CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-425

Chemistry Review(s)

NDA 21-425

ULTRAVIST™ (Iopromide) Injection
Pharmacy Bulk Package , 500 mL

300 mgI/mL and 370 mgI/mL

For Intravenous Administration

Berlex Laboratories, Inc.

Milagros Salazar, Ph.D.
Division of Medical Imaging and Radiopharmaceutical DPs
HFD-160

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. NDA #: 21-425

2. REVIEW DATE: 5-JUL-2002, 19-Jul-02 rev

3. REVIEW #: 1

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED: Original

Submission(s) Reviewed	Document Date
Original	21-NOV-2001
Amendment N-000 BZ	10-JAN-2002

7. NAME & ADDRESS OF APPLICANT: BERLEX LABORATORIES, INC.
340 Changebridge Rd.
Montville, NJ 07450-1000

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	ULTRAVIST® Injection, Pharmacy Bulk Package
Non-Proprietary Name (USAN)	Iopromide
Code Name/#:	ZK 35 760
Chem.Type/Submission Priority	3 S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY/INDICAT.: Aortography; Visceral Angiography; Coronary Arteriography/left Ventriculography; Cerebral Arteriography; Peripheral Arteriography; Contrast Enhanced Computed Tomography (Head and Body); Excretory Urography

11. DOSAGE FORM: Injection, Pharmacy Bulk Package (500 mL bottle)

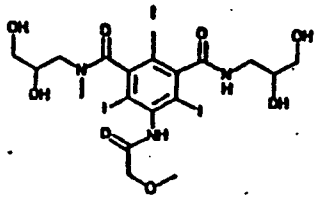
12. STRENGTH/POTENCY: 300 and 370 mgI/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC: _X_ Rx ___ OTC

15. SPOTS (Special Products On-line Tracking): ____ Yes _X_ No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
N,N'-Bis(2,3-dihydroxypropyl)-2,4,6,-triiodo-5-(2-methoxyacetamido)-N-methylisophthalamide
$C_{18}H_{24}I_3N_3O_8$ MW 791.12 Iodine content: 48.12%



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	STATUS	REVIEW DATE	COMMENTS
[redacted]	II	Schering AG	Iopromide	Acceptable	30-DEC-1998 18-SEP-2000[1] 8-APR-2002[2]	Drug Substance

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-220 / Berlex Labs., Inc. [1]SCP-011 approved (4-Jan-01) 20-220/Berlex Labs., Inc. [2]SCM-013 approved (11-Apr-02)	
NDA	20-220 / Berlex Labs., Inc. [1]SCP-011 approved (4-Jan-01)	500mL bottle clear, colorless. USP Type II glass
NDA	20-220 / Berlex Labs., Inc. [1]SCP-011 approved (4-Jan-01)	

18. STATUS OF CONSULTS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall: Pending Berlex- acceptable Schering AG Wedding- acceptable Schering AG Charlottenburg- pending	Requested : 12-FEB-2002 Final : pending (as of 19-Jul-02)	DO- IRivera CDER-OC - JDambrogio
Biostatistics	NA		
EA	Categorical Exclusion	12 -JUL-2002	Milagros Salazar, Ph.D.
Microbiology	Approvable	11-MAR-2002	Stephen E. Langille, Ph.D.
Biopharm	NA		
Other	NA		

Patent/Trademark: Patent no. 4,364,921 Expiration Date: 06-MAR-2005 Type of patent: Formulation, Composition & Method of use of Ultravist (iopromide) Injection Pharmacy Bulk Package.
Patent owner: Schering AG

19. ORDER OF REVIEW: NA

CHEMISTRY EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations and Conclusions on Approvability
Based on the chemistry section, *ULTRAVIST®* Inj., Pharmacy Bulk Package (300 and 370 mgI/mL) is recommended for APPROVAL pending an overall status of acceptability of cGMPs for the manufacturing facilities involved.

B. Recommendations on Phase 4 (post-marketing) Commitments: NONE

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

ULTRAVIST® (iopromide) Injection, Pharmacy Bulk Package is used as an X-ray contrast agent for intravascular administration during indicated X-Ray imaging diagnostic procedures. *ULTRAVIST®* is supplied in two strengths, 300 and 370 mgI/mL in 500 mL glass bottle. Each bottle is to be used as a Pharmacy Bulk Package for dispensing multiple single doses. *ULTRAVIST®* Injection is a nonionic, sterile, clear, colorless to slightly yellow, odorless, pyrogen-free aqueous solution of iopromide. Solutions of Ultravist Injection 300 mgI/mL and 370 mgI/mL have osmolalities of 607 and 774 mOsmol/kg water @ 37 °C respectively and are approximately 2.1 to 2.7 times that of plasma (285 mOsmol/kg water).

The drug substance iopromide is an nonionic aromatic iodinated compound with a molecular weight of 791.12 , a molecular formula of $C_{16}H_{24}I_3N_3O_8$ and has an Iodine content of 48.12%.

The chemistry , manufacturing and controls for the both iopromide drug substance and Ultravist drug products 150, 240, 300 and 370 mgI/mL are covered under Type II DMF [redacted] and NDA 20-220 respectively. By reference to those applications, this NDA has provided all regulatory specification and controls.

The differences between the currently approved Ultravist products and those covered in this application are their use (single use vs. multiple use) and their size presentations (50 mL , 100mL, 150mL and 250mL vials vs. 500mL bottle). This application provides description and control information for the new 500 mL bottle container-closure, and stability of the Ultravist 300 and 370 mgI/mL Injection with full term stability data in support of 36 months expiry time proposed for these products.

ULTRAVIST® Injection, PBP, products are supplied as follows:

300 mgI/mL	*1 x 500 mL bottles .... NDC 50419-344-XX*
	8 x 500 mL bottles ... NDC 50419-344-XX
370 mgI/mL	*1 x 500 mL bottles .... NDC 50419-346-XX*
	8 x 500 mL bottles ... NDC 50419-346-XX

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

ULTRAVIST® Injection, PBP, 300 and 370 mgI/mL products are intended for dispensing multiple single dose preparations using a suitable transfer device. Ultravist is intended for intra-arterial

and intravenous administration. It is contraindicated for intrathecal use. It is indicated for cerebral and peripheral arteriography; for coronary arteriography and left ventriculography, visceral angiography and aortography; for contrast enhanced computed tomography (CECT) imaging of the head and body , and excretory urography. The recommended concentration and dose are posted in the package insert for both adults and pediatric populations. The maximum recommended dose of iodine (gI) in adults is 86 grams. *ULTRAVIST®* must be used within 10 hours after first punctured. Any unused portion should be discarded. Storage conditions for the kit components and constituted product at 25°C with excursions between 15°- 30°C (59°- 86°F).

C. Basis for Approvability or Not-approvability Recommendation

The recommendation for approval is based on the following:

1. The Ultravist 300 and 370 mgI/mL products have been marketed as single dose preparations since the approval of NDA 20-220 on 14-Jun-1993. The chemistry, manufacturing, controls history is well documented for these products.
2. Adequate information and data on the new container-closure system, 500mL infusion bottle (clear colorless, glass Type II); the rubber stopper (and the cap
3. The stability data and studies are adequate in support of 36 months at CRT storage of *ULTRAVIST®* Injection, PBP, 300 & 370 mgI/mL products . Shelf-life of 10 hours after first entry based on preservative effectiveness studies. See Microbiology review dated 11-Mar-02.
4. PENDING an Establishment Evaluation report overall acceptable status: Berlex and Schering AG –Wedding plant acceptable as of 14-Feb-02; Schering AG-Charlottenburg plant is pending as 19-Jul-02.

III. Administrative

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-820/160

/S/

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-820/160

cc:
Org. NDA 21-425
HFD-160/Division File
HFD-160/Salazar/Leutzinger
HFD-160/ Nguyen

filename: **N21-425ultravist-PBP.doc**

Redacted 34

pages of trade

secret and/or

confidential

commercial

information

23 pages redacted from this section of the approval package consisted of draft labeling

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21425/000**
Priority: **S**
Org Code: **160**
Stamp: **21-NOV-2001** Regulatory Due: **21-SEP-2002**
Action Goal:
District Goal: **23-JUL-2002**
Applicant: **BERLEX LABS**
340 CHANGEBRIDGE RD
MONTVILLE, NJ 070451000
Brand Name: **ULTRAVIST(IOPROMIDE)300MGL/ML/370MGL/ML**
Established Name:
Generic Name: **IOPROMIDE**
Dosage Form: **INJ (INJECTION)**
Strength: **300 AND 370 MG I/ML**

FDA Contacts:
T. NGUYEN (HFD-160) 301-827-7510 , Project Manager
M. SALAZAR DRIVER (HFD-160) 301-827-7510 , Review Chemist
E. LEUTZINGER (HFD-160) 301-827-7510 , Team Leader

Overall Recommendation:

Establishment: **2243252**
BERLEX LABORATORIES INC SUB S(
300 FAIRFIELD RD
WAYNE, NJ 074707358
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-FEB-2002**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: **9610131**
SCHERING AG
MULLERSTRASSE 170-178
WEDDING, BERLIN, GM
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-FEB-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: **9611633**
SCHERING AG
MAX DORN STRABE 8-10
CHARLOTTENBURG, BERLIN, GM D
DMF No:
AADA No:

Profile: **LVP** OAI Status: **NONE**
Last Milestone: **INSPECTION SCHEDULED**
Milestone Date: **12-JUN-2002**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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
7/19/02 02:27:10 PM
CHEMIST
Approval recommended, with letter to the sponsor.

Eldon Leutzinger
7/22/02 12:36:29 PM
CHEMIST
I concur with all conclusions in the review, and the recommendation of APPROVAL pending a determination of acceptability of cGMP's, based on chemistry.