CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205383Orig1s003

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	3/24/2015
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA # Supplement #	205383 15
Applicant Name	Interpharma Praha
Date of Submission	9/26/2014
PDUFA Goal Date	3/26/2015
Proprietary Name Established (USAN) Name	Oraltag Iohexol
Dosage Forms Strength/ Route of Administration	Powder for Oral Solution 9.7 g iohexol (4.5 g of iodine content) in a 20 ounce beverage bottle to be reconstituted with a liquid for oral administration
Proposed Indication	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
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Harris Orzach M.D.
CMC Review	Milagros Salazar Driver Ph.D.
Pharmacology Toxicology Review	Sally J Hargus Ph.D.
Clinical Pharmacology Review	Christy John Ph.D.
DMIP Labeling Review	Nushin Todd M.D.
Microbiology Review	Jessica Cole Ph.D.
Statistical Review	Satish Misra Ph.D.
Pediatric Review	Erica Radden M.D.
Maternal Health Review	Carol Kasten M.D.
OSE/DMEPA Labeling Review	Neil Vora Pharm.D.
OPDP Review	Puja Shah Pharm. D.
OC/OMPQ Establishment Review	Robert Wittorf Pharm. D.

NDA = New Drug Application
OND = Office of New Drugs
CMC = Chemistry Manufacturing and Controls
DMIP = Division of Medical Imaging Products
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OPDP = Office of Prescription Drug Promotion
OC = Office of Compliance
OMPQ = Office of Manufacturing and Product Quality

1. Introduction

Objective

The topic of this Division Director summary review is to summarize my assessment of the approvability of a Class 2 resubmission by Interpharma Praha (the Applicant) of NDA 205383 for Oraltag (Iohexol). Oraltag is a radiographic contrast agent for oral solution proposed for use in computed tomography (CT) of the abdomen and pelvis to opacify bowel loops and delineate between normal loops and adjacent organs or areas of suspected pathology.

Regulatory history

The Applicant submitted an original application on March 20, 2013 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and proposed to rely upon supportive published literature and on FDA's findings of safety and efficacy for the reference listed drug Omnipaque (Iohexol Solution for Injection). NDA 18956 for Omnipaque is held by GE Healthcare and was approved in 1985 for use in adults and in 1988 for use in children. The indication sought for OralTag is very narrow compared with the indications for Omnipaque which include intravascular, intrathecal, oral, rectal, and body cavity radiographic imaging.

The Agency issued a Complete Response letter on January 8, 2014. The Agency withheld approval of the original NDA because of CMC deficiencies that consisted of unacceptable batch analysis and stability studies submitted in the original submission and lack of capacity of the establishment that would perform the (b) (4) operations for the drug product. With regard to the assessment of the original application by the other FDA review disciplines, the cross-discipline team leader (CDTL)and the reviewers in pharmacology/ toxicology, clinical pharmacology, biopharmaceutics, clinical, and safety disciplines recommended that that the application be approved pending resolution of labeling issues identified by preliminary review of prescribing information and container labeling. No REMS, PMC or PMR were considered necessary.

Product

The drug product Oraltag is packaged in a 20-ounce polyethylene terephthalate bottle with a polypropylene cap. Each bottle contains 9.7 grams of iohexol equivalent to 4.5 grams of iodine and is sealed in a foil (b) (4) pouch. The amount of iohexol allows the user to prepare the standard concentration of 9 mgI/mL of iodine in a volume of 500 mL of fluid and also allows other standard concentrations (12, 15, 18 and 21 mgI/mL) to be prepared by adding fluid (375, 300, 250, and 214 mL) to the indicated fill lines premolded and labeled on the bottle. No reconstitution diluents are provided with the product.

The RLD is provided as a sterile solution requiring dilution in a separate container for oral administration. Table 1 shows the differences between Oraltag and the RLD Omnipaque for oral use. The Agency determined that these differences do not affect the extrapolation of safety and effectiveness from the RLD.

Table 1. Comparison between Oraltag and Omnipaque

	Oral tag	Omnipaque for oral use
Dosage form	powder for solution	solution for injection
Excipients	none	tromethamine, Na_2Ca EDTA, HCl or NaOH
Iodine concentration in reconstituted solution	9 - 21 mgI/mL	6 - 21 mgI/mL

2. Background

The Applicant did not conduct new clinical studies and provided publications from the scientific literature in support of the findings of safety and efficacy previously established for the RLD. The clinical reviewer Dr. Barbara Stinson and the CDTL reviewer Dr. Alex Gorovets of the original application summarized the extensive favorable clinical experience with the use of dilute concentrations of iohexol (Omnipaque) administered orally for CT studies in adults and pediatric patients as an aid to delineate the GI tract and distinguish bowel from other normal or abnormal structures in the abdominal and pelvic cavities. No new toxicology or clinical pharmacology studies were conducted and none were necessary.

3. CMC/Microbiology/Establishment Inspection

CMC

CMC and inspectional deficiencies precluded approval of the original application.

I concur with the recommendation by the CMC reviewer Dr. Milagros Salazar that the resubmitted application be approved from the drug quality perspective.

Dr. Salazar determined that the CMC sections for the description, characterization, and controls for the drug substance and the drug product are acceptable. In addition the manufacturing information and stability data provided in the resubmission reflect the conditions to be used for the production of commercial product. The reviewer also determined that the cGMP status for the packager of the final drug product is now acceptable and the stability data support the proposed shelf-life of two years.

Microbiology

No new microbiology data were needed in the resubmission. Based on review of the original submission the Agency determined that the microbiological quality of the drug product is controlled by an adequate testing protocol and that the microbial limits specification is acceptable.

Establishment

I concur with the "acceptable" recommendation by Dr. Robert Wittorf on December 3, 2014 following reinspection of the facilities at the Ultra Seal Corporation site.

At the time of the original application, FDA inspection determined that the (b) (4) for the manufacture of the commercial product was not in place. Therefore the batch analysis and stability studies were not acceptable. With the present resubmission the Applicant certified that (b) (4) was installed and tested by the production of two performance qualification lots.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology

No new clinical pharmacology studies were conducted in support of this NDA and none were needed. I concur with the conclusions reached by the clinical pharmacology reviewer Dr. Christy John that the application is acceptable from the clinical pharmacology perspective provided that labeling revisions are considered by the applicant.

Biopharmaceutics

No new data are required and none are provided in the resubmission. In the original submission the Applicant provided data that the Agency determined showed comparable product quality and in vitro stability when mixed with various beverages for Oraltag and the RLD.

6. Clinical Microbiology

This section is not applicable to this submission.

7. Clinical/Statistical-Efficacy

Statistical

I concur with the assessment by the statistical reviewer Dr. Satish Misra that no new clinical data are needed for the submission.

Clinical

I concur with the recommendation by the clinical reviewer Dr. Harris Orzach that this application be approved pending modification to the product labeling.

FDA review of the original submission established that the performance characteristics of iohexol as an oral agent to opacify the GI tract in CT imaging and the supportive data from x-ray radiography are well understood. I agree with the reviewer's assessment that the relatively

minor differences between the formulation of Oraltag and the RLD do not have any implication for the performance of orally administered iohexol for GI opacification. The findings of efficacy for dilute Omnipaque administered orally can therefore be extrapolated to Oraltag.

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

8. Safety

I concur with the clinical reviewer's assessment that the safety update in the resubmission does not provide new information on the safety of oral iohexol.

The Agency review of the original application established that the safety and tolerability of iohexol for use as an oral agent are acceptable. To assess the safety profile of iohexol, the applicant had conducted a search of the clinical literature for both oral and injection usage of Omnipaque. Based on the very low systemic absorption of oral iohexol (0.1 to 0.5% in normal GI tract), most of the adverse reactions are associated with parenteral administration. For this reason the prescribing information for Oraltag will be importantly different from the prescribing information for the RLD.

9. Advisory Committee Meeting

No advisory committee meeting is necessary.

10. Pediatrics

The FDA's Pediatric Review Committee had previously determined that iohexol is appropriately labeled for use in pediatric patients.

11. Other Relevant Regulatory Issues

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

12. Labeling

In this review cycle a complete review of prescribing information, carton and immediate container labels have been performed by the primary review team and consultants under the leadership of Dr. Nushin Todd.

I concur with the changes to the proposed prescribing information involving omission of information not relevant to the proposed use and route of administration of Oraltag, removal of outdated and duplicative information and unnecessary clinical practice information, simplification of the recommended dosing and preparation and administration sections.

I concur with a number of the recommendations by the FDA OPDP reviewer Dr. Puja Shah for changes to format and content of the prescribing information. The final labeling generally reflects these recommendations.

I concur with the assessment by the FDA DMEPA reviewer Dr. Neil Vora that the proposed proprietary name and carton and container labeling are acceptable from a safety and promotional perspective. (b) (4) On the other hand, the dosage form of iohexol for the reference listed drug Omnipaque is (sterile) solution for intrathecal, intravascular and oral/body cavity use.

I concur with the observation by the pediatric reviewer Dr. Erica Radden that information on clinical data used to establish the safety and effectiveness of iohexol in adults or children are not available in the RLD prescribing information; however, it is appropriate to state that safety and effectiveness of Oraltag have been established in pediatric patients. The reviewer cites the need to include information in the labeling about the potential risk of (b) (4) I concur with this recommendation and defer action as negotiations for changes to the RLD labeling are underway.

I concur with the assessment by Dr. Carol Kasten that there are limited human data on the teratogenic risk of prenatal exposure to iohexol; the low oral bioavailability reduces the risk of neonatal iohexol exposure; the risk of iohexol exposure via breastfeeding is low and exposure can be minimized by discarding breast milk for 10 hours following iohexol exposure. This information is included in the prescribing information.

13. Decision/Action/Risk Benefit Assessment

The CMC and inspectional deficiencies that precluded approval of the original application have been addressed in the resubmission.

Agreement was reached with the Applicant on the labeling.

Based on the consensus recommendations by the primary and secondary reviewers, I conclude that the application as resubmitted is approved.

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/s/

LIBERO L MARZELLA
03/25/2015