany, Czech Republic  
US Agent for Applicant: Otsuka Novel Products, Medical Imaging  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
1 University Square Drive, Suite 500  
Princeton, New Jersey 08540  
Review Division: Division of Medical Imaging Products (DMIP)  
Reviewer: Sally Hargus, PhD  
Supervisor/Team Leader: Adebayo Lanionu, PhD  
Division Director: Louis Marzella, MD, PhD (acting)  
Project Manager: James Moore, RPh

*Template Version: September 1, 2010*

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205383 are owned by Interpharma Praha, LLC, or are data for which Interpharma Praha, LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 205383 that Interpharma Praha, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205383.

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# 1 Executive Summary

## 1.1 Introduction

The subject of this NDA review is OralTag® (Iohexol) (b) (4) Oral Solution, indicated as an opacification agent for computed tomography (CT) of the abdomen and pelvis in adults and children. The Applicant and Patent Holder is Interpharma Praha, LLC, Modrany, Czech Republic. The US Agent for the Applicant is Otsuka Novel Products, Princeton, NJ. The NDA is regulated under Section 505(b)(2) of Part 21 of the US Code of Regulations.

The Applicant has relied upon the Agency's previous finding of safety and efficacy of the Listed Drug (LD), Omnipaque™ (Iohexol Solution for Injection), NDA 18956, which is held by GE Healthcare and was approved in 1985 for use in adults. An indication for Omnipaque™ in children was approved by FDA in 1988. The Applicant also provided a summary of nonclinical information on Iohexol, which was derived from biomedical literature reports available from the public domain.

OralTag® is a nonionic, water-soluble radiographic contrast agent, *for oral ingestion only*. The LD has a much broader set of indications: oral/body cavity use, intravascular use, and intrathecal use as a radiographic contrast agent in adults and children.

## 1.2 Brief Discussion of Nonclinical Findings

No new reports.

## 1.3 Recommendations

### 1.3.1 Approvability

The Pharmacology/Toxicology recommendation for NDA 205383, OralTag® (Iohexol) (b) (4) Solution, is Approve, based on FDA's previous finding of safety and efficacy for Omnipaque™ (Iohexol Solution for Injection; NDA 18956).

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

The OralTag® Product Insert (PI) will be identical to the Omnipaque™ PI for the oral route of administration, except for the instructions regarding dissolution in an approved beverage in the manufacturer's bottle. The PI for OralTag® will be reviewed in a separate document.

## 2 Drug Information

### 2.1 Drug

Iohexol (b) (4) Oral Solution, Trade name "OralTag", when prepared as directed in the Package Insert (PI), is a non-ionic iodinated contrast agent (ICM).

CAS Registry Number: (b) (4)

Generic Name: Iohexol

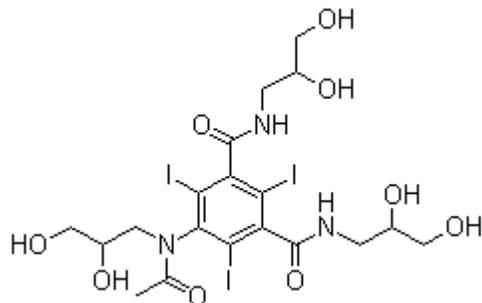
Chemical Names:

IUPAC: 5-[acetyl(2,3-dihydroxypropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide

USP: 1,3-Benzenedicarboxamide, 5-[acetyl(2,3-dihydroxypropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo

Molecular Formula/Molecular Weight:  $C_{19}H_{26}I_3N_3O_9$ / 821.14

Structure:



Established Pharmacologic Class: Radiographic Contrast Agent

Iohexol drug substance will be manufactured, tested and packaged by Interpharma Praha, as described in DMF 026641. The specifications for Iohexol drug substance are based on the USP monograph for Iohexol.

### 2.2 Relevant INDs, NDAs, and DMFs

NDA 18956: Omnipaque™ 180, 240, 300 mg I/mL Solution for Injection, Oral, or Rectal Administration (GE Healthcare)

IND 114359 Iohexol Powder (Interpharma Praha; Otsuka, US Agent)

DMF 026641 Iohexol Drug Substance for Oral Products

## 2.3 Drug Formulation

OralTag® (Iohexol (b) (4) Oral Solution) is a white to off-white powder. The product consists of Iohexol drug substance packaged in a 20-ounce polyethylene terephthalate (PET) beverage bottle with a polypropylene (PP) cap. Each bottle is individually sealed in a (b) (4) foil (b) (4) pouch. Each bottle of OralTag® has a label claim of 9.7 grams of Iohexol, equivalent to 4.5 grams of iodine.

The drug product is for oral administration after dissolution in up to 500 mL of water, juice, milk, or other compatible beverage. One or two units of Iohexol (b) (4) Solution will be administered to a patient, prior to a scheduled CT examination of the abdomen or pelvis.

In comparison with the LD, Iohexol (b) (4) Oral Solution does not contain any of the excipients present in the Omnipaque™ formulation. The Applicant stated that the excipients in Omnipaque™ are present specifically for the parenteral solution, not for the oral solution. The Applicant provided a tabular comparison between Omnipaque™ and Iohexol (b) (4) Oral Solution, shown below.

**Table 1. Formulation Comparison between OralTag® and Omnipaque™ (Listed Drug).**

<b>Table 2.5-1: Comparison of the Listed Drug, OMNIPAQUE, with Iohexol Powder for Oral Solution</b>		
<b>Drug Product Name</b>	<b>OMNIPAQUE (Iohexol) Injection</b>	<b>Iohexol (b) (4) Oral Solution</b>
<b>Dosage Form</b>	Concentrated solution (sterile)	Powder, for oral solution (non-sterile, powder in bottle)
<b>Preparation for Oral Use During CT</b>	Solution is further diluted with water or beverage prior to oral administration to patient	Powder is dissolved in water or beverage prior to oral administration to patient
<b>How Supplied</b>	Vials, glass and polymer bottles (140, 180, 240, 300, 350 mgI/mL, multiple pre-packaged volumes designed to support a variety of IV, intra-arterial (IA) and intrathecal (IT) uses) <sup>a</sup>	Single use beverage bottle (equivalent to 9 gI, designed to support concentrations and volumes used during CT of the abdomen and pelvis)

Source: NDA 205203, Section 2.5.

## 2.4 Comments on Novel Excipients

The Applicant stated that the drug product does not contain any excipients.

## 2.5 Comments on Impurities/Degradants of Concern

None.

## 2.6 Proposed Clinical Population and Dosing Regimen

The Applicant has sought an OralTag® indication in adults and children "...as an opacification agent during computed tomography of the abdomen and pelvis."<sup>1</sup> In adults, the recommended oral dosage of OralTag® for use during CT of the abdomen and pelvis is one or two bottles of prepared solution (4.5 or 9 g Iodine), prepared in a volume of 500 mL or 1000 mL. For children, the recommended concentration for oral administration for contrast use during CT is 9 to 21 mg I/mL. The total oral dose in grams of iodine should generally not exceed (b) (4) g Iodine for children under 3 years of age or (b) (4) g Iodine for children from 3 to 18 years of age (Section 2.5.4.2.2). (b) (4)

(b) (4)

The indication sought for OralTag® is narrow compared with the LD. Omnipaque™ is indicated for intravascular, intrathecal, rectal, and body cavity radiographic CT imaging, in addition to the oral indication.

## 2.7 Regulatory Background

Interpharma Praha, Otsuka, and the Agency met on 20 March 2012 for a pre-NDA meeting regarding Iohexol (b) (4) Oral Solution (IND 114359) and the Applicant's intention to file an NDA under 21 CFR, Section 505(b)(2), in the future.

The Agency previously approved the Listed Drug, Omnipaque™ 70, 140, 180, 210, 240, 300, and 350 mg I/mL Solution for injection, oral/body cavity, and intrathecal administration (GE Healthcare; NDA 18956). Omnipaque was approved initially in 1985.

## 3 Studies Submitted

No studies were submitted for this 505(b)(2) application.

### 3.1 Studies Reviewed

Not applicable.

### 3.2 Studies Not Reviewed

Not applicable.

### 3.3 Previous Reviews Referenced

Not applicable.

## 4 Pharmacology

No new information.

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<sup>1</sup> Module 1, Table 1.14.1.2-1, Proposed Draft Product Insert

## **5 Pharmacokinetics/ADME/Toxicokinetics**

No new information.

## **6 General Toxicology**

No new information.

## **7 Genetic Toxicology**

No new information.

## **8 Carcinogenicity**

No new information.

## **9 Reproductive and Developmental Toxicology**

No new information.

## **10 Special Toxicology Studies**

None.

## **11 Integrated Summary and Safety Evaluation**

No new information on Iohexol, the active ingredient in OralTag®, was submitted in the NDA. The sponsor of the OralTag® 505(b)(2) NDA has relied on FDA's previous finding of safety and efficacy of the Listed Drug, Omnipaque™ (NDA 18956). The Pharmacology and Toxicology recommendation for NDA 205383 is Approve.

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/s/  
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SALLY J HARGUS  
10/09/2013

ADEBAYO A LANIYONU  
10/09/2013