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RESEARCH**

APPLICATION NUMBER:

205383Orig1s000

OTHER REVIEW(S)

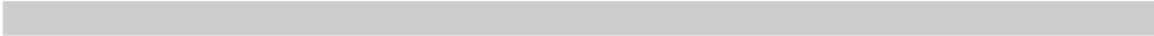
505(b)(2) ASSESSMENT

Application Information		
NDA # 205383	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Oraltag™ Established/Proper Name: Iohexol Dosage Form: (b)(4) Oral Solution Strengths: 9.7 g iohexol		
Applicant: Interpharma Praha, a.s Agent for Applicant: Otsuka Pharmaceutical Development & Commercialization		
Date of Receipt: September 26, 2014		
PDUFA Goal Date: March 26, 2015		Action Goal Date (if different):
RPM: Thuy M. Nguyen, M.P.H.		
Proposed Indication: The use of Oraltag™ in computed tomography of the abdomen and pelvis to opacify bowel loops and delineate between normal loops and adjacent organs or areas of suspected pathology. Oraltag™ is not indicated for diagnostic examination of the gastrointestinal tract.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	Nonclinical toxicology
	FDA's previous finding of safety and effectiveness (e.g., clinical or nonclinical or both)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

*Note: The applicant requested a waiver of in vivo bioequivalence (BE) studies and that the waiver was granted per the OCP review.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Omnipaque (Iohexol)	18956	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*Note: This application provides for a new dosage form (^{(b) (4)} Oral Solution).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 20608 (Omnipaque Injection)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

THUY M NGUYEN
03/26/2015

LIBERO L MARZELLA
03/26/2015

Oraltag (iohexol) (b) (4) oral solution
NDA 205383

Division of Pediatric and Maternal Health Review
Mar 2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D.
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Pediatric Team Leader,
Division of Pediatric and Maternal Health,
Office of New Drugs

Lynne Yao, M.D., Acting Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Medical Imaging Products (DMIP)

Drug: Oraltag (iohexol) (b) (4) oral solution

Application number: NDA 205383

Applicant: Interpharma Praha, a.s.

Note: Approved indications, and dosing and administration refer to Omnipaque (iohexol), the approved reference listed drug for this 505(b)(2) application. Omnipaque is marketed by GE Healthcare, Inc.

Approved indications: For various intravascular and intrathecal indications, in addition to oral and rectal use in gastrointestinal imaging in adults and pediatric patients.

Approved Dosing and Administration: "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.”

Note: Proposed indications and dosing and administration refer to Oraltag (iohexol).

Proposed indication: Use as an opacification agent during computed tomography (CT) of the abdomen and pelvis.

Proposed Dosing and Administration: Same as approved Dosing and Administration except powder is reconstituted to concentrations from 9 mgI/mL to 21 mgI/mL (b) (4)
(b) (4)

Consult Request:

DMIP requests Division of Pediatric and Maternal Health (DPMH) participation in the labeling discussions.

Materials Reviewed:

- DPMH Consult request (February 5, 2015)
- Pediatric Waiver Request (March 11, 2013)
- Pediatric Review Committee Meeting Minutes from the November 12, 2013 meeting (dated November 25, 2013 in DARRTS)
- Complete Response Letter (January 8, 2014)
- Current Omnipaque (iohexol) labeling (September, 2010)
- Cover Letter and Draft Oraltag (iohexol) labeling (September 26, 2014)
- Previous DPMH consult reviews by Dr. Donna Snyder for Iodinated contrast media for medical procedures, DARRTS Reference ID: 3229688 (December 12, 2012) and DARRTS Reference ID: 3382408 (October 2, 2013)

Background:

Iohexol is a nonionic iodinated radiopaque contrast agent originally approved under the trade name Omnipaque, on December 26, 1985 for multiple intravascular and intrathecal imaging indications in adults, and subsequently in pediatric patients. The agent was also subsequently approved for multiple body cavity imaging indications and gastrointestinal imaging (via oral, rectal and intravenous administration) in adults and pediatric patients. Omnipaque is marketed in multiple concentrations ranging from 140 mgI/mL to 350 mgI/mL depending on the route of administration. With regards to imaging of the

gastrointestinal tract via oral and rectal administration, Omnipaque is provided in three strengths (180 mgI/mL, 240 mgI/mL and 300 mgI/mL). Omnipaque is also approved as a dilute solution of iohexol 9-21 mgI/mL for oral use as an opacification agent during computed tomography (CT) of the abdomen and pelvis. Note that Omnipaque is only provided as a sterile parenteral solution, which must be diluted in a separate container for oral administration.

Interpharma Praha, a.s. has submitted a 505(b)(2) application seeking approval for iohexol powder for oral solution in the adults and pediatric patients using Omnipaque (iohexol) Injection as the reference listed drug (RLD). This application does not include any new clinical trials. In addition to the previous findings of safety and effectiveness for Omnipaque, the applicant proposes to support approval of the new formulation with safety and efficacy data from the published literature for adults and pediatric patients. The applicant is seeking approval for only one of the multiple indications, namely the dilute solution of iohexol 9-21 mgI/mL for oral use during CT of the abdomen and pelvis, and proposes a new oral powder formulation. The proposed formulation provides a single-use oral presentation. The formulation is prepared by adding water or a beverage to a premeasured dose of iohexol powder directly in a beverage bottle without the need to transfer containers. The applicant asserts this presentation offers more convenience than administering the current Omnipaque parenteral solution. The applicant also provides compatibility data for use with several age-appropriate diluents or beverages, including infant formula, juice, carbonated beverages and sports drinks.

The Division of Medical Imaging Products (DMIP) consulted the Division of Pediatric and Maternal Health Staff (DPMH) to provide input on the applicant's proposed labeling related to pediatrics.

Review of Pediatric Use Labeling:

The DPMH labeling review will focus on edits to section 5 (Warnings and Precautions) and 8.4 (Pediatric Use).

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013)

See Appendix 1 for proposed applicant labeling for Oraltag dated September 26, 2014.

Discussion on Pediatric Use Labeling Recommendations:

(b) (4)

Additionally, a review by the Division of Pharmacovigilance (DPV) in September, 2012 described 17 cases of new-onset hyperthyroidism and 11 cases of new-onset hypothyroidism following exposure to iodinated contrast media (ICM). Of the 11 cases of hypothyroidism, 10 involved infants less than 4 months of age, including 4 premature infants. DPV recommended including labeling regarding the risk of hypothyroidism in pediatric patients, specifically infants less than 1 year with an emphasis on premature and very young infants. DMIP consulted DPMH (formerly Pediatric and Maternal Health Staff) to assist with labeling recommendations for ICM products. DPMH completed reviews and provided recommended changes to labeling.¹ Therefore, DPMH continues to recommend that the concern for hypothyroidism in patients less than 1 year of age be conveyed in labeling which is reflected in our labeling recommendations. However, DPMH noted that DMIP has elected to collect more information from sponsors of iodinated contrast products and plans to make class labeling changes addressing this concern.

DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's draft labeling and participated in the internal meetings in February, 2015. Recommended labeling for the pediatric population based on labeling discussions between DMIP and DPMH is provided below per 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

¹ Previous DPMH consult reviews by Dr. Donna Snyder for Iodinated contrast media for medical procedures, DARRTS Reference ID: 3229688 (December 12, 2012) and DARRTS Reference ID: 3382408 (October 2, 2013).

1 INDICATIONS AND USAGE

Oraltag is indicated for use in computed tomography of the abdomen and pelvis to opacify bowel loops and delineate between normal loops and adjacent organs or areas of suspected pathology.

Limitations of Use

Oraltag is not indicated for diagnostic examination of the gastrointestinal tract.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

For oral use only [see Warnings and Precautions (5.1)]

Refer to Table 1 for dosing information.

Table 1 Dosing Guidelines for Oraltag

Patient Age	Recommended Dose*	Volume of Prepared Solution to Administer (at a concentration of 9 mg I per mL)	Maximum total iodine dose
Adults	Give 4.5 g to 9 g of iodine (1 to 2 bottles of prepared solution), orally	500 mL to 1000 mL	9 grams
3 to 18 years of age	Give up to 9 g of iodine (from less than 1 bottle up to 2 bottles of prepared solution), orally	280 mL to 750 mL, depending on size of patient	9 grams
Less than 3 years of age	Give up to 4.5 g of iodine (portion of 1 bottle of prepared solution), orally	120 mL to 300 mL, depending on size of patient	4.5 grams

*Total volume of Oraltag administered will vary depending on the size of the patient

The variables of patient age, weight, or medical condition, may require adjustment of the concentration and/or volume of solution to be prepared for administration. If it is anticipated that the patient will have difficulty in consuming the required volume, a higher concentration of solution can be prepared and a smaller volume administered (up to 21 mgI per mL) see Table 2.

Table 2	
Preparation of Higher Concentrations of Oraltag at Lower Volumes	
For Final Concentration (mgI/mL)	Add Water or a Beverage* to the Indicated Mark on the Bottle (mL)
9	500
12	375
15	300
18	250
21	214

*Examples include infant formula, milk, juice, carbonated beverage or a sports drink

5 WARNINGS AND PRECAUTIONS



8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of oral iohexol have been established in pediatric patients.



4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ERICA D RADDEN
03/12/2015

HARI C SACHS
03/13/2015
I agree with these recommendations

LYNNE P YAO
03/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: March 12, 2014 **Consult Received:** February 5, 2015

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health,
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Acting Team Leader
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Acting Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Medical Imaging Products

Drug: Oraltag (Iohexol) (b) (4) Oral Solution, NDA 205-383

Proposed Indication: Oral administration during computed tomography of the abdomen and pelvis

Subject: Labeling Review

Applicant: Interpharma Praha, A.S.

Consult Request: The Division of Medical Imaging Products (DMIP) would like to request review of DMIP draft labeling.

Materials Reviewed:

- Oraltag labeling February 10, 2015 working version from DMIP
- Pediatric and Maternal Health Team Follow-up Review dated October 1, 2013, primary author Donna L. Snyder, M.D. DARRTS Reference ID: 3382408.

- PMHS Memo Nursing Mothers labeling dated November, 28, 2012, primary author Jeanine Best, M.S.N., R.N., DARRTS Reference ID: 3222904.¹
- PMHS Pediatric Labeling Review dated November 30, 2012, primary author Donna L. Snyder, M.D., DARRTS Reference ID: 3229688.¹

INTRODUCTION

The applicant, Interpharma Praha, A.S., re-submitted the application for Oraltag (iohexol, NDA 205383) on September 26, 2014 in response to a Complete Response action taken on January 10, 2014. Oraltag (iohexol) is a radiographic contrast agent proposed (b) (4) for opacification of the gastrointestinal tract during computed tomography (CT) of the abdomen and pelvis. The Division of Medical Imaging Products (DMIP) consulted the Division of Pediatric and Maternal Health - Maternal Health Team (DPMH-MHT) on February 5, 2014 to review and provide labeling recommendations for Pregnancy (Section 8.1) and Lactation (Section 8.2).

BACKGROUND

Regulatory History

The original application for this NDA was submitted on April 3, 2013, as a 505(b)(2) product. The reference listed drug identified was Omnipaque® which is indicated for radiographic imaging of the gastrointestinal tract in both adults and children. It has two separate NDAs.

NDA 18-956 (Omnipaque 140)	NDA 20-608 (Omnipaque 240)
140 mg and 210 mg injection	240 mg and 300 mg oral and rectal
180 mg, 240 mg, 300 mg oral and rectal	350 mg oral only
350 mg oral only	
70 mg urethral only	

Clinical Pharmacology

Iohexol is a nonionic, water soluble, iodinated contrast medium (ICM) used for visualization of the gastrointestinal tract when administered orally. There are formulations of iohexol for administration via intravascular injection, trans-urethral or rectal instillation. Iohexol is minimally absorbed from the gastrointestinal tract.² Following oral administration only 0.1% to 0.5% of the iohexol dose enters the systemic circulation to be excreted via the kidneys.³ Intravascular iohexol is not significantly metabolized, biotransformed, deiodinated or bound to plasma proteins.⁴ The half-life of iohexol is approximately two hours with normal renal function.⁵

¹ On October 1, 2014, the Pediatric and Maternal Health Staff (PMHS) became the Division of Pediatric and Maternal Health (DPMH) within the Office of Drug Evaluation IV.

² Clinical pharmacology online®, www.clinicalpharmacology-ip.com Elsevier. Gold Standard.

Revision date: July 14, 2014. Accessed February 14, 2015.

³ *Ibid.*

⁴ American College of Radiology (ACR) Manual on Contrast Media, version 9, 2013. ISBN: 978-1-55903-012-0

⁵ See ACR.

Oral Iohexol Use in Pregnancy

Pregnant women are at risk of serious medical problems which may require CT with ICM just as non-pregnant adults. Intestinal obstruction may occur in pregnancy, particularly in women with a previous history of abdominal or pelvic surgery.⁶ If plain films are not diagnostic it may be necessary to use an ICM such as iohexol, alone or in conjunction with computed tomography to identify the obstruction. The serious risks to mother and fetus posed by an undiagnosed intestinal obstruction justify the use of CT.⁷

Mechanism of Potential Iohexol Exposure to the Fetus

There is a risk of neonatal hypothyroidism following prenatal iohexol exposure based on endocrine auto-regulation.^{8,9} The risk exists because ICM, such as iohexol, contain a small amount of free iodine. Iodine may cross the placenta to a greater or lesser extent based on the individual characteristics of the iodinated product used.¹⁰ Other factors which affect the risk of neonatal hypothyroidism following prenatal ICM exposure include the gestational age at which the fetus is exposed and maternal factors such as the iodine intake, thyroid function, thyroid antibodies and renal function.¹¹

LITERATURE AND DATABASE REVIEW

Pregnancy and Lactation

There are no available studies of prenatal exposure to orally administered iohexol. There is, however, one retrospective study in which intravenously administered iohexol alone was evaluated.¹² In this publication, 343 neonates of 322 pregnant women undergoing multidetector computed tomography with intravenous iohexol for suspected pulmonary embolism were evaluated for postnatal hypothyroidism. All the pregnancies included in the study were required to have accessible neonatal thyroid function tests. All the neonates had thyroxine (T4) levels that were appropriate for their gestational age. Eighty-five of the neonates had thyroid stimulating hormone (TSH) levels tested. One of those 85 neonates had an abnormally low TSH level at two days of age. At day 6 and again at day 20 of life, the neonate's TSH level was normal. This neonate was born at term to a mother with no history of thyroid disease but who had multiple drug exposures and was treated with opioids for withdrawal symptoms during the perinatal period.¹³ The authors' conclusion regarding this study of iohexol was:

Our study has shown that the effect of a single, high-dose, in utero exposure to water-soluble, low-osmolar, iodinated intravenous products, such as iohexol, on biochemical neonatal thyroid function is probably not clinically important, partly

⁶ Augustin G, Majerovic M. Non-obstetrical acute abdomen during pregnancy. Eur J Obstet Gynec Reprod Biol.2007;131: 4–12.

⁷ See Augustin, Majerovic.

⁸ Rajaram S, Exley C, et al. Effect of antenatal iodinated contrast agent on neonatal thyroid function. Brit J Radiol 85 (2012), e238–e242

⁹ Bourjeily G, Chalhoub M, et al. Neonatal thyroid function: Effect of a single exposure to iodinated contrast medium *in utero*. Radiology.2010;256:744-750.

¹⁰ See Bourjeily et al.

¹¹ See Bourjeily et al.

¹² See Bourjeily, et al

¹³ See Bourjeily et al.

because of short-term exposure to the product, rapid elimination by the maternal kidneys, and physical characteristics of iohexol.

There is one other publication, a case report, on prenatal exposure to intravenous iohexol.¹⁴ Seventeen hours after maternal injection, iohexol was visualized radiographically in the gut of twin premature neonates who were born at an estimated gestational age of 28 weeks. The publication reported that the iohexol was eliminated in their feces with no adverse effects reported for either neonate.¹⁵

The TERIS¹⁶ review does not comment on the teratogenic risk of iohexol, stating that the data are very limited. The review of iohexol in Reprotox¹⁷ notes that it is the iodine at issue and which may affect neonatal thyroid function.

Reviewer's Comment

The data reviewed above were from reports of intravenously, not orally, administered iohexol. With only one case of a low TSH level (and normal T4) following prenatal intravenous iohexol exposure it is difficult to draw a conclusion as to risk posed by iohexol, oral or intravenously administered during pregnancy.

The LactMed review stated that iohexol is poorly absorbed orally and is not likely to reach the bloodstream of the breastfed infant.¹⁸ A study of six lactating women receiving either iohexol (n=4) or metrizoate (n=2) found that ICM was transferred to breast milk at a very slow rate and in small amounts.¹⁹ The amount of iohexol transferred to the infants during the first 24 hours after intravenous iohexol injection was 0.5% of the maternal dose. The authors suggested that the low lipid solubility of iohexol may be one reason for the small amount of drug transferred after an intravenous administration.²⁰

American College of Radiology (ACR) and ICM Exposure Prenatally or via Breast Milk

The ACR has reviewed the effects of prenatal exposure to intravenously administered ICM. They state there have been rare reports of hypothyroidism in neonates prenatally exposed to a fat-soluble ICM. The ACR report also discusses other publications on prenatal exposure to ICM. They note that no adverse effects, other than possible neonatal hypothyroidism, have been reported following prenatal exposure to water-soluble

¹⁴ Moon A, Katzberg R, Sherman M. Transplacental passage of iohexol. *Pediatrics* 2000;136:548-9.

¹⁵ See Moon *et al.*

¹⁶ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Last revised: February, 2011.

http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/ Accessed February 14, 2015.

¹⁷ Reprotox®: Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed February 14, 2015.

¹⁸ LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last revised September 7, 2013. Accessed February 14, 2015.

¹⁹ Nielsen S, Matheson I, et al. Excretion of uohexol and metrizoate in human breast milk. *Acta Radiologica* 1987; 28:523-526.

²⁰ *Ibid.*

intravenous ICM.²¹ They note specifically that a single exposure to an ICM during pregnancy is unlikely to have an effect on the thyroid function of neonates. Specifically,

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Reviewer's Comment

Note that iohexol, whether for oral or intravenous administration, composes only a portion of the data reviewed above by the ACR. The two studies described above^{23,24} which provided data on use of iohexol only, administered the drug intravenously.

The ACR notes that there is very little published on the presence of ICM in breast milk. Given that only 0.1 to 0.5% of the dose of iohexol administered orally will be absorbed into the maternal circulation, the ACR reports that the expected dose of ICM absorbed by a breastfeeding infant is extremely low.²⁵ The ACR recommendation is,

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The ACR recommendation on the use of iohexol during pregnancy is consistent with the published data demonstrating minimal adverse effects to prenatal iohexol exposure for the fetus and the neonate. The ACR recommendations regarding possible iohexol exposure via breast milk is also consistent with the published data and the known low

²¹ See ACR Manual 2013.

²² See ACR Manual 2013.

²³ See Bourjeily et al.

²⁴ See Moon et al.

²⁵ *Ibid.*

²⁶ *Ibid.*

bioavailability of orally administered iohexol. The long term effects of prenatal and infantile exposures to iohexol are not known as noted by the ACR.

DPMH and, previously as PMHS,²⁷ has provided three reviews on the use of ICM including iohexol, in pregnant women,²⁸ lactating women²⁹ and children.³⁰ The conclusion of the 2013 PMHS review³¹ of prenatal exposure to ICM concurs with that from the ACR above. The 2012 PMHS review of use of ICM in lactating women notes that the risk of thyroid dysfunction in a breastfeeding infant following maternal exposure to ICM is extremely limited.

DISCUSSION

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”³² also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule³³ format to include information about the risks and benefits of using these products during pregnancy and lactation.

There are no human data available of sufficient quality/quantity to support substantive changes in the pregnancy labeling that differ from previously reviewed ICM products. Based on the database reviews, published literature, ACR recommendations and prior PMHS reviews, there is no additional information that describes a specific teratogenic risk from orally administered iohexol. There may be a risk of thyroid dysfunction in neonates following prenatal exposure to iohexol; however, neonatal screening for congenital hypothyroidism will likely identify an infant who may develop thyroid dysfunction because of prenatal exposure to an ICM, including iohexol. The risk of neonatal or infant hypothyroidism following maternal exposure to iohexol while

²⁷ On October 1, 2014 the Pediatric and Maternal Health Staff (PMHS) became the Division of Pediatric and Maternal Health (DPMH) within the Office of Drug Evaluation IV.

²⁸ Pediatric and Maternal Health Team Follow-up Review dated October 1, 2013, primary author Donna L. Snyder, M.D. DARRTS Reference ID: 3382408.

²⁹ PMHS Memo Nursing Mothers labeling dated November, 28, 2012, primary author Jeanine Best, M.S.N., R.N., DARRTS Reference ID: 3222904.

³⁰ PMHS Pediatric Labeling Review dated November 30, 2012, primary author Donna L. Snyder, M.D., DARRTS Reference ID: 3229688.

³¹ See DARRTS Reference ID: 3382408.

³² *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

³³ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

breastfeeding also appears to be low based on the sources reviewed here and in previous DPMH reviews.

Finally, as required under PLLR, DPMH recommends the addition of a Clinical Consideration to the lactation labeling providing information about reducing the risk of iohexol exposure in the breastfeeding infant. Specifically, a breastfeeding mother administered iohexol orally may reduce the risk of iohexol exposure to her infant by pumping and discarding her breast milk for 10 hours (5 x half-life) following iohexol administration.

CONCLUSIONS

- There are limited human data on the teratogenic risk of prenatal exposure to iohexol.
- The low oral bioavailability of Oraltag reduces the risk of neonatal iohexol exposure; however, a small risk remains which may be reduced by neonatal thyroid screening.
- The risk of iohexol exposure via breastfeeding appears to be low and any exposure can be minimized by discarding any breast milk produced for 10 hours following iohexol exposure.

RECOMMENDATIONS

DPMH-MHT attended meetings with DMIP to discuss labeling recommendations on February 10 and 23, 2015.

The following are the DPMH Maternal Health Team recommendations for the proposed labeling for iohexol in PLLR format.

Language was provided in the following sections of the Oraltag labeling:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data on risks associated with the use of Oraltag during pregnancy. The background risk in the U.S. general population of major birth defects is 2% to 4% and risk of miscarriage is 15% to 20% of clinically recognized pregnancies. (b) (4)

doses up to 100 times the maximum recommended human intravenous dose.

8.2 Lactation

Risk Summary

Iohexol administered intravenously is present in human milk at concentrations approximately 0.5% of the maternal dose; however, it is not known to what extent iohexol administered orally is present in human milk. Iodinated contrast media is poorly

excreted into human milk and is poorly absorbed by the gastrointestinal tract of a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Oraltag and any potential adverse effects on the breastfed infant from Oraltag.

Clinical Considerations

Interruption of breastfeeding after exposure to iodinated contrast media is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 half-lives) after Oraltag administration in order to minimize potential drug exposure to a breastfed infant.

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/s/

CAROL H KASTEN
03/12/2015

TAMARA N JOHNSON
03/12/2015

LYNNE P YAO
03/16/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 3, 2015

To: Thuy Nguyen, MPH
Project Manager
Division of Medical Imaging Products (DMIP)

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 205383
ORALTAG™ (iohexol) for oral solution

Background

This consult review is in response to DMIP's December 8, 2014, request for OPDP's review of the draft package insert (PI) and carton/container labeling ORALTAG™ (iohexol) for oral solution. OPDP reviewed the substantially complete version of the draft PI (titled "DMIP to OPDP Feb 26 Oraltag labeling full track changes LM 3.xml") emailed to us by DMIP on February 26, 2015. Our comments on the PI are included directly on the attached copy of the labeling.

OPDP reviewed the following carton/container labels accessed via DARRTS on March 3, 2015:

- draft-bottle.pdf
- draft-carton.pdf
- draft-foil.pdf

OPDP has no comments on the above carton/container labels at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

7 Page(s) of Draft Labeling have been
Withheld in Full as b4 (CCI/tS) immediately
following this page

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/s/

PUJA J SHAH
03/03/2015

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

PHARMACOLOGY/TOXICOLOGY NDA LABEL REVIEW MEMO

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 adult and pediatric patients
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
Project Manager: Thuy Nguyen, MS, RPM

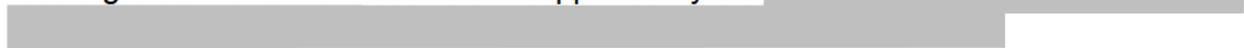
Template Version: September 1, 2010

1.3.3 Labeling

This review documents Sections 8.1, 8.2 and 13.1 of the Product Insert (PI; "Label") submission for NDA 205383, Oraltag™ (Iohexol) for Oral Administration, submitted under the US Code of Federal Regulations, Part 21, Section 505(b)(2). Omnipaque™ is the Reference Listed Drug (RLD) for Oraltag. The format and content of the Omnipaque™ PI (2010) was outdated and not compliant with current Label regulations. The Applicant and the FDA DMIP reviewers relied upon information from the RLD Label for the Oraltag PI, although the format and content were structured such that the Oraltag™ PI will be in compliance with the content and format required in the Physicians Labeling Rule and the Pregnancy and Lactation Labeling Rule (References 1-4).

An Information Request was sent to the Applicant by email on 24 December, 2013, which requested clarification on the source of the specific nonclinical dose levels and the dose multiples of animal-to-human safety factors proposed in the Oraltag™ PI, Section 8.1.

The Applicant replied to the Information Request on 06 Jan 2014 (SD11; eCTD 008). It stated that the rat and rabbit reproduction studies on which the proposed Oraltag labeling statements were based are supported by the (b) (4)



The attached Tabular Summary (Attachment 1) shows the Omnipaque™ 2010 PI language (first column), the Applicant's proposed PI language (second column), and DMIP Pharmacology and Toxicology recommendations for the Oraltag™ PI (third column). The fourth column shows DMIP/PT explanations for the recommendations. Final formatting (e.g., font size, italicized, bolded, etc.) and changes in verbiage of the PI will occur in the context of DMIP labeling meetings and communications with the Applicant.

References:

1. 21 CFR Parts 201, 314, and 601 [Docket No. 2000N–1269] (formerly Docket No. 00N–1269); RIN 0910–AA94; Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (01/24/2006).
2. 21 CFR Part 201; [Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467)]; RIN 0910-AF11; Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (12/04/2014).
3. FDA Draft Guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format; Guidance for Industry, 12/04/2014.
4. FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 2013).
5. OMNIPAQUE, 2006 (Health Canada Label).
6. OMNIPAQUE, 2010 (GE Healthcare, US Label).
7. ATTACHMENT 1: 205383 Label Review: Pharmacology and Toxicology Tabular Summary of Oraltag™ Product Insert Review

Attachment 1: 205383 Label Review: Pharmacology and Toxicology Tabular Summary of OralTag™ Product Insert Review

8 USE IN SPECIFIC POPULATIONS			
Section 8.1 Pregnancy			
Omnipaque 2010 Label	Proposed OralTag™ (26 Sept 2014 Version)	P/T recommendation	Reviewer Notes
<p>Pregnancy Category B</p> <p>Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.</p>	<p>(b) (4)</p>	<p>Risk Summary</p> <p>There are no available human data on risks associated with the use of ORALTAG during pregnancy. The background risk in the U.S. general population of major birth defects is 2% to 4% and risk of miscarriage is 15% to 20% of clinically recognized pregnancies. In animal reproduction studies, no evidence of fetal harm was observed with intravenous administration of iohexol to rats and rabbits at doses up to 100 times the maximum recommended human intravenous dose. (b) (4)</p> <p>_____</p> <p>_____</p>	<p>P/T changed the format and content to be consistent with Pregnancy and Lactation Labeling Rule (PLLR; Dec. 2014).</p> <p style="text-align: right;">(b) (4)</p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div>

	<p>(b) (4)</p>	<p>(b) (4)</p>	<p>(b) (4)</p>
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Section 8.2 Nursing Mothers	Section 8.2 (b) (4)	Section 8.2 Lactation	Section heading is "8.2 Lactation" under PLLR.
Omnipaque 2010 Label	Proposed OralTag™ (26 Sept 2014 Version)	P/T recommendation	Reviewer Notes
<p>It is not known to what extent iohexol is excreted in human milk after oral administration. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.</p>	<p>(b) (4)</p> <p>[Redacted]</p>	<p><i>Risk Summary</i></p> <p>Clinical lactation studies have not been conducted to assess the presence of iohexol in human milk, the effects of iohexol on the breastfed infant, or the effects of iohexol on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Oraltag and any potential adverse effects on the breastfed infant from Oraltag.</p> <p><i>Clinical Considerations</i></p> <p>A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 half-lives) after ORALTAG</p>	<p>Changed format to be consistent with PLLR. Used most recent language from Isovue converted label (IsoVueV4; 20Jan2015).</p> <p>(b) (4)</p> <p>[Redacted]</p> <p>Clinical Pharmacology Reviewer verified the appropriate interval for interruption of breastfeeding.</p>

		administration in order to minimize potential drug exposure to a breastfed infant.	
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13 NONCLINICAL TOXICOLOGY			
Carcinogenesis, Mutagenesis, Impairment of Fertility	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	
Omnipaque 2010 Label	Proposed OralTag™ (26 Sept 2014 Version)	P/T recommendation	Reviewer Notes
No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether iohexol can affect fertility in men or women.	No long-term animal studies have been performed to evaluate carcinogenic potential (b) (4) (b) (4)	No long-term animal studies have been performed to evaluate carcinogenic potential or mutagenesis. In animal reproduction studies, no evidence of impaired fertility was observed with intravenous administration of iohexol to rats and rabbits at doses up to 100 times the maximum recommended human intravenous dose.	No Section 13 in Omnipaque 2010 Label. (b) (4) . .

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/s/

SALLY J HARGUS
02/25/2015

ADEBAYO A LANIYONU
02/25/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: December 16, 2014
Requesting Office or Division: Division of Medical Imaging Products (DMIP)
Application Type and Number: NDA 205383
Product Name and Strength: Oraltag (iohexol) (b) (4) Oral Solution
9.7 grams of iohexol powder (4.5 grams of Iodine)
Submission Date: January 6, 2014 and September 26, 2014
Applicant/Sponsor Name: Interpharma Praha, A.S.
OSE RCM #: 2014-2136
DMEPA Primary Reviewer: Neil Vora, PharmD, MBA
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Medical Imaging Products (DMIP) requested that we review the revised carton and container labeling, prescribing information (PI) and Instruction for use (IFU) for Oraltag (iohexol) (b) (4) Oral Solution (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

¹ Wright K. Label, Labeling and Packaging NDA for ORALTAG (NDA 205383). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 OCT 03. 9 p. OSE RCM No.: 2013-1320.

2 CONCLUSIONS

We confirm that our previous recommendations were implemented after reviewing the revised carton and container labeling, PI and IFU for Oraltag (iohexol) ^{(b) (4)} Oral Solution.

Therefore, we find the labels and labeling for this product to be acceptable from a medication error perspective. DMEPA has no further comments at this time.

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/s/

NEIL H VORA
12/16/2014

YELENA L MASLOV
12/16/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 8, 2014

To: James Moore, Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Emily Baker, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205383
OralTag (Iohexol) (b) (4) Oral Solution

OPDP acknowledges receipt of your June 12, 2013, consult request for the proposed Package Insert and Carton/Container Labeling for OralTag (Iohexol) (b) (4) Oral Solution. Reference is made to the Division Director Summary Review dated January 6, 2014, which indicates that labeling will not be finalized during the current review cycle and that a Complete Response letter will be issued. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DMIP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Emily Baker at 301-796-7524 or Emily.Baker@fda.hhs.gov.

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/s/

EMILY K BAKER
01/08/2014

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging Products

Application Number: NDA 205-383

Name of Drug: OralTag® (Iohexol) [REDACTED] (b) (4) Oral Solution

Applicant: Interpharma, Praha, a.s., U.S. Agent-Otsuka Pharmaceutical Co. Ltd.

Date: December 30, 2013

Material Reviewed:

Submission Date: March 11, 2013

Receipt Date: March 11, 2013

Submission Date of Structure Product Labeling (SPL): March 11, 2013

Type of Labeling Reviewed: Word/SPL

Background and Summary

Labeling was received from Otsuka in their submission of March 11, 2013. The 74 day letter was issued on May 9, 2013 and cited no known deficiencies with regard to the application. The following labeling for the product was submitted: (1) carton (2) immediate container label (3) package insert and (4) the label for the foil packet for the product.

The first request for review of the Proprietary Name was submitted by Otsuka to IND 114, 359 on January 16, 2013. That submission contained a request for the review of Otsuka's proposed product name for their Iohexol product [REDACTED] (b) (4). The Division of Medication Error Prevention and Risk Analysis (DMEPA) initially reviewed the Proprietary Name of the Otsuka product under IND 114,359. During the review, the name [REDACTED] (b) (4) was deemed to be unacceptable. A telephone conference was held with the Sponsor (Otsuka) and DMEPA's concerns about the product's Proprietary Name were expressed at that time. Because of those concerns, Otsuka withdrew the request for review of the product name on April 30, 2013.

The request for review of a different Proprietary Name-OralTag was submitted by Otsuka under NDA 205-383 on June 4, 2013. The Division of Medication Error Prevention and Analysis reviewed the new Proprietary Name request and found it acceptable on August 30, 2013.

Because of regulatory requirements that the Proprietary Name must be reviewed a second time within 90 days of the PDUFA due date, a second review was conducted on October 3, 2013 by DMEPA and the Proprietary Name was again found to be acceptable. In their labeling review of October 3, 2013, DMEPA recommended a number of changes to the labeling for the product that were incorporated in an information request sent to the Applicant on December 24, 2013.

Review

The package insert from the March 11, 2013 submission was reviewed by the OralTag review team. The carton, the container labels for the immediate container, the label for the foil package, and the package insert in the July 5, 2013 submission were reviewed by DMEPA and they provided a number of label revision recommendations. The recommendations from DMEPA as well as those recommended by the review team were sent to the Applicant in the information request of December 24, 2013. Here is the list of requested changes:

Package Insert

1. Remove the abbreviations (e.g., gI, mgI, CLL, SLL) and replace them with this information spelled out (e.g., grams of Iodine, milligrams of Iodine, etc).
2. In order to facilitate a more clinically meaningful presentation of the dose to be administered, [REDACTED] (b) (4), please clarify how the product is being currently administered in practice and use such a clarification for wording of the Dosage and Administration section.
3. Consider revising the Dosage and Administration section to recommend the same concentration of OralTag, [REDACTED] (b) (4). [REDACTED] (b) (4). If this approach is objectionable, please justify the objection.
4. The range of [REDACTED] (b) (4) to 750 mL listed in the Dosage and Administration section for Pediatrics is outside the range of the table presented in the [REDACTED] (b) (4) section. Revise one or both items to attain consistency. Consider adding a table to the Dosage and Administration section that specifies pediatric doses across ages and body sizes.

5. You state that [REDACTED] (b) (4)
[REDACTED]” What is the source of this information?
6. We refer to the proposed Oraltag™ PI statement, “[REDACTED] (b) (4)
[REDACTED] (Oraltag™ PI, Section 8.1). Please state the route of administration used in the rat and rabbit studies on which the statement is based.
7. The Omnipaque™ PI states “Reproduction studies in rats and rabbits with doses up to 100 times the recommended human dose...” (Omnipaque™ PI, 2010; Section II, Precautions). In your Section 8.1 statement, specify the clinical dose and route of administration on which the comparisons are based. For example, if the referenced studies used the intravascular route, [REDACTED] (b) (4)
[REDACTED] ...” should be used.

We have the following recommendations in relation to the **Container, Foil and Carton Labels:**

Container Label

8. Revise the container label to support the measurement of volume found in the Dosage and Administration section of the package insert for pediatric patients.
9. Delete the statement: [REDACTED] (b) (4) from the [REDACTED] (b) (4) box.
10. Rearrange the following phrases on the container label:

[REDACTED] (b) (4)

Change to the following;

9.7g of Iohexol Powder
(equivalent to 4.5 g of [REDACTED] (b) (4) bound Iodine)
Single Use Bottle-Discard Unused Portion

9. Relocate the NDC number to the upper one-third of the container label.
10. Delete the following statements from the container label: “[REDACTED] (b) (4)
[REDACTED]”.

Foil Label

11. Delete the statement: [REDACTED] ^{(b) (4)} from the [REDACTED] ^{(b) (4)} box.

Carton Label

12. Delete the statement [REDACTED] (b) (4) .

The package insert submitted on March 11, 2013 requires a number of changes before the application can be approved. The following are changes recommended by the Regulatory Health Project Manager.

- (1) Change the product name from [REDACTED] (b) (4) to OralTag on the carton and container labels, the foil package, and in the package insert text.
- (2) Reformat the text of the package insert so that the format and font size is consistent throughout the package insert.
- (3) Add the Initial U.S. Approval date to the package insert below the product name in the Highlights of Prescribing Information.
- (4) Add the phrase: “revised: MM/YY” beneath section 17 in Highlights of Prescribing Information.
- (5) Change the font color from [REDACTED] (b) (4) of the text regarding reporting of adverse reactions in the Highlights of Prescribing Information [REDACTED] (b) (4) .

Recommendations

Based on the number of deficiencies noted from reviews of the labeling for the product and a recommendation from Compliance to withhold approval of this product, the Regulatory Health Project Manager does not recommend that the labeling be approved at this time and that deficiencies noted in the labeling be communicated to the Applicant early in the review process in the second cycle.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP
December 30, 2013

Supervisory Concurrence
Kyong Kang, PharmD.
Chief, Project Management Staff
January 7, 2014

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/s/

JAMES W MOORE
01/07/2014

KYONG A KANG
01/07/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205-383 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Iohexol Dosage Form: (b) (4) Oral Solution Strengths: 9.7g Iohexol Powder/500mL		
Applicant: Interpharma Praha, a.s. Agent for Applicant (if applicable): Otsuka		
Date of Application: March 11, 2013 Date of Receipt: March 11, 2013 Date clock started after UN:		
PDUFA Goal Date: January 10, 2014		Action Goal Date (if different): January 3, 2014
Filing Date: May 10, 2013		Date of Filing Meeting: April 18, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Indicated for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis. It may be used with or without concomitant intravenous administration of a radiopaque contrast agent.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): NA				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	x	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	x		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p>xPaid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p>x</p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p>x</p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p>x</p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p>x</p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p>x</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	x	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	x	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	x	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	x	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input type="checkbox"/>	<input type="checkbox"/>	x	
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	x	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	x	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	x	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	x	<input type="checkbox"/>		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	x	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	x		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	x	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	x	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	x	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	x Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	x	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>	x	
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Mrch 20, 2012	x	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>	x	
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 18, 2013

BLA/NDA/Supp #: 205-383

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Iohexol

DOSAGE FORM/STRENGTH: 9-21gI/20oz bottle

APPLICANT: Interpharma, P{raha, a.a., Otsuka, US Agent

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis. (b) (4)

BACKGROUND: This application is a 505(b)(2) application that relies on the reference listed drug Omnipaque (RLD), NDAs 18-956, 22-066 for support of its safety and efficacy. The dosage form of the RLD is injection. This product is a (b) (4) Oral Solution.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	James Moore	y
	CPMS/TL:	Kyong Kang	n
Cross-Discipline Team Leader (CDTL)	Alexander Gorovets		y
Clinical	Reviewer:	Barbara Stinson	y
	TL:	Alexander Gorovets	y
Social Scientist Review (for OTC products)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (for OTC products)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (for antimicrobial	Reviewer:		

<i>products)</i>			
	TL:		

Clinical Pharmacology	Reviewer:	Safaa Burns	y
	TL:	Gene Williams	y
Biostatistics	Reviewer:	NA	
	TL:	Jyoti Zalkikar	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sally Hargus	y
	TL:	Adebayo Laniyonu	n
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Milagros Salazar-Driver	y
	TL:	Eldon Leutzinger	
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	y
	TL:	Bryan Riley	n
CMC Labeling Review	Reviewer:	NA	
	TL:		
Facility Review/Inspection	Reviewer:	NA	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	n
	TL:		
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:	NA	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES x NO x YES <input type="checkbox"/> NO Literature
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? If no, explain: 	xYES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments List comments: 	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable x FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? If no, explain: 	<input type="checkbox"/> YES x NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <input type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p>x N/A</p> <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p>x YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Kyong Kang</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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/s/

JAMES W MOORE
01/07/2014

KYONG A KANG
01/07/2014



Memorandum

Date December 17, 2013

From Robert H. Wittorf, PharmD
Division of Good Manufacturing Practice Assessment (DGMPA)

Subject Concurrence with New York District Office (NYK-DO) Withhold Recommendation for:
NDA 205383, lohexol (b) (4) Oral Solution, 9.7 g

Thru Mahesh Ramanadham, Branch Chief (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

To Danae Christodoulou, Branch Chief, OMPT/CDER/OPS/ONDQA/DNDQA III/ Branch VII

Applicant: Interpharma Praha, a.s.
Komoranska 955
Praha 4- Modrany
Czech Republic, 143 10

Establishment: Ultra Seal Corporation
521 Main Street
New Paltz, New York 12561
FEI: 1317759

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of the EIR and evidence provided by Ultra Seal Corporation covering a pre-approval inspection (PAI) and GMP inspection conducted by the New York District Office (NYK-DO) investigators from 01-Oct-2013 to 07-Oct-2013 at the Ultra Seal Corporation facility. This inspection was initiated by NYK-DO to provide pre-approval coverage of NDA 205383. (b) (4)

The Division of Good Manufacturing Practice Assessment (DGMPA) concurs with NYK-DO's withhold recommendation for NDA 205383. NYK-DO recommended withholding approval of this application due to product specific deficiencies. The following deficiencies specific to NDA 205383, lohexol (b) (4) Oral Solution, 9.7 g were observed:

1. During the course of the pre-approval inspection, (b) (4)

As a result a pre-approval inspection could not be conducted. NYK-DO informed Ultra Seal Corporation management that a withhold recommendation would be submitted for NDA 205383.

A letter dated 10-Oct-2013 was submitted from Ultra Seal Corporation to NYK-DO. This letter outlines the (b) (4). The letter also states the current location of the equipment and the expected completion of

qualification activities in the beginning of January, 2014. The firm did not provide indication that it would be ready prior to the January 11, 2014 PDUFA date.

DGMPA has reviewed the EIR by the district and the letter provided by Ultra Seal Corporation. (b) (4) Ultra Seal Corporation, DGMPA recommends a follow-up inspection with pre-approval coverage. The inspection findings hold that the site demonstrated a lack of capacity to manufacture the drug product (CPGM 7346.832, Part V Item 1).

CDER/OC/OMPQ/DGMPA Recommendation:

Based on the above assessment of the inspection findings, OMPQ concurs with the NYK-DO's recommendation to withhold approval of NDA 205383; Iohexol (b) (4) Oral Solution, 9.7 g. DGMPA recommends that an on-site evaluation of the firm (per Compliance Program Guidance Manual 346.832, Pre Approval Inspections) for manufacturing operations listed in this memo.

If you have any questions, please contact me at 240-402-3113 or by email at robert.wittorf@fda.hhs.gov.

Robert H. Wittorf, PharmD
Compliance Officer

Iohoexol (b) (4) Oral Solution, 9.7 g
NDA 205383

cc:

New York District Office (NYK-DO) - Pre-Approval Manager (PAM), Kevin Gonzalez
NDMAB Acting Team Leader
CMS case #: 71446

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/s/

ROBERT H WITTORF
12/18/2013

MAHESH R RAMANADHAM
12/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 3, 2013

Reviewer: Kevin Wright, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Oraltag (Iohexol) (b) (4) Oral Solution
9.7 grams of Iohexol Powder (4.5 grams of Iodine)

Application Type/Number: NDA 205383

Applicant/sponsor: Interphama Praha, A.S.

OSE RCM #: 2013-1320

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Oraltag (Iohexol) (b) (4) Oral Solution under NDA 205383 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The reference listed drug, Omnipaque (Iohexol), was approved under NDA 018956 on December 26, 1986. The Applicant submitted NDA 205383 on March 11, 2013.

1.2 PRODUCT INFORMATION

The following product information is provided in the April 3, 2013 submission.

- Active Ingredient: Iohexol
- Indication of Use: for oral use in adults and children as an opacification agent during computed tomography of the abdomen and pelvis.
- Route of Administration: Oral
- Dosage Form: (b) (4) Oral Solution
- Strength: 9.7 grams of Iohexol (equivalent to 4.5 grams of Iodine)
- Dose and Frequency:
 - Adults: 4.5 to 9 grams of Iodine for one dose
 - Children: 1.62 to 6.75 grams of Iodine for one dose
 - Children (less than 3 years of age): maximum dose is 4.5 grams of Iodine
 - Children (3 to 18 years of age): maximum dose is 9 grams of Iodine
- How Supplied: 500 mL beverage bottle packaged in a (b) (4) foil pouch
- Storage: 20°C to 25°C (68°F to 77°F); excursions permitted to 15 to 30C (59 to 86 F).
- Container and Closure Systems: 500 mL transparent polyethylene terephthalate beverage bottle. The secondary package is a (b) (4) pouch made from a foil (b) (4)

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 4, 2013 (Appendix A)
- Foil Pouch Labeling submitted June 4, 2013 (Appendix B)
- Carton Labeling submitted June 4, 2013 (Appendix C)
- Instructions for Use submitted June 4, 2013 (Appendix D)
- Insert Labeling submitted April 4, 2013 (no image)

3 CONCLUSIONS

DMEPA concludes 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.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

I. Comments to the Division

A. General Comments

1. We note the use of the abbreviations (e.g. gI, mgI, CLL, SLL) in the Dosage and Administration Sections in the Highlights of Prescribing and Full Prescribing Information. We recommend the Applicant, provide the intended meaning of those abbreviations prior to their use to prevent misinterpretation and confusion (e.g. grams of Iodine, milligrams of Iodine, etc).
2. We recommend the Dosage and Administration Section of the Highlights of Prescribing Information and Full Prescribing Information be revised to state the grams of Iodine to be administered (b) (4)
3. We recommend that the Dosage and Administration in the Highlights of Prescribing Information be revised to include subheadings detailing the dosing for the different categories of children (e.g. neonates, infants, etc) or dosing according to an age range.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

II. Comments to the Applicant

A. Container Label

1. We recommend you revise the container label to support the measurement of volumes found in the dosing and administration section of the insert labeling. For example, children may receive a volume of 120 mL or 180 mL, however the container label or bottle do not reflect this this volume.
2. Revise the statement “ [REDACTED] (b) (4) [REDACTED] ” to read as follows:

9.7 g of Iohexol Powder
(equivalent to 4.5 g of [REDACTED] (b) (4) bound Iodine)

Single Use Bottle – Discard Remainder

3. Delete the statement [REDACTED] (b) (4) from the [REDACTED] (b) (4) box.
4. Relocate the NDC number to the upper one-third of the container label.
5. Delete the statement [REDACTED] (b) (4) [REDACTED] This information is redundant and appears more prominently under the statement of strength.

B. Foil Labeling

1. Ensure the foil labeling complies with recommendations A1, A2, A4, and A5.

C. Carton Labeling

1. Ensure the carton labeling complies with recommendations A1, A2, and A4.

If you have further questions or need clarifications, please contact Teena Thomas, project manager, at 301-796-0549.

4 Ages of Draft Labeling have
been Withheld in Full as b4 (CCI/
TS) immediately following this
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/s/

KEVIN WRIGHT
10/03/2013

YELENA L MASLOV
10/03/2013