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Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance Review

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Product Names: Oraltag (*iohexol*)

**Pediatric Labeling
Approval Date:** March 26, 2015 (original approval)

Application Type/Number: NDA 205383

Applicant/Sponsor: Interpharma Praha, a.s.

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TABLE OF CONTENTS

Executive Summary.....	2
1 Introduction.....	3
1.1 Pediatric Regulatory History.....	3
1.2 Highlights of Labeled Safety Issues.....	4
2 Postmarket Adverse Event Reports.....	5
2.1 Methods and Materials.....	5
2.1.1 FAERS Search Strategy.....	5
2.2 Results.....	6
2.2.1 Total Number of FAERS Reports by Age.....	6
2.2.2 Selection of Serious Pediatric Cases in FAERS.....	6
2.2.3 Summary of Fatal Pediatric Cases (N=0).....	7
2.2.4 Summary of Non-Fatal Pediatric Serious Cases with Oral Iohexol (N=2).....	7
3 Discussion.....	7
4 Conclusion.....	7
5 Recommendations.....	7
6 Appendices.....	8
6.1 Appendix A. FDA Adverse Event Reporting System (FAERS).....	8
6.2 Appendix B. FAERS Case Numbers, FAERS Version Numbers and Manufacturer Control Numbers for the Pediatric Case Series with Oral Iohexol (N=2).....	9

EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for the iodinated radiopaque oral contrast agent iohexol in pediatric patients.

Oraltag was first approved on March 26, 2015 in a 505(b)(2) application based on NDA 18-956, Omnipaque (iohexol), approved in 1985. Oraltag is indicated for use in all ages for 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 supplied as a nonsterile powder to be reconstituted with various compatible diluents to an oral solution with concentrations of 9, 12, 15, 18, or 21 milligrams of iodine per milliliter (mgI/mL). Omnipaque is supplied in sterile injectable solutions that are diluted to concentrations from 9 mgI/mL to 21 mgI/mL for oral administration in conjunction with Omnipaque 240 at a concentration of 240 mgI/mL or Omnipaque 300 at a concentration of 300 mgI/mL administered intravenously (IV). Oral, diluted Omnipaque is indicated in conjunction with IV Omnipaque in children for use in contrast enhanced computed tomography of the abdomen. Oraltag labeling does not mention concomitant IV contrast. The maximum labeled dose of dilute oral Omnipaque for children 3 to 18 years old is 10 grams iodine. The maximum labeled dose of Oraltag is 9.5 grams iodine for children from 3 to 18 years old.

We reviewed all serious FDA Adverse Event Reporting System (FAERS) reports with orally administered iohexol at concentrations between 9 and 21 mgI/mL or with a total dose of 10 grams iodine or less in the pediatric population (ages 0 - < 17 years) received by FDA from December 26, 1985 through December 31, 2017.

We included two cases reporting serious outcomes after oral administration of iohexol to pediatric patients in our case series. Neither of the cases contains sufficient information to assess the drug-event relationship.

There is no evidence from these data that there are new pediatric safety concerns with oral iohexol at this time. OSE recommends no regulatory action at this time and will continue to monitor adverse events associated with the use of oral iohexol.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Oraltag (iohexol) was first approved on March 26, 2015 in a 505(b)(2) application based on NDA 18-956, Omnipaque (iohexol), approved in 1985. Oraltag is indicated for oral use in all ages for 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. Oraltag is supplied as a nonsterile powder to be reconstituted with various compatible diluents to an oral solution with concentrations of 9, 12, 15, 18, or 21 milligrams of iodine per milliliter (mgI/mL).

Our search retrieved no FAERS reports with Oraltag, the focus of this review; therefore, FAERS reports with the reference product, diluted, orally administered Omnipaque were used. Relevant differences between Oraltag and Omnipaque follow.

Omnipaque, is supplied in sterile injectable solutions that are diluted to concentrations from 9 mgI/mL to 21 mgI/mL for oral use and administered in conjunction with intravenous (IV) Omnipaque 240 at a concentration of 240 mgI/mL or Omnipaque 300 at a concentration of 300 mgI/mL. Oraltag labeling does not mention concomitant IV contrast.

The volume of a single dose of oral, diluted iohexol solution in a child is labeled as 180 to 750 mL for Omnipaque and 120 to 750 mL for 9 mgI/mL Oraltag, with higher concentrations used when lower volume is needed.

Oraltag is not indicated for diagnostic examination of the gastrointestinal tract. Undiluted Omnipaque is approved for oral and rectal use in children 3 months of age and older for examination of the gastrointestinal tract at concentrations of 180, 240, and 300 mgI/mL. Oral volumes of Omnipaque for this indication are 5 to 100 mL.

Oraltag contains only iohexol powder with no excipients. Omnipaque contains excipients, as follows: “Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide.”

2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Information is from Oraltag labeling approved March 2015.

4 CONTRAINDICATIONS

Oraltag is contraindicated in patients with a known hypersensitivity to iodinated contrast agents, including iohexol.

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with Inadvertent Parenteral Administration

Oraltag is not a sterile product and is not suitable for a parenteral route of administration. Serious adverse reactions such as sepsis can occur if administered parenterally. Do not administer Oraltag parenterally.

5.2 Hypersensitivity Reactions

Administration of Oraltag can cause life-threatening hypersensitivity reactions including anaphylaxis [see Contraindications (4)]. Patients at increased risk include those with a previous reaction to an iodinated contrast agent and allergic disorders (i.e., bronchial asthma, allergic rhinitis, and food allergies). Emergency resuscitation equipment and trained personnel should be available.

5.3 Alteration of Thyroid Function Tests

Iodinated contrast agents may alter the results of thyroid function tests [that] depend on iodine estimation, e.g., radioactive iodine uptake test. Therefore, such testing, if indicated, should be performed prior to the administration of this preparation.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In studies involving 44 adult and 69 pediatric patients who received oral and intravenous iohexol for CT examinations of the abdomen, two reports of vomiting (2%) were noted.

6.2 Postmarketing Experience

The following adverse reactions have been reported following oral administration of the dilute, hypotonic solutions of iohexol (9 mgI/mL to 21 mgI/mL):

- Gastrointestinal: nausea, diarrhea

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

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

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5% of the oral dose is excreted by the kidneys. This amount may increase in the presence of bowel perforation, bowel obstruction, or severe inflammatory bowel disease.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FAERS Search Strategy

DPV searched FAERS with the strategy described in **Table 1**. See **Appendix A** for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of Search	January 30, 2018
Time Period of Search	December 26, 1985* - December 31, 2017
Search Type	FBIS Quick Query
Product Names	Product active ingredient: iohexol
Search Parameters	All ages, all outcomes, worldwide

*December 26, 1985 is the approval date for the reference product, Omnipaque, upon which Oraltag approval was based.

We searched the FAERS database for all reports of iohexol received from December 26, 1985, through December 31, 2017. December 26, 1985 was the approval date of the comparator product, Omnipaque, upon which Oraltag approval was based. Omnipaque was approved before Best Pharmaceuticals for Children Act (BPCA) became law in 2002 and DPV has not done a comprehensive pediatric review of oral administration, so the entire FAERS history of Omnipaque was searched. This review is focused on cases with serious outcomes in pediatric patients who received oral doses of iohexol 9 to 21 mgI/mL solution, the approved route and concentrations for Oraltag, or who received an oral dose of 10 grams iodine or less, the maximum labeled dose of dilute oral Omnipaque for children 3 to 18 years old. The maximum labeled dose of Oraltag is 9.5 grams iodine for children from 3 to 18 years old.

We reviewed all FAERS pediatric reports (patients under 17 years of age) with a serious outcome and all FAERS reports with a blank age field and an outcome of death. We included reports in our case series as described in the preceding paragraph unless the serious adverse event was attributable to co-morbid diseases or concomitant medications, the adverse event occurred prior to iohexol oral exposure, no adverse clinical events were reported, or the patient's age could not be determined.

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from December 26, 1985 to December 31, 2017 with use of iohexol by any route of administration and with orally administered iohexol in pediatric patients. All pediatric reports identified the iohexol product as Omnipaque; there were no pediatric reports with Oraltag.

Table 2. Total Adult and Pediatric FAERS Reports* December 26, 1985 to December 31, 2017 with Iohexol

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	5893 (3921)	4818 (2863)	466 (249)
Pediatrics (0 - <17 years)	170 (100)	145 (75)	9 (4)
Oral administration	4 (0)	4 (0)	0

* May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified four pediatric reports with orally administered iohexol that reported a serious outcome from December 26, 1985 to December 31, 2017. None of these four cases reported death. Our pediatric case series includes two cases.

The other two cases were excluded because

- the adverse events were temporal to another drug (Eosinophilia peaked six times over 5 months in a premature infant; five occurrences followed courses of intravenous vancomycin.)
- an adverse medical event may have begun prior to receipt of iohexol. (A 23-day-old neonate born at 26 weeks gestation who had sepsis, bile-stained gastric aspirates, and fresh blood in stools before receiving oral iohexol subsequently developed possible loss of mucosal integrity and gut perforation.)

3.2.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases in our case series.

3.2.4 Summary of Non-Fatal Pediatric Serious Cases with Oral Iohexol (N=2)

We included two FAERS cases with oral iohexol in the pediatric population reporting non-fatal serious outcomes.

FAERS Case #13164999, Manufacturer Control Number (MCN) GB-GE HEALTHCARE MEDICAL DIAGNOSTICS OMPQPR-1701S-0156, Expedited, 2017

This case from Great Britain was reported by the patient's parent. A 2-month-old male received an unknown dose of Omnipaque orally for an unknown indication. The patient got a "double dose" for an unknown imaging procedure and developed diarrhea and skin rash that were resolving. No other information was provided.

FAERS Case #11293202, MCN IN-GE HEALTHCARE MEDICAL DIAGNOSTICS-OMPQ-PR-1507S-1096, Expedited, 2015

A physician in India reported that a 15-year-old female received 20 mL of Omnipaque 300 mgI/mL (6 grams iodine) orally for CT of the abdomen. Ten minutes after administration, the patient experienced seizures, which resolved in 15 minutes. No other information was provided.

4 DISCUSSION

Of the reports reviewed, there were no new safety signals identified and no increased severity or frequency of any labeled adverse events. Neither included case provides sufficient information, such as medical history and presence or absence of concomitant medications, to fully assess the relatedness of the adverse events to iohexol.

5 CONCLUSION

There is no evidence from these data that there are new pediatric safety concerns with oral iohexol at this time.

6 RECOMMENDATIONS

DPV recommends no regulatory action at this time and will continue to monitor adverse events associated with the use of oral iohexol.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH ORAL IOHEXOL (N=2)

FAERS Line Listing of Pediatric Cases for the Pediatric Case Series with Oral Iohexol (N=2)									
Case	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country	Serious Outcome(s)*
1	1/30/2017	13164999	1	GB-GE HEALTHCARE MEDICAL DIAGNOSTICS OMPQPR-1701S-0156	Expedited (15-Day)	0.167	Male	GBR	OT
2	7/22/2015	11293202	1	IN-GE HEALTHCARE MEDICAL DIAGNOSTICS-OMPQ- PR-1507S-1096	Expedited (15-Day)	15	Female	IND	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. A report may have more than one serious outcome.
Abbreviations (country): GBR=Great Britain, IND=India
Abbreviations: OT=Other medically significant

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/s/

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