CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 018956/S043

Trade Name: OMNIPAQUE

Generic Name: IOHEXOL INJECTION

Sponsor: NYCOMED INC.

Approval Date: 06/15/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 018956/S043

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 018956/S043

APPROVAL LETTER

JUN 15 1995

NDA 9-561 + 3 others

Nycomed Inc.
90 Park Avenue
New York, New York 10016

Attention: Linda Nardone, Ph.D.
Director, Regulatory Affairs

Dear Dr. Nardone:

Please refer to your supplemental new drug applications submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic act and dated as follows:

Dated July 9, 1993:

NDA 9-561/S-077	Hypaque 20% (Diatrizoate Sodium 20%)
" "	Hypaque 25% (Diatrizoate Sodium 25%)
" "	Hypaque 50% (Diatrizoate Sodium 50%)
" "	Hypaque-Cysto (Diatrizoate Meglumine 30%)
" "	Hypaque-M 75% Diatrizoate Meglumine 50% and Diatrizoate Meglumine sodium 30%)
NDA 16-403/S-068	Hypaque Meglumine 30% (Diatrizoate Meglumine 30%
" "	Hypaque Meglumine 60% (Diatrizoate Meglumine 60%)
NDA 18-956/S-043	Omnipaque 140 (Iohexol Injection)
" "	Omnipaque 350 (Iohexol Injection)

Dated July 28, 1993:

NDA 11-386/S-033	Hypaque Sodium Oral Solution (Diatrizoate Sodium)

We acknowledge receipt of your amendments and correspondence dated March 7 and 25, April 25 and 28, May 5, September 12, and November 9, 1994, and March 23 and 24, 1995. We also refer to our February 18, 1994, supplement approvable letter. The September 12 and November 9, 1994, correspondence provided for commitments to revised labeling as requested in our July 13, 1995, FAX communication. The March 23 and 24, 1995, amendments provided for additional labeling revisions to the package insert for Omnipaque (18-956/S-043).

These supplements provide for revised vial, carton, and package insert labeling to include a boxed warning **"NOT FOR INTRATHECAL USE"** or **"NOT FOR MYELOGRAPHY"**.

We have completed our review of these supplemental applications including the submitted draft labeling as amended and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective as recommended in the May 5, 1994 (NDAs 9-561/S-077, 11-386/S-033 and NDA 16-403/S-068) and March 24, 1995 (NDA 18-956/S-043) draft labeling. Accordingly, these supplemental applications are approved effective the date of this letter.

Please note that all current labeling should include the Nycomed Inc. name on all vial, carton, and package insert labeling.

We also wish to advise you that when available the Agency will issue recommendations concerning labeling for controlled room temperature storage statements which will probably differ from the statement currently used in your labeling.

We note from your May 5 and September 12, 1994, letters that you do not intend to supply revised labeling for Hypaque-M 75% and Hypaque-M 90% (NDA 10-220) since these products have been discontinued and no are longer maintained in inventory. We also note in your September 12, 1994, letter that you are presently in the process of establishing a tracking program for these products and intend to provide an attached letter to customer accounts that addresses our concerns about the "M" in the product trade names. This appears to be a reasonable solution as an alternative to a sticker program and should be implemented as soon as possible.

Please submit fifteen copies of the FPL identical with the draft labeling with the above revisions within 6 months or at the next printing, whichever is sooner. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 9-961 + 3 others. Approval of the FPL is not required before it is used. Marketing the products with FPL that is not identical to the draft labeling dated May 5, 1994 (NDA 9-561/S-077, NDA 11-386/ S-033 and NDA 16-403/S-068) and March 24, 1995 (NDA 18-956/ S-043), with the above revision, may render the products misbranded and unapproved drugs.

Should additional information relating to the safety and effectiveness of the drugs become available, further revision of the labeling may be required.

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

Should there be any questions please contact:

Steve McCort
Consumer Safety Officer
(301) 443-7515

Sincerely yours.

/S/

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CC: ARCHIVE
HFD-160/DivFile
HF-2/MedWatch w/Labeling
HFD-2/Lumpkin
HFC-130/District Office
HFD-80 w/Labeling
HFD-101 w/Labeling
HFD-244 w/Labeling
HFD-638 w/labeling
HFD-735 w/Labeling
HFD-Love
HFD-160/Chow
HFD-160/Jones
HFD-160/Sheinin
HFD-161/McCort

Drafted by: Steve McCort 5-9-95
Revised by: Steve McCort 5-30-95
Revised by:Steve McCort 6-5-95
Acknowledgements: Cheever, 5.30.95
F/T by: Wilson, 5.30.95
F/T by: Wilson, 6.6.95

SUPPLEMENTS APPROVAL

/S/ 6/13/95

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018956/S043

APPROVABLE LETTER

NDA 9-561 + 3 others

FEB 18 1994

Sterling Winthrop Inc.
90 Park Avenue
New York, New York 10016

Attention: Linda Nardone, Ph.D.
Director Regulatory Affairs

Dear Dr. Nardone:

We refer to your supplemental new drug applications dated July 9 and July 28, 1993, for the following products:

July 9:

NDA 9-561/S-077	Hypaque Sodium 20% (Diatrizoate Sodium 20%)
NDA 9-561 "	Hypaque Sodium 25% (Diatrizoate Sodium 25%)
NDA 9-561 "	Hypaque Sodium 50% (Diatrizoate Sodium 50%)
NDA 9-561 "	Hypaque-Cysto (Diatrizoate Meglumine 30%)
NDA 9-561 "	Hypaque-M 75% (Diatrizoate Meglumine 50% and Diatrizoate Meglumine Sodium 30%)
NDA 16-403/S-068	Hypaque Meglumine 30% (Diatrizoate Meglumine 30%)
"	Hypaque Meglumine 60% (Diatrizoate Meglumine 60%)
NDA 18-956/S-043	Omnipaque 140 (Iohexol Injection)
NDA 18-956 "	Omnipaque 350 (Iohexol Injection)

July 28:

NDA 11-386/S-033	Hypaque Sodium Oral Solution (Diatrizoate Sodium)

These supplements provide for revised vial, carton, and package insert labeling to include a boxed warning **"NOT FOR MYELOGRAPHY"** submitted in response to our letters dated April 14 and June 8, 1993.

We also refer to your correspondence dated July 9 and August 9, 1993, for Isopaque 440 (NDA 16-847), Isopaque 280 (NDA 17-506), Isopaque 370 (NDA 17-530) and Hypaque-M-90% (NDA 10-220) requesting exclusion of these compounds from the box warning labeling requirement. Additionally we refer to your correspondence dated May 13, July 2, and September 28, 1993, responding to our letters dated April 14, June 8, and September 13 and 17, 1993.

We have completed our review of these supplemental applications, as amended, including the draft labeling dated July 9 and July 28, 1993, and they are approvable. However, we wish to note that subsequent internal discussions have concluded that the either **"NOT FOR INTRATHECAL USE"** or **"NOT FOR MYELOGRAPHY"** can lead to miscommunication. The former statement is more direct. Hence all manufacturers should use the statement **"NOT FOR INTRATHECAL USE"** in the package insert and labels. Before the applications may be approved, however, we request that you submit revised labeling as an amendment to these applications which respond to our recommendations and comments as follows:

For immediate container and carton labels:

1. The color of the warning statement **"NOT FOR INTRATHECAL USE** on the immediate container and carton labels should be such that the warning stands out from the rest of the labeling. We request that the warning statement is in red for consistency and to alert the user that there is a warning associated with a particular product.

2. The size of the lettering should be such as to assure that the statement stands out from the rest of the label. The size of the warning statement should be at least 50% that of the largest letter in the trademark. The lettering on all of the labels, both immediate container and carton, needs to be changed so that the size of the warning statement is at least 50% that of the largest letter in the trademark. This labeling revision applies also to all foil overwraps for these products.

3. Under 21 CFR 211.137(b), the immediate container labels are required to have the recommended storage temperature indicated. None of the labels for the products covered under these NDA's have such a statement. This statement should read "Protect from light. Store at controlled room temperature 15°C to 30°C (59°F to 86°F)." This requirement is applicable to the plastic containers as well. Similarly, the carton labels must include the storage conditions for these products.

4. The size (volume) of the immediate container should be indicated on the foil overwrap. Additionally, the expiration date and lot number should appear on the immediate containers, carton labels, and overwrap.

5. Representative cartons were submitted for the 10-100 mL vials of Hypaque Meglumine 30% (NDA 9-561/S-077) and for the 25-50 mL vials and 10-100 mL vials of Hypaque Meglumine 60% (NDA 16-403/S-068). Please submit representative cartons for the other products covered under these NDAs.

For package inserts:

1. As stated in our June 8, 1993, letter the boxed warning labeling, **"NOT FOR INTRATHECAL USE"** should be placed on the package insert on page 1, below the drug name, and above the **DESCRIPTION SECTION**.

2. Under the **WARNINGS** section the following paragraph should be added:

   "SEVERE ADVERSE EVENTS- INADVERTENT INTRATHECAL ADMINISTRATION

   Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not administered intrathecally."

3. Under 21 CFR 201.57(k)(4), the **"How Supplied"** section, under Storage, the °F and °C temperatures should be reversed to coincide with the recommended statement on the container and carton labels. The new statement should read:

   "Protect from sunlight. Store at controlled room temperature 15°C to 30°C (59°F to 86°C)."

   Note that this labeling recommendation applies also to the foil overwrap.

Based upon the information supplied in your letter dated August 9, 1993, Hypaque-M 90% (NDA 10-220) cannot be exempted from the boxed warning requirement, since the final batch for this product will not expire until May 1996. Therefore you are required to submit revised labeling. Alternatively, a sticker program could be used for this product.

Please note that these recommended labeling changes do not apply to the drug products Isopaque 440 (NDA 16-847), Isopaque 280 (NDA 17-506), Isopaque 370 (NDA 17-530). This is based upon your letters dated July 9, 1993, which stated that these products are currently not marketed and the expiration for the last lots was in 1985.

In addition to the above discussed labeling changes we also request that the trademark names for both Hypaque-M 75% (NDA 9-561) and Hypaque-M 90% (NDA 20-220) be revised to exclude "M" from the name. The "M" stands for "meglumine" and may be confused with the term "myelography" and result in mis-administration during myelographic procedures.

Within 10 days after the date of this letter, you are required to amend these applications, or notify us of your intent to file amendments under 21 CFR 314.110. Failure to submit amendments within 30 days of this letter date may render these products misbranded according to section 502(a) of the Act. The changes indicated above cannot be legally implemented until you have been notified in writing that the applications are approved.

Should there be any questions please contact:

Steve McCort
Consumer Safety Officer
(301) 443-7515

Sincerely yours,

/S/

Patricia Y. Love, M.D., M.B.A.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CC: NDA 9-561/S-077 + 3 others
HFD-160/DivFile

HFC-130
HFD-80
HFD-Love
HFD-160/Chow
HFD-160/Jones
HFD-160/Sheinin/Salazar
HFD-161/McCort/Kummerer

/S/ 2/16/94

Drafted by: Steve McCort 12-14-93
Acknowledgements: Cheever-02-04-94 sterl.box
F/T by: AChapman-02-04-94
SUPPLEMENTS APPROVABLE

APPEARS THIS WAY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018956/S043

CHEMISTRY REVIEW(S)

DIV

CHEMIST'S REVIEW	1. ORGANIZATION HFD-160	2. NDA Number 18-956
3. Name and Address of Applicant (City & State) Sterling Winthrop, Inc. 90 Park Avenue New York, NY 10016 AUG 10 1993		4. Supplement(s) Number(s) Date(s) SLR-043 7-9-93
5. Drug Name Omnipaque Injection	6. Nonproprietary Name Iohexol	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Revised labeling to include a warning concerning Intrathecal use.		
9. Pharmacological Category Contrast Agent	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s)	13. Potency(ies) 140, 180, 210, 240, 300, 350 mgI/mL	
14. Chemical Name and Structure N,N'-Bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodoisophthalamide		15. Records/Reports Current ☒ Yes ☐ No Reviewed ☒ Yes ☐ No
16. Comments:		
17. Conclusions and Recommendations: The proposed labeling is not acceptable. The supplement is approvable pending receipt of draft labeling with the recommended changes.		
18. REVIEWER		
Name Eric B. Sheinin, Ph.D.	Signature /S/	Date Completed 8-6-93
Distribution: ☒ Original Jacket ☒ Reviewer ☒ Division File ☒ CSO (mail cart)		

HFD-160/Salazar
HFD-160/Chow/Leutzinger
HFD-160/See
HFD-160/Hussong

/S/ 8/10/93

JUN 27 1994

DIV.

CHEMIST'S REVIEW	1. ORGANIZATION HFD-160	2. NDA Number 18-956
3. Name and Address of Applicant (City & State) Sterling Winthrop, Inc. 90 Park Avenue New York, NY 10016		4. Supplement Number: SLR-043 Date: 07-09-93
5. Drug Name Omnipaque	6. Nonproprietary Name Iohexol Injection	
8. Supplement Provides For: Revised labeling to include a warning regarding intrathecal use		7. Amendments & Other (Reports, etc)-Dates: NC (05-06-94)
9. Pharmacological Category Radicpaque	10. How Dispensed RX_X_ OTC___	11. Related IND(s), NDA(s), DMF(s)
12. Dosage Form (s)	13. Potency(ies) 140, 180, 210, 240, 300, 350 mgI/mL	
14. Chemical Name and Structure N,N'-Bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido-2,4,6-triiodoisophthalamide		15. Records/Reports Current Yes_X_ No___ Reviewed Yes_X_ No___
16. Comments: The warning statement, "NOT INTENDED FOR INTRATHECAL USE," is not sufficiently prominent. Also, some of the information on storage and how the system should be used has been omitted on the flexible bag. Basically, everything that is on the overwrap should also be on the flexible bag.		
17. Conclusions and Recommendations: (contd. next page)		

18. REVIEWER		
Name E. Leutzinger, Ph.D.	Signature /S/ 5-20-94	Date Completed 05-20-94

6-22-94

FILE: N18956.186

17.Contd.(Conclusions and Recommendations)
In my opinion, this supplement continues to be approvable, pending satisfactory responses from Sterling to make the labeling revisions as being recommended in the current draft comments.

cc:
Orig. NDA 18-956
HFD-160/Division File
HFD-160/Chow
HFD-160/E.Leutzinger
HFD-160/Kummerer
HFD-160/McCort
HFD-160/See
HFD-160/Hussong
R/D Init. by E.B.Sheinin
F/T by E.Leutzinger

/S/
6.27.94

DIV

JUN 27 1994

CHEMIST'S REVIEW	1. ORGANIZATION HFD-160	2. NDA Number 18-956
3. Name and Address of Applicant (City & State) Sterling Winthrop, Inc. 90 Park Avenue New York, NY 10016		4. Supplement(s) Number(s) Date(s) SLR-043 7-9-93
5. Drug Name Omnipaque Injection	6. Nonproprietary Name Iohexol	8. Amendments & Other (reports, etc) - Dates BL May 5, 1994
7. Supplement Provides For: Revised labeling to include a warning concerning intrathecal use.		
9. Pharmacological Category Contrast agent	10. How Dispensed ☐ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s)	13. Potency(ies) 70, 140, 180, 210, 240, 300, 350 mg I/mL	
14. Chemical Name and Structure N,N'-Bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodoisophthalamide		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No
16. Comments:		
17. Conclusions and Recommendations: The supplement is approvable pending receipt of draft labeling with the recommended changes.		
18. REVIEWER		
Name Eric B. Sheinin, Ph.D.	Signature /S/	Date Completed 6-27-94
Distribution: ☐ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO		

cc: NDA 18-956/S-043 (original)
HFD-160/Division File
HFD-160/Chow
HFD-160/Leutzinger
HFD-161/McCort

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018956/S043

ADMINISTRATIVE DOCUMENTS

DIV.

DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
LABELING REVIEW

DRAFT LABELING PACKAGE INSERT

APR 25 1995

NDA: 18-956/S-043

SPONSOR: Nycomed Inc.

DRUG PRODUCTS: Omnipaque 140 (Iohexol Injection)
Omnipaque 350 (Iohexol Injection)

SUPPLEMENT SUBMISSION DATE: July 9, 1993

AMENDMENTS: March 25, May 5, September 12, November 9, 1994; March 23 and March 24, 1995

DOCUMENT REVIEWED: March 24, 1995, draft package insert

SUPPLEMENT PROVIDES FOR: Revised labeling to include the "NOT FOR INTRATHECAL USE" boxed warning statement on the package insert and additional revisions to the PRECAUTIONS and HOW SUPPLIED sections of the package insert.

REVIEWER: Stephen McCort

REVIEW DATE: January 4, 1994

BACKGROUND:

The firm submitted draft labeling which included a red warning statement "NOT FOR INTRATHECAL USE" on white background for Omnipaque 140 and Omnipaque 350 (NDA 18-956/S-043 in response to supplement request letters dated April 14 and June 8, 1993.

An approvable letter dated February 18, 1994, was sent to the firm.

The firm responded on March 7, 1994, advising the division that a full response to our February 18, 1994, letter would be made shortly.

In an April 25, 1994, T/Con with the firm controlled room temperature statements and were discussed for these products.

Draft labeling for Omnipaque 140 and 350 were submitted to our division dated May 5, 1994.

Draft comments regarding the May 5, 1994, labeling were FAXED to the firm.

In a t/Con dated August 3, 1994, the firm responded to the division's FAXED comments. They agreed to making submitting FPL with these revisions within 6 months or by the next printing which ever comes first for these products.

In a September 12, 1994, correspondence the firm agrees to the revisions requested or had satisfactory answers for our requests.

In a March 23, and 24, 1995, the firm revised their labeling to include ~~two~~ these additional changes:

1. The boxed warning on page one, **"NOT FOR INTRATHECAL USE"** has been changed to read, **"140/350/NOT FOR INTRATHECAL USE".**

2. Under the **WARNINGS** section, **SEVERE ADVERSE EVENTS-INADVERTENT INTRATHECAL ADMINISTRATION**, the last sentence that reads,

   "Special attention must be given to insure that this drug product is not inadvertently administered intrathecally."

   has been revised to read,

   "Special attention must be given to insure that OMNIPAQUE 140 AND 350 are not administered intrathecally (all other concentrations of OMNIPAQUE are approved for intrathecal administration)."

3. The company name has been changed from Sanofi Winthrop Pharmaceuticals to Nycomed Inc. as reflected on page 14 (the last page) of the package insert."

4. Reference to the 70 mgI/mL concentration has been removed on page 1, (top of the page under trade name), on page 13 under **"VOIDING CYSTOUROGRAPHY"** paragraph 1, on page 14, under the **HOW SUPPLIED** section.

LABEL REVIEW PACKAGE INSERT:

The revised labeling dated March 24, 1995, submitted for the Omnipaque were compared with currently approved labeling. The following revisions to the labeling were made as requested to our February 18, 1994 supplement request letter as follows:

1. The boxed warning **"140/350/NOT FOR INTRATHECAL USE"** was placed on the package insert on page 1, below the drug name, and above the **DESCRIPTION SECTION.**

Reviewer comment: The sponsor has made the revision as requested except for the addition of 140 and 350 before the warning statement. In the opinion of the reviewer this appropriate since only the 140 and 350 mgI/mL concentrations are not approved for intrathecal administration, while all other concentrations (180, 210, 240 and 300 mgI/mL) are approved for intrathecal use.

2. Under the **WARNINGS** section the following paragraph was added and revised per the March 24, 1995 amendment:

"SEVERE ADVERSE EVENTS- INADVERTENT INTRATHECAL ADMINISTRATION

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that OMNIPAQUE 140 AND 350 are not administered intrathecally (all other concentrations of OMNIPAQUE are approved for intrathecal administration)."

Reviewer Comment: The sponsor has made the change as requested with the March 24, 1995 amendment to this supplement revising the last sentence restricting the Warnings statement to the 140 and 350 mgI/mL concentrations. In the opinion of the reviewer this last change in the labeling is appropriate.

3. The company name has been changed from Sanofi Winthrop Pharmaceuticals to Nycomed Inc. as reflected on page 14 (the last page) of the package insert."

Reviewer Comment: The sponsor has made the name change as requested by the division.

4. Reference to the 70 mgI/mL concentration has been removed as follows:

a. On page 1, (top of the page under trade name), 70 mgI/mL concentration removed.

b. Under **DESCRIPTION** section the following sentences have been deleted:

"OMNIPAQUE 70 contains 151 mg of Iohexol equivalent to 70 mg of organic iodine per mL;"

"OMNIPAQUE 70 has an osmolality of approximately 0.55 times that of plasma (285 mOsm/kg water) or cerebralspinal fluid (301 mOsm/kg water) as shown in the above table and is hypotonic under conditions of use."

c. On page 13 under **"VOIDING CYSTOUROGRAPHY"** paragraph 1, the sentence that reads,

"OMNIPAQUE at a concentration of 70 mgI/mL is indicated in children for voiding cytstourography."

and replaced with,

"OMNIPAQUE diluted to concentrations from 50 mgI/mL to 100 mgI/mL is indicated in children for voiding cystourography."

d. Under **VOIDING CYSTOURTHROGRAPHY, Dosage and Administration** section the sentence which reads,

"Sufficient volume of contrast medium should be administered to adequately fill the bladder. The usual volume of OMNIPAQUE ranges from 50 mL to 300 mL at a concentration of 70 mgI/mL."

has been changed to read,

Reviewer Comment: These changes were made by the sponsor with their reason being that they do not intend to market the 70 mgI/mL concentration at this time. The sponsor has removed all of the labeling changes that were in the draft labeling approved June 1, 1994 for these supplements. The sponsor has replaced this labeling with what existed in the labeling prior to the approval of these supplements, S-035 and S-036. The old language for this section indicated the use of Omnipaque for Cystourography in concentrations from 50 to 100 mgI/mL.
On the surface the changes look approvable. However the revisions will need a review by the medical officer.

5. On page 14, under the **HOW SUPPLIED** section, the 70 mgI/mL dose concentration has been deleted.

Reviewer Comment: The 70 mgI/mL concentration was approved June 1. 1994 for Voiding Cystourography.

6. Under the "**HOW SUPPLIED**" section, under Storage, the following change has been made:

"Store at room temperature 15°C to 30°C (59°C to 86°C)."

Reviewer Comment: The sponsor has made the change per April 23, 1994, T/Con with Dr. Nardone of Nycomed and Dr. Sheinin of this division (See April 23, 1994, t/Con).

RECOMMENDATIONS:

The draft package insert dated March 24, 1994 is approvable. All changes have been made as requested. However, the following additional changes/reviews are recommended in the labeling:

1. Under WARNING section paragraph 1, the paragraph which begins,

   "SEVERE ADVERSE EVENTS- INADVERTENT INTRATHECAL ADMINISTRATION"

   should be in bold type.

In addition revisions requested by the sponsor to remove reference to the 70 mgI/mL concentration from the labeling because they do not wish to market the 70 mgI/mL concentration at this time, will need a review by the medical officer.

With the concurrence of the medical and Chemistry staff, an Approval letter should be drafted with the approval contingent upon the sponsor submitting FPL containing the above revision.

/S/

Stephen McCort, CSO 4-25-95

CC:
HFD-160/Archive
HFD-160/DivFile
HFD-160/Sheinin
HFD-160/Leutzinger
HFD-160/Jones/Chow
HFD-160/Love
HFD-161/McCort

Concurrence:

/S/

A. Eric Jones, M.D.
Medical Imaging Group Leader

/S/

Silas Chow, M.D.
Medical Reviewer

/S/ 4-25-95

Eric B. Sheinin, Ph.D.
Supervisory Chemist

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

18-956
DIV 1

MEMORANDUM OF A MEETING

DIVISION OF MEDICAL IMAGING,

SURGICAL AND DENTAL DRUG PRODUCTS

for

IODINATED CONTRAST AGENTS

DATE: July 28, 1993, **TIME:** 2:30 p.m. **PLACE:** 18B-09

SUBJECT: Boxed Warning labeling for Inadvertent Intrathecal Administration of the Wrong Iodinated Contrast Agent

PARTICIPANTS:

Patricia Love, M.D., M.B.A., Acting Director
A. Eric Jones, M.D., Group leader
Silas Chow, M.D., Medical Reviewer
Milagros Salazar, Ph.D., Chemistry Reviewer
Elton Leutzinger, Ph.D., Chemistry Reviewer
Stan Koch, Chemistry Reviewer
James Cheever, D.M.D., Supervisory CSO
Steve McCort, CSO, recorder

POINT OF DISCUSSION:

Discussion of **BOXED WARNING** labeling on the box and vial labels. Two issues:

1. the size of the boxed warning labeling **"Not For Intrathecal Use"** or **"Not For Myelography."**

2. The color of the boxed warning labeling.

BACKGROUND:

Mallinckrodt, Squibb, Sterling and Savage have all submitted revised draft labeling in response to our April 14, and June 2, 1993, letters asking for such labeling.

At issue here was:

a. The size of the boxed warning "Not for Intrathecal Use," or "Not for Myelography."

   Dr. Love and Dr. Jones have recommended making the size of the boxed warning twice the size of the

current lettering (example Squibb- **"Not for Parenteral Use"** on the current box and vial label should be substituted with **"Not for Intrathecal Use,"** or **"Not for Myelography."**

b. The color of the boxed warning statement.

Dr. Love has recommended a contrasting color to the background labeling. Her recommendation was a "red" color.

CONCLUSIONS:

A. Regarding the **size** and **color** of the boxed warning statement:

1. As a guiding principle, the **size** of the lettering for the boxed warning statement should be not less than 50% of the size of the largest lettering in the packaging.

2. The **color** of the boxed warning statement should be red. Whether white lettering on red background or visa versa, prominence should be evaluated on an individual basis. This may need a case by case adjustment.

B. Implementation of the above recommendations:

Each sponsor will be called to alert them of additional comments regarding the boxed warning labeling. During the time the Agency is looking at examples of revised boxed labeling submitted by each sponsor, each sponsor should be advised not to print FPL until the revised labeling has been reviewed.

/S/

Stephen McCort, CSO

8-1-93

CC:
NDA

18-956
HFD-160/DivFile
HFD-160/Chow/Jones
HFD-160/Leutzinger/Salazar/Sheinin
HFD-160/Love
HFD-161/McCort/Kummerer

Acknowledgements: Jones 7.29.93/Koch 7.29.93
Cheever 7.29.93/Love 7.30.93

NDA 18-956

MEMO REGARDING

LABELING CHANGES RECOMMENDED BY DR. LOVE AND DR. JONES
(Review of Squibb's proposed labeling)

1. The Boxed Warning labeling **"Not for Intrathecal Use"** or **"Not For Myelography"** should be twice the size of the current lettering, i.e. for parenteral use. In addition the color should include a color which contrasts to the background labeling (The suggestion was a red color).

2. The package insert should include a bold printed **boxed warning** included under the **WARNINGS** subsection. This should include the list of serious adverse reactions that could occur with intrathecal mis-administration of the contrast agents not approved for intrathecal use.

   Therefore the following addition as a **boxed warning** to the **WARNINGS** section of the package insert is recommended:

   "SEVERE ADVERSE EVENTS - INADVERTENT INTRATHECAL ADMINISTRATION

   Serious Adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia and brain edema. Special attention must be given to insure that this drug product is not inadvertently administered intrathecally."

DEAR DOCTOR LETTERS

1. Mallinckrodt, Squibb and Sterling submitted drafts (as requested by FDA) of "Dear Doctor" letters to be sent to physicians using iodinated contrast products. We will use these "Dear Doctor" letters to prepare a uniform final draft.

2. After preparing the final "Dear Doctor" letter the sponsors will be sent the letter for comment. An immediate response to this letter should be requested.

OTHER ISSUES

Investigators doing non intrathecal contrast studies under existing INDs should be notified of the potential harm due to inadvertent intrathecal administration of the wrong contrast agent.

/S/ 7-26-93

Stephen McCort, CSO

CC: NDA

18-956

HFD-160/SUBJECT FILE/Contrast Agents
HFD-160/Jones/Chow
HFD-160/Love
HFD-161/McCort/Kummerer

APPEARS THIS WAY
ON ORIGINAL