CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20808/S1

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 28 1999

NDA 20-808/S-001

Nycomed Inc.
101 Carnegie Center
Princeton, NJ 08540-6231

Attention: Lucine Karjian
Manager, Regulatory Compliance

Dear Ms. Karjian:

Please refer to your supplemental new drug application dated October 15, 1998, received October 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Visipaque (iodixanol) Injection Pharmacy Bulk Pack, 270 and 320 mgI/mL.

This supplemental new drug application provides for a labeling change to extend the maximum time permitted to complete fluid transfer from four (4) to eight (8) hours.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 15, 1998). Accordingly, the supplemental application is approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Catalina Ferre-Hockensmith, Consumer Safety Officer, at (301) 827-7510.

Sincerely,

/S/

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20808/S1

FINAL PRINTED LABELING

SHIPPER LABEL

NDC 0407-2222-07

Sterile Aqueous Injection **200mL**

VISIPAQUE®

(IODIXANOL) Injection

PHARMACY BULK PACKAGE-
Not for Direct Infusion

270mgI/mL

NOT FOR INTRATHECAL USE

Each 1 mL contains 550 mg of iodixanol (270 mg organically bound iodine), 0.074 mg calcium chloride dihydrate, 1.87 mg sodium chloride, 1.2 mg tromethamine, and 0.1 mg edetate calcium disodium.

The pH is adjusted to 7.4 with hydrochloric acid and/or sodium hydroxide to achieve a range between pH 6.8 - 7.7. Osmolality is 290 mOsm/kg water. No preservative added.

Once a sterile transfer needle or spike has been inserted into the container outlet site, withdrawal of container contents should be completed without delay. If fluid transfer cannot be completed without delay, discard the container no later than 8 hours after initial puncture.

Protect from light. Do not freeze. For indications, dosage and further information on the use of the Pharmacy Bulk Package, see circular. Store at USP controlled room temperature, 20°C to 25°C (68°F to 77°F).

R_X ONLY

NYCOMED

Distributed by Nycomed Inc. Princeton, NJ 08540
For inquiries call 1-800-654-0118.

Lot: _____

Expires: _____

Bottle Label

NDC 0407-2222-07

Sterile Aqueous Injection

200mL

VISIPAQUE®

(IODIXANOL) Injection

PHARMACY BULK PACKAGE-
Not for Direct Infusion

270mgI/mL

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R_X ONLY

NYCOMED

Distributed by Nycomed Inc. Princeton, NJ 08540
For inquiries call 1-800-654-0118.

Date Entered: _____

Time of Entry: _____

Lot: _____

Expires: _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20808/S1

CHEMISTRY REVIEW(S)

WW file

1999

CHEMIST'S REVIEW	1.ORGANIZATION HFD-160	2. NDA Number(s) N 20808
3. Name and Address of Applicant (City & State): NYCOMED, INC. 101 Carnegie Center Princeton, NJ 08540 - 6231		4. AF No. 5. Supplement(s) Number(s) Date(s) SLR-001 15-Oct-98
6. Drug Name: Visipaque® Injection	7. Nonproprietary Name: Iodixanol Injection	8. Amendments & Other (reports, etc.) - Dates
9. Supplement Provides For: A labeling change to extend the maximum time permitted to complete fluid transfer from four (4) to eight (8) hours after the septum of the pharmacy bulk pack has been punctured.		
10. Pharmacological Category: Radiopaque Contrast Agent	11. How Dispensed: ☒ Rx ☐ OTC	12. Related IND(s)/ NDA(s)/DMF(s)
13. Dosage Form(s): Injection	14. Potency(ies): 270 mgI/mL 320 mgI/mL	
15. Chemical Name and Structure: **5,5'-[(2-hydroxy-1,3-propanediyl)bis (acetylimino)]bis[N,N -bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benxenedicarboxamide]**		16. Records/Reports Current: ☐Yes ☐ No Reviewed: ☐Yes ☐No
17. Comments: The supplement requests a labeling change to allow the use of this pharmacy bulk pack product up to 8 hours, instead of the current 4 hours, after the container septum has been punctured. This is primarily a microbiological issue in that whether product remains sterile for 8 hours after the septum has been punctured. The sponsor has provided appropriate data to support this change which the microbiologist has found to be acceptable. The reviewing microbiologist recommends approval of this supplement. The sponsor has made appropriate changes in the labeling of this product, which is submitted.		
18. Conclusions and Recommendations: The supplement is recommended for approval. CC: Original NDA# 20,808 HFD-160/Division File HFD-160/Kasliwal R/D initialed by : Leutzinger		
19. REVIEWER		
Name Ravindra K. Kasliwal, Ph.D.	Signature /S/	Date Completed 12-Jan-99

/S/ 1/21/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20808/S1

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-160
MICROBIOLOGIST'S REVIEW #1 OF SUPPLEMENT
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY REVIEW STAFF

October 29, 1998

NDA/Supplement Number: 20-808

Document Date: 15 October 1998

Date Assigned for Review: 27 October 1998

Amendments and Others: none

Name and Address of Applicant: NYCOMED INC.
101 Carnegie Center
Princeton, NJ 08540-6231

Name of Drug: Visipaque (Iodixanol) Injection Pharmacy Bulk Pack

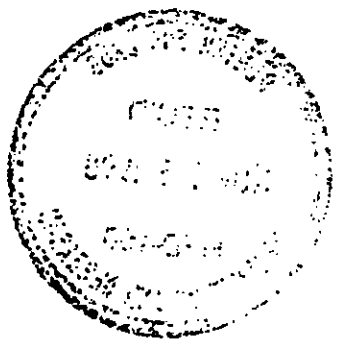
Supplement Provides For: A labeling change to extend the maximum time permitted to complete fluid transfer from four (4) to eight (8) hours.

Pharmacological Category: Radiopaque Agent

Dosage Form: A sterile injectable product in 200 and 500 mL bottles at concentrations of 270 and 320 mg I/mL

Related Documents: Original NDA 20-808

Comments: The applicant has provided data in support of their request for a labeling change. A study report entitled: Microbiological challenge test of iodixanol injection, was included with the supplement.



Conclusions and Recommendations: The submission is recommended for approval.

/S/

Bryan Riley, Ph.D.

cc: /S/ 11/10/98

Original NDA
HFD 160/Consult File
HFD 120/CSO/
HFD 120/Chemist/
HFD 805/B. Riley

Drafted by: B. Riley,
R/D initialed by: P. Cooney

Filename, d:\nda\s\00-000rx.s00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20808/S1

ADMINISTRATIVE DOCUMENTS

New file

JAN 25 1999

LABELING REVIEW

Application Number: NDA 20-808/S-001

Name of Drug: Visipaque Injection Pharmacy Bulk Package

Sponsor: Nycomed, Inc.

Material Reviewed

Submission Date(s): October 15, 1998

Receipt Date: October 20, 1998

Background: This supplement provides for a labeling change to extend the maximum time permitted to complete fluid transfer from four to eight hours for Visipaque (iodixanol) Injection Pharmacy Bulk Package 270, and 320 mgI/mL, packaged in 200 and 500 mL bottles. A comparison between the most recently approved labeling for Visipaque (iodixanol) Injection was completed. Any differences between the two labels are noted below:

Review

1. **LABORATORY TEST FINDINGS** Section, 2nd paragraph, 6th sentence:

Currently approved labeling (Visipaque) reads:

> "Erythrocyte rigidification (measured by half-conductance of the Mynipore sieve with hematocrit adjusted to 8%) was comparable to that of other nonionic comparators."

Proposed labeling (Visipaque Pharmacy Bulk Package) reads:

[

ACCEPTABLE ☐✓ **UNACCEPTABLE** ☐

/S/ 1/25/99

A. Eric Jones, M.D.
Medical Team Leader

2. **STORAGE** Section, 2nd sentence:

Currently approved labeling (Visipaque) reads:

> "Store vials, bottles, and flexible containers at temperatures between 15°C to 30°C (59°F to 86°F). Do not remove foil overwrap, which serves as a moisture and light barrier, from flexible containers until ready to use."

Proposed labeling (Visipaque Pharmacy Bulk Package) reads:

ACCEPTABLE ☑ **UNACCEPTABLE** ☐

/S/
Bryan S. Riley, Ph.D.
Microbiology Reviewer

/S/ 1/25/99
Peter Cooney, Ph.D.
Microbiology Team Leader

/S/
Eldon Leutzinger, Ph.D.
Chemistry Team Leader

3. **DIRECTIONS FOR PROPER USE OF VISIPAQUE PHARMACY BULK PACKAGE** Section, item c, 2nd sentence:

Currently approved labeling (Visipaque) reads:

> "However, should this not be possible, a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operations. The container should not be removed from the aseptic area during the entire 4 hour period."

Proposed labeling (Visipaque Pharmacy Bulk Package) reads:

ACCEPTABLE ☑ **UNACCEPTABLE** ☐

/S/
Bryan S. Riley, Ph.D.
Microbiology Reviewer

/S/ 1/25/99
Peter Cooney, Ph.D.
Microbiology Team Leader

/S/
Eldon Leutzinger, Ph.D.
Chemistry Team Leader

Nycomed want to go to ICH storage conditions in all their stability studies - That means room temp is 25°C upper limit. They can label to reflect that in two ways, but it must be consistent with USP CRT if that is what they want; that range would be 20-25°C. PbP Visipaque [illegible] comes as bottle [illegible] without need of overwrap.
[illegible] 1/28/99

Recommendation: Pending that all changes to the labeling are found acceptable the supplement can be approved. Otherwise, the supplement should be approved on marked-up draft labeling.

/S/

Catalina Ferre-Hockensmith
Consumer Safety Officer

/S/ 1/25/99

Concur:
Robert K. Leedham, Jr.
Chief, Project Management Staff

/S/

Concur:
Bryan S. Riley, Ph.D.
Microbiology Reviewer

/S/ 1/25/99

Concur:
Peter Cooney, Ph.D.
Microbiology Team Leader

/S/ 1/25/99

Concur:
A. Eric Jones, M.D.
Medical Team Leader

/S/

Concur:
Eldon Leutzinger, Ph.D.
Chemistry Team Leader

/S/ 01/28/99

Concur:
Patricia Y. Love, M.D., M.B.A.
Director, Division of Medical Imaging and
Radiopharmaceutical Drug Products