CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18956/S28

CORRESPONDENCE

DIV.

APR 20 1994

NDA 18-956/S-028, 031, 032, 033, 034

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

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

Dear Dr. Nardone:

Reference is made to your approved supplemental new drug applications dated January 10, 1990 (S-028), May 30 (S-031), June 28 (S-032) and August 30, 1991 (S-033 and S-034) for Omnipaque (iohexol) Injection.

The supplements provided for the following:

S-028: A revision in the labeling to include the use of orally or rectally administered Omnipaque 180, 240, and 300 mgI/mL in children for the examination of the gastrointestinal tract.

S-031: Two new fills of Omnipaque Injection, 75/100, and 125/200 in bottles for the strength of 240 mgI/mL and 300 mgI/mL.

S-032: One new fill of Omnipaque Injection, 250/300, in bottles for the strength of 350 mgI/mL.

S-033: One new fill of Omnipaque Injection, 200/200, in bottles for the strength of 300 mgI/mL.

S-034: Labeling revision to include one new fill of Omnipaque Injection, 200/200, in bottles for the strength of 300 mgI/mL.

We acknowledge receipt of your communications dated May 13 (S-031, 032) and July 26, 1993 (S-028), providing final printed labeling (FPL) as requested in our supplement approval letters dated March 1 (S-031-034) and July 13, 1993 (S-028).

We also acknowledge receipt of your May 14, 1993, letter providing FPL for S-033 and S-034. We note that the fill size of bottles for the strength of 300 mgI/mL is not currently marketed and therefore is not included in the labeling.

We have reviewed the FPL dated July 26, 1993, and it is acceptable.

If there are any questions regarding this communication, please contact, Stephen McCort, Consumer Safety Officer, at (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

cc: NDA Arch
HFD-160/DivFile
HFC-130/District Office/w/labeling
HFD-80 w/labeling
HFD-100/w/labeling
HFD-600 w/labeling
HFD-232 w/labeling
HFD-730 w/labeling
HFD-160/Salazar/Chow
HFD-160/McCort/Kummerer

Drafted by: Steve McCort 4-7-94
Acknowledgements: Cheever-04-11-94/Chow-04-12-94/Jones-04-13-94/
Sheinin-04-14-94/Salazar-04-14-94
F/T by: AChapman-04-15-94 cso\18956031.ak
ACKNOWLEDGE AND RETAIN LETTER (S-028, 031-034)

4/18/94 4/22/94

STERLING DRUG INC.
A subsidiary of
Eastman Kodak Company

NDA SUPPLEMENT
NDA SUPPL...
5E3-028
BL

June 19, 1990

ORIGINAL

Division of Medical Imaging, Surgical
and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation & Research HFD-160
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

JUN 2 0 1990

Attention: Silas Chow, M.D.

Re: NDA 18-956/S-028; Omnipaque® Ped. G.I.

Dear Dr. Chow:

Following is our response to the changes requested in the Omnipaque (iohexol) Package Insert, as discussed with Mr. Robert West on May 10, 1990.

We have made the following changes in the Package Insert (proposed text for the Pediatric G.I. indication has been applied to OW-107-CC, which is the current approved insert):

Page 12 - Adverse Reactions

Added the heading "Adults" before paragraph 2

Added the heading "Children" before paragraph 4

Page 13 - Dosage and Administration

Added the word "undiluted" before Omnipaque in the first sentence of paragraph 3

Added the following as the next to last sentence in paragraph 3: "Based on clinical experience, it is recommended that OMNIPAQUE 180 be used in children less that 3 months of age. OMNIPAQUE 180, OMNIPAQUE 240 or OMNIPAQUE 300 may be used in children 3 months of age and older."

Added the words "of Omnipaque" for the second column heading in the table.

Relative to the request to delete the European study (N-121) from the discussion of adverse reactions (Page 12, paragraph 4), it is our position that both the U. S. and European studies are valid, with the results of these studies verified by Sterling and Nycomed personnel, respectively, and should remain in the Package Insert.

We have contacted both investigators subsequent to receiving your request and have determined that the results submitted accurately reflect the prior (as well as current) incidence of reactions seen in the two areas. The only difference in study population or procedure we can identify is in the distribution of age groups (mean ages were similar). The proportion of pediatric patients less than or equal to 1 year is 24 of 38 (63%) for Dr. Stake (N-121) vs. 28 of 60 (47%) for Dr. Cohen (P-1058). In Dr. Cohen's study, the incidence of ADEs was 50% in children older than 1 year and 25% in those 1 year or less.

While these results do not completely explain the total lack of ADEs in Dr. Stake's study, they do suggest that fewer events can be expected in younger patients, and Dr. Stake's study population was more heavily weighted toward infants than Dr. Cohen's.

Please contact me at (215) 889-6431 if you have further questions.

Sincerely,

James G. Taggart, M.D.
Senior Director, Staff Functions
Drug Regulatory Affairs
Sterling Research Group

JGT:dwm
Attachment

cc: Mr. Robert West HFD-633 (Desk Copy)

Sterling Winthrop Inc.
9 Great Valley Parkway
Malvern, PA 19355
Tel 215 889 8600

STERLING WINTHROP

August 18, 1992

Wiley Chambers M.D., Acting Director
Division of Medical Imaging, Surgical and
Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research HFD-160
Document Control Room 18B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

ORIGINAL
NDA SUPPLEMENT
SE3-028
BL

RE: NDA 18-956/S-028; Omnipaque® Pediatric Oral Gastrointestinal Indication

Dear Dr. Chambers:

Reference is made to the subject NDA and to your letter dated June 29, 1992 to Dr. Linda Nardone, Sterling Winthrop Inc., New York, New York. We have reviewed the proposed revisions to the package insert for the pediatric oral gastrointestinal indication, Supplement 028 and responses to the suggested changes are noted below. Four copies of final draft labeling are also included.

1. <u>FDA Proposed Change:</u>

SECTION III, PRECAUTIONS-General (page 11) should be revised as follows (the new language is in brackets):

Orally administered hypertonic contrast media draw fluid into the intestines which, if severe enough, could result in hypovolemia. Likewise, in infants and young children, the occurrence of diarrhea may result in hypovolemia. Plasma fluid loss may be sufficient to cause a shock-like state which, if untreated, could be dangerous. This is especially pertinent to the elderly, cachectic patients of any age as well as normal infants and small children.

<u>Response:</u>

The proposed change has been made and is included in the enclosed revised package insert.

2. FDA Proposed Change:

Despite your request stated in the June 19, 1990 amendment that the data from the European study (N-121) should be factored into the ADVERSE REACTIONS section pertaining to oral pediatric use, it remains our opinion that this open label clinical trial was not adequately controlled to support labeling statements pertaining to safety. The absence of any reported adverse reactions in this study (as well as the absence of laboratory results), brings into question the adequacy of monitoring in the study. For this reason, please revise the ADVERSE REACTIONS subsection pertaining to children (page 12) to state:

> "In controlled clinical studies involving 58 pediatric patients for examination of the gastrointestinal tract at concentrations of 180 and 300 mgI/mL, the following adverse reactions were reported: diarrhea (36%), vomiting (7%), nausea (5%), fever (5%), hypotension (2%), abdominal pain (2%) and urticaria (2%). In clinical studies an increased frequency and severity of diarrhea was noted with an increase in the administered concentration and dose of the radiocontrast agent."

The frequency rate of these reactions, particularly with regard to diarrhea, are in line with those currently reported for the adult population for oral pass-through examinations.

Response:

The proposed change has been made and is included in the enclosed revised package insert.

3. FDA Proposed Change:

In Section III (page 12) under INDIVIDUAL INDICATIONS AND USAGE, Oral Use, Dosage and Administration, please add the word "undiluted" in the "Adults" subsection as follows:

"Adults: The recommended dosage of undiluted Omnipaque® 350 at a concentration of 350 mgI/mL for oral pass-thru examinations of the gastrointestinal tract in adults is 50 mL to 100 mL depending on the nature of the examination and the size of the patient."

Response:

The proposed change has been made and is included in the enclosed revised package insert.

We understand that the subject NDA and all information contained herein, unless otherwise made public by Sterling Winthrop Inc., is **CONFIDENTIAL.**

An FDA Form 356h is attached.

Please contact me (215) 889-6412 if you have any questions concerning this submission.

Sincerely,

STERLING WINTHROP INC.

Helen M. Hammes
Associate Director
Project Operations
Drug Regulatory Affairs

HMH/dmw
Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1991
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT Sterling Winthrop Inc.	DATE OF SUBMISSION August 18, 1992
ADDRESS *(Number, Street, City, State and Zip Code)* Pharmaceuticals Research Division 9 Great Valley Parkway Malvern, PA 19355	TELEPHONE NO. *(Include Area Code)* (215) 889-6412
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 18-956

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Iohexol	Omnipaque®
CODE NAME *(If any)* WIN 39424	CHEMICAL NAME N, N-Bis(2,3 dihydroxypropyl)-5-(N-(2,3-dihydroxypropyl)acetamido)-2,4,6-triiodoisophthalamide
DOSAGE FORM Sterile Solution for Injection	ROUTE OF ADMINISTRATION Intravascular or Intrathecal Injection
	STRENGTH(S) 140,180,210, 240,300,350 mgI/mL

PROPOSED INDICATIONS FOR USE

Response to labeling for Pediatrics

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND

NDA 18-956 Omnipaque Injection (Intravascular and Intrathecal use)

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*