

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205383Orig1s000

CHEMISTRY REVIEW(S)

CMC Assessment Section

NDA 205-383**OraltagTM****Iohexol for Oral Solution****9.7 g iohexol powder****(equiv. to 4.5 g (b) (4) bound iodine) / 20 oz. bottle****Interpharma Praha, a.s.****Milagros Salazar, Ph.D.
OPQ, ONDP, DNDP II, Branch VI**for
The Division of Medical Imaging Products

CMC Assessment Section

Chemistry Review Data Sheet

1. NDA 205-383
2. REVIEW # 2
3. REVIEW DATE: 12-Feb-2015
4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11-Mar-2013
SD-2 Quality Information	09-Apr-2013
SD-7 Quality Response to information request	05-Sep-2013
SD-8 Quality Response to information request	01-Oct-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Re-Submission, Class 2, SD-18	26-Sep-2014
Proprietary name review, SD-19	30-Sep-2014
GI-1/Administrative change, SD-20	17-Dec-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Interpharma Praha, a.s. (IPP)
Komořanská 955
Address: 143 10 Praha 4 – Modřany - CZECH REPUBLIC

Representative: Otsuka Pharmaceutical Development &
Commercialization, Inc.
508 Carnegie Center Drive
Princeton, NJ 08540

US Agent: Marjory Kadash-Director, Regulatory Affairs, Otsuka
Novel Products, Medical Imaging

Contact
Information: (609)-524-6876 Email: Marjory.kadash@otsuka-.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Oraltag™
- b) Non-Proprietary Name (USAN): Iohexol
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (new dosage form), 5 (new formulation/new manufacturer)
 - Priority: S

CMC Assessment Section

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2) RLD Onmipaque Inj. (NDA 18-956)

10. PHARMACOL. CATEGORY: Diagnostic, iodinated non-ionic X-ray contrast agent

11. DOSAGE FORM: (b)(4) oral solution

12. STRENGTH/POTENCY: 9.7 g iohexol (equiv. to 4.5 g iodine) in 20-oz bottle

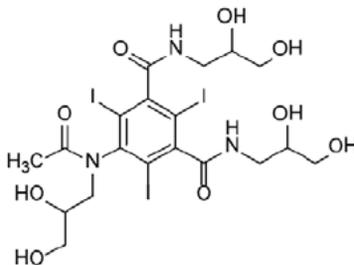
13. ROUTE OF ADMINIST.: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-[Acetyl(2,3-dihydroxypropyl)amino]-1-*N*,3-*N*-bis(2,3 dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide MW: 821.14 Molecula Formula: C₁₉H₂₆I₃N₃O₃



Iodine content: 46.36%

CAS no: (b)(4)

17. RELATED/SUPPORTING DOCUMENTS: See Review #1.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES: OC-OMPQ Div. GMP assessment	Overall manufacturing facilities recommendation: Acceptable in Panorama	12/03/2014	Robert Wittorf, Pharm D.
DMEPA*/OMEPRM ***	Labels: (container, carton, PI instruction): Acceptable	12/16/2014	Neil Vora, Parm.D., MBA
DMEPA*/OMEPRM ***	Proprietary name: Acceptable	12/17/2014	Neil Vora, Parm.D., MBA

* DMEPA: Division of Medication Error Prevention and Analysis

** Office of Prescription Drug Promotion (formerly DDMAC)

***Office of Medication Error, Prevention and Risk Management / Div. of Risk Management I. Introduction

CMC Assessment Section

Based on the Chemistry, Manufacturing and Controls (CMC) requirement for approval under 21 CFR 314.50 the application is adequate to support the manufacturing equipment and the drug product used for the primary stability study which are representative of the commercial production.

In addition, the cGMP status for the packager of the final drug product is now acceptable after inspection for Ultra Seal Corporation, New Paltz, NY 12561.

CMC recommendation is approval based on the CMC responses in this resubmission and the acceptable recommendation from the Office of Compliance following inspection of the manufacturing facilities.

NDA 205-383 for Oraltag™ (Iohexol) for Oral Solution is submitted for approval under the 505(b)(2) regulatory status according to Part 21 of the US Code of Federal Regulations as agreed at the pre-NDA meeting held on 20-Mar-2012.

The reference approved drug, Omnipaque™ (Iohexol Solution for Injection), NDA 18-956, which is held by GE Healthcare was approved in 1985 for use in adults. An indication for Omnipaque™ in children was approved by FDA in 1988.

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, Oraltag™ (iohexol) for oral solution, 9.7 g, is a white to off-white iohexol powder packaged in a 20-ounce polyethylene terephthalate (PET) beverage bottle with a lined polypropylene (PP) cap. Each bottle is individually sealed in a (b) (4) foil (b) (4) pouch. The drug product consists of 100% iohexol and contains no excipients.

Each bottle of Oraltag™ has a label claim of 9.7 grams of iohexol, equivalent to 4.5 grams of iodine.

No accompanying constitution diluents will be provided with the drug product.

After reconstitution of the Oraltag™ with water, or other recommended beverages, using the 5 fill lines premolded and labeled in the bottle, the resulting solution will have 5 target concentrations of 9, 12, 15, 18 and 21 mgI/mL; the amount of water (beverage) added is 500, 375, 300, 250 and 214 mL respectively.

When prepared according to the directions for oral administration, a 9 mgI/mL solution of iohexol in water has an osmolality of 30 mOsmol/kg. Thus the solution is hypotonic relative to human plasma, which has an osmolality of approximately 285 mOsmol/kg water.

CMC Assessment Section

The drug product, Oraltag™ (iohexol) for Oral Solution, 9.7 g, is manufactured in Ultra Seal Corporation in New Paltz, NY 12561 (b)(4). The NDA label presents an NDC 54702-501-20 for this presentation.

The manufacturing process consists of (b)(4)

The application presented manufacturing and stability data for three production batches said to be manufactured at USC, New Paltz (b)(4) to be used for commercial production. Upon FDA inspection from 10/1/13 to 10/7/13, the investigator found the company did not (b)(4) the commercial production of Iohexol powder in place and neither they have (b)(4) at their facility and where they plan (b)(4). Therefore, the batch analysis and stability studies are not acceptable in support of this application. The (b)(4) not the (b)(4) intended for the (b)(4) the iohexol powder product. (b)(4) is now installed and it has been tested by the production of two performance qualification (PQ) lots.

The proposed shelf-life of 2 years, when stored at proposed storage conditions of 20°C-25°C, with excursions permitted to 15°C- 30°C. The stability data provided supports this expiration time.

The risk assessment on the product attributes impacted by the revisions covering the resubmission are presented for each issue listed in the complete response letter as part of this chemistry review. The summary of assessment is that based on the CMC established in the NDA, the risk to the overall product quality is low.

B. Description of How the Drug Product is Intended to be Used

Oraltag™ for oral solution is indicated as an opacification agent for computed tomography (CT) of the abdomen and pelvis in adults and children.

CMC Assessment Section

The bottle of Oraltag™ for oral solution contains 9.7 grams of iohexol, equivalent to 4.5 grams of iodine. It is intended for reconstitution with water or other recommended beverages, using the 5 fill lines premolded and labeled on the bottle, the resulting solution will have 5 target concentrations of 9, 12, 15, 18 and 21 mgI/mL to achieve desired dosing; the amount of water (beverage) added to obtain the target concentration is 500, 375, 300, 250 and 214 mL respectively.

[Redacted]

(b) (4)

The CMC review team performed risk assessment on the product attributes that can impact product quality and concluded the risk of the overall product is low. See the table below for an executive summary of the risk assessment for Oraltag™ (iohexol) for oral solution.

[Redacted]

(b) (4)

CMC Assessment Section

(b) (4)

C. Basis for Approval Recommendation

The CMC sections for the description, characterization and controls for the drug substance and the drug product are acceptable in support of requirements under 21 CFR 314.50 to assure the identity, purity, quality and strength of the product.

The manufacturing information and stability data provided in this resubmission does reflect the conditions to be used for the production of commercial product, these sections are

CMC Assessment Section

acceptable in support of the CMC requirements under 21 CFR 314.50 for Oraltag™ for oral solution in this NDA submission.

Expiration time requested is 24 months which is granted.

In addition, the applicant does have a manufacturing site ready for inspection and for commercial production of the Oraltag™ for oral solution.

The application is recommended for approval from the product quality perspective.

III. Administrative

A. Reviewer's Signature

Senior Review Chemist/ Milagros Salazar, Ph.D.

B. Endorsement Block

Quality Lead/ Eldon Leutzinger, Ph.D.

Acting Branch Chief/Danae Christodoulou, Ph.D.

C. CC Block

Project Manager, DMIP/Thuy Nguyen, Pharm. D.

Project Manager, OQA/DNDP II/Cathy Tran-Zwanetz

NDA 205-383

OraltagTM

Iohexol (b) (4) Oral Solution
9.7 g (equiv. to 4.5 g iodine) / 20 oz. bottle

Interpharma Praha, a.s.

Milagros Salazar, Ph.D.
ONDQA, Division III, Branch VII

for
The Division of Medical Imaging Products

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 205-383
2. REVIEW #1
3. REVIEW DATE: 31-Oct-2013
4. REVIEWER: Milagros Salazar, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11-Mar-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	11-Mar-2013
SD-2 Quality Information	09-Apr-2013
SD-7 Quality Response to information request	05-Sep-2013
SD-8 Quality Response to information request	01-Oct-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Interpharma Praha, a.s. (IPP)
Komořanská 955
Address: 143 10 Praha 4 – Modřany - CZECH REPUBLIC

Representative: Otsuka Novel Products, Medical Imaging (ONPMI)
One University Square Dr. Suite 500
Princeton, NJ 08540

Telephone: (609)-524-6788

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Oraltag™
- b) Non-Proprietary Name (USAN): Iohexol
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (new dosage form), 5 (new formulation/new manufacturer)
 - Subm. Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2) RLD Onmipaque Inj. (NDA 18-956)

10. PHARMACOL. CATEGORY: Diagnostic, iodinated non-ionic X-ray contrast agent

11. DOSAGE FORM: (b) (4) solution

12. STRENGTH/POTENCY: 9.7 g iohexol (equiv. to 4.5 g iodine) in 20 oz bottle

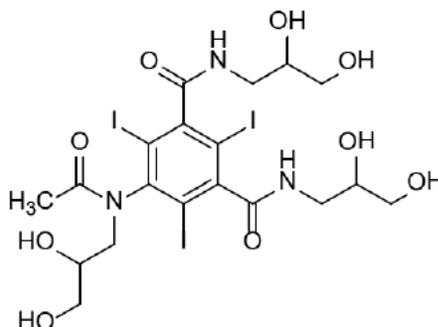
13. ROUTE OF ADMINIST.: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-[Acetyl(2,3-dihydroxypropyl)amino]-1-*N*,3-*N*-bis(2,3 dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide MW: 821.14 Molecular Formula: C₁₉H₂₆I₃N₃O₃



Iodine content: 46.36%

CAS no: (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
26641	II	Interpharma Praha, a.s.	API - Iohexol powder, for oral	1	Adequate	11-Jul-2013	LOA, Yes 1/24/13
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	31-Oct-2013	LOA, Yes 10/25/12
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	31-Oct-2013	LOA, Yes 10/26/12

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	Adequate	31-Oct-2013	LOA, Yes 10/25/12
	III		4	Adequate	31-Oct-2013	LOA, Yes 10/25/12
	III		4	Adequate	31-Oct-2013	LOA, Yes 12/12/12

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114,359	iohexol (b) (4) Oral Solution
NDA	18-956	RLD Onmipaque Inj.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	No Action Indicated		Satish Misra, Ph.D.
EES: OC-OMPQ Div. GMP assessment	EIR recommendation: VAI- Hold for iohexol powder product in Ultra Seal Corp. site.	Pending final EES overall recommendation	Robert Wittorf, Pharm D.
Pharm/Tox	Acceptable	10/09/2013	Sally Hargus, Ph.D.
Biopharm	Acceptable Biowaver granted (reviewer comments, not in DARRTS yet)	pending	Mien (Albert) Chen, Ph.D.

Chemistry Review Data Sheet

DMEPA*/OMEPRM ***	Labels (container, carton, insert): Acceptable pending revision requested to improve readability	10/03/2013	Kevin Wright, Parm.D.
OPDP**		Pending	
DMEPA*/OMEPRM ***	Proprietary name Acceptable	8/30/2013 8/30/2013	Kevin Wright, Parm.D. Carol Holquist R.Ph.
Division of Pharmacovigilance II		Pending	Michael E. Kieffer, Pharm. D., M.A.
Methods Validation	N/A, based on proposed USP methodology	31-Oct-2013	Milagros Salazar, Ph.D.
EA- categorical exclusion requested under 21 CFR 25.31(a) and 25.31(b)	Categorical exclusion granted. The basis for the request are acceptable. (section 1.12.14, orig. NDA)	14-Aug-2013	Milagros Salazar, PhD.
Microbiology	Acceptable	24-Apr-2013	Jessica Cole, Ph.D.

* DMEPA: Division of Medication Error Prevention and Analysis

** Office of Prescription Drug Promotion (formerly DDMAC)

***Office of Medication Error, Prevention and Risk Management / Div. of Risk Management

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes

____ No If no, explain reason(s) below:

Executive Summary

The Chemistry Review for NDA 205-383

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 205-38 for OralTag® (Iohexol) (b)(4) Oral Solution is submitted for approval under the 505(b)(2) regulatory status according to Part 21 of the US Code of Federal Regulations as agreed at the pre-NDA meeting held on 20-Mar-2012.

The Applicant is Interpharma Praha, LLC, Modřany, Czech Republic. The US Agent for the Applicant is Otsuka Novel Products, Princeton, NJ.

The Reference Listed Drug (RLD), Omnipaque™ (Iohexol Solution for Injection), NDA 18956, which is held by GE Healthcare was approved in 1985 for use in adults. An indication for Omnipaque™ in children was approved by FDA in 1988.

Based on the Chemistry, Manufacturing and Controls (CMC) requirement for approval under 21 CFR 314.50 the application is deficient because the manufacturing equipment and the drug product used for the primary stability study are not representative of the commercial production.

In addition, the cGMP status for the packager of the final drug product is pending due to the company, Ultra Seal Corporation, New Paltz, NY 12561, not being ready for inspection.

Therefore, CMC recommendation is not approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

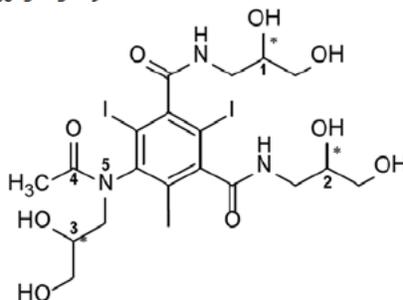
II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is Iohexol, Intepharma Praha, a.s. is manufactured, tested and packaged by the applicant Intepharma Praha, a.s. (IPP), Modřany, Czech Republic under DMF 26641. This DMF was acceptable by this reviewer via Review #1 dated 22-Jul-2013.

Executive Summary

Iohexol, 5-[Acetyl(2,3-dihydroxypropyl)amino]-1-*N*,3-*N*-bis(2,3 dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide, CAS number 66108-95-0, is a nonionic, water soluble radiographic contrast agent with molecular weight of 821.14 (iodine content 46.36%). In aqueous solution each triiodinated molecule remains undissociated. The molecular formula of iohexol is C₁₉H₂₆I₃N₃O₉. The chemical structure is:



Iohexol, drug substance is a white to off-white, hygroscopic, odorless powder. It is very soluble (1 gram dissolves in less than 1 mL off water). The partition coefficient of iohexol between *n*-octanol and water (log P) is -2.8; its melting point is 246.8 - 254.5 °C by differential scanning calorimetry.

Two types of isomerism are present in iohexol: **stereoisomerism** related to three asymmetric carbon atoms at C1, C2 and C3 (as indicated in the number-labeled iohexol molecule above) and **rotational isomerism** resulting from restricted rotation around the single bond between carbon C4 and amidic nitrogen N5.

Although iohexol has 3 asymmetric carbons, (b) (4) iohexol appears as optically inactive and its specific rotation is -0.5° to +0.5°. It possesses rotational isomerism, resulting from *exo-* and *endo-* isomers as described in the USP.

The drug product is a white to off-white powder. The drug product consists of 100% iohexol and contains no excipients. The product is packaged in a 20-ounce polyethylene terephthalate (PET) beverage bottle with a lined polypropylene (PP) cap. Each bottle is individually sealed in a (b) (4) foil (b) (4) pouch.

Each bottle of Iohexol (b) (4) Oral Solution has a label claim of 9.7 grams of iohexol, equivalent to 4.5 grams of iodine.

No accompanying constitution diluents will be provided with the drug product.

After reconstitution of the Iohexol Powder with water, or other recommended beverages, using the 5 fill lines premolded and labeled in the bottle, the resulting solution will have 5 target concentrations of 9, 12, 15, 18 and 21 mgI/mL; the amount of water (beverage) added is 500, 375, 300, 250 and 214 mL respectively.

Executive Summary

When prepared according to the directions for oral administration, a 9 mgI/mL solution of iohexol in water has an osmolality of 30 mOsmol/kg. Thus the solution is hypotonic relative to human plasma, which has an osmolality of approximately 285 mOsmol/kg water.

The drug product, Oraltag® (Iohexol) (b) (4) Oral Solution, 9.7 g, is manufactured in Ultra Seal Corporation in New Paltz, NY 12561 (b) (4). The NDA label presents a tentative NDC 54702-xxx-xx for this presentation.

The manufacturing process consists of (b) (4)

The application presented manufacturing and stability data for three production batches said to be manufactured at USC (b) (4) for commercial production. Upon FDA inspection from 10/1/13 to 10/7/13, the investigator found the company did not have (b) (4) of Iohexol powder in place and neither they have ready (b) (4) at their facility and where they plan to (b) (4). Therefore, the batch analysis and stability studies are not acceptable in support of this application. (b) (4) not the intended for the (b) (4) iohexol powder product.

B. Description of How the Drug Product is Intended to be Used

Oraltag® (Iohexol) (b) (4) Oral Solution is indicated as an opacification agent for computed tomography (CT) of the abdomen and pelvis in adults and children.

The bottle of Iohexol (b) (4) Oral Solution, 9.7 grams of iohexol, equivalent to 4.5 grams of iodine is intended for reconstitution with water or other recommended beverages, using the 5 fill lines premolded and labeled on the bottle, the resulting solution will have 5 target concentrations of 9, 12, 15, 18 and 21 mgI/mL to achieve desired dosing; the amount of water (beverage) added to obtain the target concentration is 500, 375, 300, 250 and 214 mL respectively.

Executive Summary

(b) (4)

C. Basis for Not-Approval Recommendation

The CMC sections for the description, characterization and controls for the drug substance and the drug product are acceptable in support of requirements under 21 CFR 314.50 to assure the identity, purity, quality and strength of these products.

On the other hand, the manufacturing information and stability data provided do not reflect the conditions to be used for the production of commercial product, these sections are not acceptable in support of the CMC requirements under 21 CFR 314.50 for Oraltag® (b) (4) Oral Solution in this NDA submission.

In addition, the applicant does not have a manufacturing site ready for inspection and for commercial production of the Oraltag® (b) (4) Oral Solution.

The application is not recommended for approval from the product quality perspective.

III. Administrative**A. Reviewer's Signature**

Senior Review Chemist/ Milagros Salazar, Ph.D.

B. Endorsement Block

Chemistry Lead/ Eldon Leutzinger, Ph.D.

Acting Branch Chief/Danae Christodoulou, Ph.D.

C. CC Block

Project Manager, DMIP/James Moore, Pharm. D.

Project Manager, ONDQA/Youbang Liu, Ph.D.

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

/s/

MILAGROS SALAZAR DRIVER

10/31/2013

CMC recommendation: not approval with items for the CR letter.

ELDON E LEUTZINGER

10/31/2013

DANAE D CHRISTODOULOU

11/01/2013

I concur with the reviewer's conclusion and recommendations

**PRODUCT QUALITY – CMC
INITIAL QUALITY ASSESSMENT and
FILING REVIEW**

NDA number: 205-383
Applicant: Interpharma Praha, a.s.
Letter Date: 11 MAR 2013
Stamp Date: 11 MAR 2013
Filing Date: 10 MAY 2013 (Filing meeting, 18 Apr 2013)
PDUFA Goal Date: 10 JAN 2014
GRMP Primary Rev Date: 31 OCT 2013
Trade name: (b) (4)
Established Name: iohexol

Dosage Form/ Strength: (b) (4) Solution, 9.7 g iohexol (equiv. to 4.5 g of iodine) bottle
Route of Administration: Oral

Indication: (b) (4) is indicated in adults as an opacification agent during computed tomography of the abdomen and pelvis.
(b) (4)

Application format: Electronic format as an CTD

Chemical Type: 3 New dosage form
5 New formulation, New manufacturer

Review classification: S (standard)

Regulatory Filing: 505 (b)(2) ...RLD Omnipaque Inj. (NDA 18-956)
Related IND: IND 114359

Assessed by: Milagros Salazar, Ph.D.
OND Division: Division of Medical Imaging Products

Summary

This application proposes the drug product (b) (4) (iohexol) (b) (4) oral solution, for adults and pediatrics as an opacification agent during computed tomography of the abdomen and pelvis.

A (b) (4) ® is a iohexol (b) (4) for oral administration. The drug product consists of 100% iohexol powder and contains no excipients. This is a 505(b)(2) application is aiming to establish bioequivalence to the referenced approved product Omnipaque (iohexol) injection NDA 18-956.

Iohexol Injection radioopaque contrast agent is approved by the Agency as a sterile solution for Injection as OMNIPAQUE under NDAs 18-956 and 20-608. The proposed drug product is a non-sterile, (b) (4) reconstitution with water or (b) (4) drinks that contains the same active ingredient in a formulation capable to provide different concentrations than the Reference Listed Drug (RLD) OMNIPAQUE. The excipients differ from those used in the RLD (prepackaged in multiple

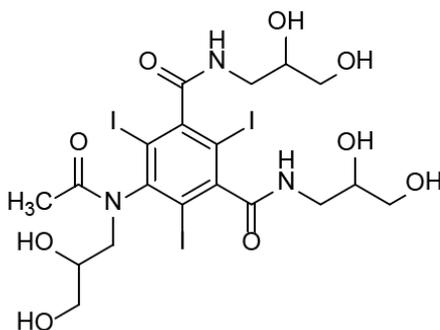
concentrations) and it is comprised of only iohexol, the drug substance without any excipients. The proposed drug is formulated as powder 9.7 g iohexol (equiv. 4.5 g of iodine) per bottle for oral solution, upon reconstitution in water or a beverage the concentration range is from 9 to 21 mg I/mL. The RLD range concentration is 6 mgI/mL to 21 mgI/mL (when diluted for oral use).

The applicant references the meeting minutes of a Pre-NDA Type B Meeting minutes (19-Apr-2012), Facsimile (23-May-2012) relating to Question 3 and 8 (cmc) and Question 9 (biowaver) and the NDA preparation status update (19-Dec-2012).

Review Comments and Critical Issues

Drug Substance (DS)

The applicant references the drug substance information to DMF 26641- Iohexol drug substance, for oral drug products submitted by Interpharma Praha, a.s. Minimal drug substance nomenclature and structural information is provided in the NDA. An Establishment Evaluation Request was submitted to the Office of Compliance to evaluate cGMP compliance for the drug substance manufacturing site listed in the submission. The Iohexol, drug substance chemical (IUPAC) name is 5-[Acetyl(2,3-dihydroxypropyl)amino]-1-*N*,3-*N*-bis(2,3 dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide and is identified with following structure.



Iodine content: 46.36%

CAS no: (b) (4) MW: 821.14 Molecula Formula: C₁₉H₂₆I₃N₃O₃

The proposed drug substance manufacturing site is:

Interpharma Praha, a.s.

Komořanská 955

143 10 Praha 4 – Modřany - CZECH REPUBLIC

DMF 26641 Type II. Holder: Interpharma Praha, a.s. LoA dated 24-Jan-2013 is provided.

Based on six months accelerated and up to 24 months long term stability data on four commercial batches, the applicant proposes a (b) (4) retest period for the drug substance. Acceptance criteria for drug substance stability are found to be identical to the corresponding acceptance criteria for drug substance release specification. All manufacturing information, methods and controls are referenced to the DMF. The analytical methods and validation are provided in the DMF and verification of methods is presented in the application.

Drug Substance Critical Issues

- The drug substance, iohexol DMF 26641 should be reviewed for adequacy.

- The drug substance impurities should be justified as per ICHQ3A. The CMC reviewer should alert the Pharmacology/Toxicology reviewer regarding any impurities present at levels about those stated in ICH Q3A.
- The acceptance criterion for Individual Unknown Related Substance (Maximum Individual Unknown, NMT ^{(b) (4)} %) should be evaluated to assure that all unknown impurities are accounted for in the total for impurities.
- The identified impurities in the drug substance should be compared to those in the RLD specification for its DS.
- A ^{(b) (4)} retest period is proposed for the drug substance, this should be confirmed with the stability data provided in DMF 26641.

Drug Product (DP)

The finished drug product, iohexol ^{(b) (4)} solution, is proposed as a non-sterile, powder which is intended for oral administration. The drug product requires dilution prior to administration. The single dose product is filled with 9.7 g of iohexol (4.5 g of iodine) in a 20 oz. transparent polyethylene terephthalate (PET) bottle capped with a white polypropylene (PP) cap with liner. The cap liner is made of ^{(b) (4)}

The composition of the drug product consists of only the active ingredient iohexol and contains no excipients. The proposed drug is formulated as powder with 9.7 g of iohexol (equiv. 4.5 g of iodine) per bottle. Upon reconstitution with water or a beverage, the amount of iohexol per bottle allows several standard concentrations (9, 12, 15, 18 and 21 mgI/mL) to be prepared by filling to the indicated fill line on the bottle's label.

The proposed commercial drug product manufacturing site is:

Ultra Seal Corporation (USC)

521 Main Street

New Paltz, NY 12561 - USA

Drug product release will be performed by:

^{(b) (4)}

An Establishment Evaluation Request was submitted to the Office of Compliance to evaluate cGMP compliance for the drug product manufacturing and release sites listed in the submission.

Drug product specifications include Appearance, Identification (IR), content uniformity, Assay (Argentometry), ^{(b) (4)} microbial tests (aerobic, yeast/mold and E. coli). The specifications for the drug product stability are consistent with the corresponding specifications for drug product release.

Batch analysis is presented for three batches (same 3 used for stability batches) manufacture by Ultra Seal Corporation (USC) ^{(b) (4)} for commercial production. All batches were packaged in the container closure system to be used for commercialization.

Long term and accelerated stability data is presented for three lots of drug product manufactured in 2011. The batches were pilot scale of (b) (4) bottles ((b) (4) of commercial batch size). For each primary stability batch, a different batch of drug substance was used. Nine months of long term (25°C/60% RH) stability data is presented as well as six months of accelerated (40°C/75% RH) stability data for all three lots.

As requested in the pre-NDA meeting the application contains in-use stability studies. Chemical stability (assay by HPLC) was assessed at 24, 48, and 72 hours at ambient room temperature and refrigerated conditions (5 ±3°C) for product (1 lot) reconstituted with water, apple juice and Gatorade. The microbiological stability was evaluate of product (3 lots) reconstituted with tap water and incubated at ambient room temperature for up to 2 days. Microbial growth (cfu) was determined on TSA agar plates after 5 days of incubation.

The applicant proposes 24 months shelf-life for iohexol (b) (4) oral solution stored at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) based on a maximum of 9 months at CRT and 6 months accelerated stability data for 3 lots of product. In addition, one supporting lot with 18 months storage at CRT for 18 months and accelerated data with 6 months of storage. The lot was an early development lot (b) (4) and packaged in same container to be used for commercialization.

According to the Pre-NDA Type B Meeting minutes (19-Apr-2012), Facsimile (23-May-2012) relating to Question 3 and 8 (CMC) the applicant will submit to the Agency on-going stability data in electronic form with statistical analysis of all stability indicating quality attributes by mid-cycle review timeline. The FDA response agree with the plan and stated that 12 months long term and 6 months stability would be required at the time of NDA submission. The NDA only provided 9 months long term so, an inquiry about this was made by the Agency on 3-Apr-2013. The company responded on 9-Apr-2013 explaining their understanding is that the FDA allowed the company to add the 12 months stability data during the review of the NDA. Therefore, the stability data available in support of the proposed expiry is considered a review issue.

Drug Product Critical Issues

- Assure that all requests from the Pre-NDA Type B Meeting (19-Apr-2012) and Facsimile (23-May-2012) relating to Question 3 and 8 (CMC) are adequately addressed in the NDA.
- Determine if all appropriate tests for an oral powder are included in the drug product specifications.
- The identified degradants in the drug product should be compared to those in the RLD specification.
- The DMFs for drug product container/closure systems need to be reviewed for adequacy.
- Determine if the applicant appropriately established impurity acceptance limits based on ICH Q3B(R2). The applicant states that ICH Q3B(R2) allows for limits of NMT 0.5% for individual degradation products, but based on the daily dose, the limits should be lower (NMT (b) (4) %) unless adequately justified. The reviewer should discuss the proposed acceptance limits for the identified degradation products to determine if the limits (NMT (b) (4) %) are justified by toxicological exposure and /or compared to those degradation products in the RLD specifications.
- Determine if the stability of data for the batches manufactured at Ultra Seal Corporation support the proposed 24-months expiration.
- The statistical analysis of stability data should be requested and evaluated for relevance in establishing the product shelf life.

- The relevant CMC sections for the proposed labeling, should be evaluated.

Recommendations for Fileability

NDA Number: 205-383 **Chemical Type/ Review Status:** 3, 5 / Standard **Trade / Established Name:** (b) (4)® / Iohexol

Applicant: Interpharma Praha, a.s. **Letter Date:** 03/11/2013 **Stamp Date:** 03/11/2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		IND 114,359: pre-NDA 20-Mar-2012

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			N/A
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> Name of facility, Full address of facility including street, city, state, country FEI number for facility (if previously registered with FDA) 	X		Interpharma Praha a.s., Iohexol, DS DMF 26641, Type II

	<ul style="list-style-type: none"> • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		(M1)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF 26641
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF 26641
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		(M1)
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?		X	Only 9 months for 3 lots at CRT and 6 months accelerated stability for DP are provided in support of requested 24 mos. Expiry.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		Referenced to DMF 26641

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Solid oral dosage form

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF Number	Holder	Description	LOA Included
26641 (Type II)	Interpharma Praha, a.s.	API - Iohexol powder, for oral (b) (4)	Yes 1/24/13
			Yes 10/25/12
			Yes 10/26/12
			Yes 10/25/12
			Yes 10/25/12
			Yes 12/12/12
			No

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		Based on sufficient body of data

35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		No

Yes No

ONDQA Fileability:

x

Comments for 74-Day Letter:

x

Comments and Recommendations

The application is fileable although the stability data to support the requested expiration dating of 24 months is not sufficient in support of such expiry period. Facilities are entered into EES for inspection. Even though this is a non-sterile product, a request to Microbiology review consult is recommended to assess the microbial quality of the reconstituted product which part of the stability testing and the microbiology specifications for the iohexol powder. A biopharmaceutics reviewer has been assigned to assess a bioequivalence waiver for the iohexol (b) (4) oral solution product. A team review including a microbiologist and a biopharmaceutics is recommended for this NDA, and only one chemist reviewer because the drug substance and drug product manufacturing processes are not complex.

Consults:

1. **Microbiology, ONDQA** (Jessica Cole, Ph.D.)
2. **Biopharmaceutics, ONDQA** (Albert (Tien Mien) Chen, Ph.D.)

EERequests: Entered in EES and submitted to OC on 5-Apr-2013

{See appended electronic signature page}

Milagros Salazar, Ph.D., Senior Review Chemist, Branch VII 18-Apr-2013 Date
 Division III, Office of New Drug Quality Assessment

{See appended electronic signature page}

Eldon Leutzinger, Ph.D., CMC Lead, Branch VII Date
 Division III, Office of New Drug Quality Assessment

{See appended electronic signature page}

Danae Christodoulou, Ph.D., Active Branch Chief, Branch VII Date
 Division III, Office of New Drug Quality Assessment

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

/s/

MILAGROS SALAZAR DRIVER

04/18/2013

CMC Recommendation: to file this application.

ELDON E LEUTZINGER

04/19/2013

DANAE D CHRISTODOULOU

04/19/2013