

New Drug Application (NDA 205383)

NDA Resubmission – Amendment to Original NDA Submission, Sequence 0015

Product: Iohexol Powder for Oral Solution (Oraltag)

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

Reviewer: Harris E. Orzach, M.D.

Recommendation for regulatory Action:

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

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

Summary of Regulatory History:

This is a resubmission of NDA 205383, originally submitted March 20, 2013. OralTag is an iodine-based oral contrast agent, which is used to opacify the gastrointestinal tract, for abdominal and pelvic CT scanning. (b) (4) Omnipaque 300

(iohexol), which is the reference listed drug (RLD) for oral use. The physicochemical properties (density, osmolality and viscosity) of iohexol powder for oral solution (b) (4) when mixed with various solutions for administration. The original clinical reviewer, Barbara Stinson, D.O., recommended approving the 505(b)(2) NDA for the product, which at that time was called (b) (4). This was based on the FDA's previous finding of safety and effectiveness of Omnipaque, which was approved under NDAs 18,956 and 20,608.

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

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

assemble [REDACTED] ^{(b) (4)} dedicated to commercial production of iohexol powder for oral solution. Batch analysis and stability studies submitted in the present application are not acceptable, [REDACTED] ^{(b) (4)}
[REDACTED].

CMC:

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

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

1. The manufacturing facility, Ultra Seal (USC) in New Paltz, New York, has done the following:
 - Installation and qualification of the manufacturing equipment to be used for commercial production.
 - Release testing on two (2) performance qualification (PQ) batches.
 - Preparation of the validation protocol.
2. No significant changes have been made to [REDACTED] ^{(b) (4)} used for commercial production, compared to [REDACTED] ^{(b) (4)} Proper manufacturing conditions are maintained, with no change in manufacturing process flow.
3. Appropriate batch analysis and stability data provided for OralTag manufactured at the drug product site.
4. Stability results of batches produced on [REDACTED] ^{(b) (4)} are comparable to those on [REDACTED] ^{(b) (4)}
5. Post-approval stability program instituted as directed, with testing of free iodine and free iodide at each testing interval.
6. Appropriate photostability testing instituted as directed.

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

Clinical:

Efficacy

No new efficacy data were required and none were submitted.

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

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

Safety Update

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

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

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

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

Table 1 Exposure Data from Published Articles Pertinent to Summary of Clinical Safety			
Study Grouping	Original NDA	120-Day Safety	Final Safety Update
CT in Adults (Oral)	278	444	114
X-ray Radiography in Adults (Oral)	152	NA	1,978
CT in Pediatrics (Oral)	557	NA	86
X-ray Radiography in Pediatrics (Oral or rectal)	493		

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

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

Labeling:

With regard to the labeling, Dr. Stinson recommended

(b) (4)

. The reviewer reserved comment on labeling because the application was not approvable due to CMC deficiencies.

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

Multiple revisions to the labeling are necessary.

(b) (4)

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

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

/s/

HARRIS E ORZACH
02/27/2015

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