CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18956/S28

ADMINISTRATIVE DOCUMENTS

DIV.

DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS

LABELING REVIEW

FINAL PRINTED LABELING APR -5 1994

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

SPONSOR: Sterling Winthrop

DRUG PRODUCT: Omnipaque (brand of iohexol)

SUBMISSIONS PROVIDED FOR:

S-028: 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.

DATE OF SUBMISSION FPL: July 26, 1993

REVIEWER: Stephen McCort
Consumer Safety Officer

DATE OF REVIEW: April 5, 1994

BACKGROUND:

The company submitted supplemental applications dated January 10, 1990 (S-028), May 30 (S-031), June 28 (S-032) and August 30, 1991 S-033 and 034).

Approval letters were sent to the firm dated March 1 (S-031-034), and July 13, 1993 (S-028).

Final Printed Labeling was submitted to FDA dated May 13 (S-031, 032) and July 26, 1993 (S-028). The labeling submitted July 26, 1993 for S-028 also included the labeling approved revisions for S-031 and S-032. Based upon the May 14, 1993

communication from the firm, the fill size of 200/200 bottles for the strength of 300 mgI/mL was not included in the labeling for Omnipaque since this size will not be marketed at this time.

REVIEW OF FINAL PRINTED LABELING:

I have reviewed the Final Printed labeling submitted with the July 26, 1993, submission for S-028, and compared it to draft labeling dated August 18, 1992 for this supplement.

The FPL submitted is identical to the draft labeling dated August 18, 1992 except for the addition to the **HOW SUPPLIED SECTION** of the package insert as follows:

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.

Based upon the May 4, 1993, letter for S-033 and S-034, the fill size of in bottles for the strength of 300 mgI/mL was not included in the **HOW SUPPLIED** section of the package insert, since this size will not be marketed at this time.

RECOMMENDATION:

An **"Acknowledge and Retain"** letter for S-028, S-031-034 should drafted and be sent to the firm.

/S/ 9-5-94

Stephen McCort

CC: NDA 18-956/S-028
HFD-160/DivFile
HFD-160/Chow
HFD-160/Salazar
HFD-161/McCort/Kummeret

9/12/94

DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS

LABELING REVIEW

NDA: 18-956/S-028 APR 30 1993

SPONSOR: Sterling Winthrop

DRUG PRODUCT: Omnipaque (brand of iohexol)

SUBMISSION PROVIDES FOR: Use of orally or rectally administered Omnipaque 180, 240, and 300 mgI/mL in children for the examination of the gastrointestinal tract.

DATE OF ORIGINAL SUBMISSION: January 10, 1990

AMENDMENTS: February 16, April 17, and June 19, 1990, and August 18, 1992.

REVIEWER: Stephen McCort
Consumer Safety Officer

DATE OF REVIEW: April 12, 1993

BACKGROUND:

The company submitted the original supplement (S-028) dated January 10, 1990, providing for the use of orally or rectally administered Omnipaque 180, 240, and 300 mgI/mL in children for the examination of the gastrointestinal tract. An amendment to this supplement dated April 17, 1990, submitted requested information regarding the tabulation of pediatric G.I. patients by weight and volume of contrast medium administered. An approvable letter dated June 29, 1992, was sent to the firm requesting the following revisions to the draft labeling submitted June 19, 1990:

1. In Section III, the **PRECAUTIONS**, general section should be revised to read as follows:

2. In the **ADVERSE REACTIONS** subsection pertaining to children, page 12, should be revised to read:

> "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 (9%), 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."

3. In Section III, under INDIVIDUAL INDICATIONS AND USAGE, Oral Use, Dosage and Administration, the words "undiluted" in the "Adults" subsection as follows:

On August 18, 1992 the firm submitted an amendment which included revised draft labeling in response to the Agency's June 29, 1992 approvable letter.

REVIEW OF DRAFT LABELING:

I have reviewed the draft labeling submitted with the August 18, 1992 amendment and compared it to draft labeling dated June 19, 1990, and to currently approved labeling. All the labeling revisions asked for in the June 29, 1992, approvable letter are included in the August 18, 1992, draft labeling.

CONCLUSIONS:

The draft package insert submitted with the August 18, 1992, amendment for Omnipaque (iohexol) Injection (S-028) includes draft revisions to the June 9, 1990, draft labeling as recommended in the June 29, 1992, approvable letter to the firm. All the labeling changes recommended in the approvable letter have been made.

However, as part of the approvable letter to be drafted, approval of S-028 should be contingent upon the approval of S-039 with requested labeling revisions as follows:

1. The labeling revisions recommended in the approvable letter dated June 29, 1992, for S-039 included revisions and condensations of the **ADVERSE REACTION** sections of the package insert. In further discussions with our staff the following guidelines were communicated to the firm in a February 24, 1993, telephone conversation:

   a. Delete the **General Adverse reaction** subsections found under each route of administration.

   b. Revise each **ADVERSE REACTION** section by route of administration to include the following:

      (1) List the adverse reactions by organ systems in order of decreasing frequency and severity.

      (2) Delete all promotional claims unless supported by adequate and well controlled clinical studies and all references that include actual incidences or numbers of events. (Not by number this also includes % of events).

   Note that these changes in the **ADVERSE REACTION** sections of the package insert also include revisions in the pediatric information contained in Section III, **INDICATIONS AND USAGE, Adverse Reactions**, page 12.

RECOMMENDATION:

The revised draft labeling submitted with the August 18, 1992, amendment for S-028, included all the labeling revisions requested in the June 29, 1992 approvable letter.

I recommend that an approvable letter be drafted which makes the approval contingent upon the approval of the following:

> Labeling revisions in the **ADVERSE REACTIONS** sections as requested in the December 11, 1992, approvable letter for must be approved. The firm should be reminded of their commitment to submit revised labeling to include these revisions within 60 days of the approval of S-031-034, as indicated in their letter to FDA dated January 18, 1993.

/S/ 4/13/93
Stephen McCort

Concurrence by:
/S/ 4/30/93
Silas Chow
Reviewing Medical Officer

/S/ 4/29/93
A. E. Jones
Group Leader Medical Imaging

CC: NDA 181-956/S-027
HFD-160/DivFile
HFD-160/Chow
HFD-161/McCort/Kummerer

DIV

EXCLUSIVITY SUMMARY FOR NDA # 18-956 SUPPL # 28

Trade Name OMNIPAQUE Generic Name IOHEXOL

Applicant Name STERLING WINTHROP HFD # 160

Approval Date If Known 7-13-93

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE3

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 7-90
cc: Original NDA Division File HFD-85 Mary Ann Holovac

HFD-160: McGoff / Kummerer HF-2 / MED WATCH

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18956 OMNIPAQUE

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of (1) new (2) clinical investigations (other than bioavailability studies) (3) essential to the approval of the application and (4) conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Domestic: # IOH-1058A MERVYN COHEN, M.D.
IOH-1058B RICHARD TOWBIN, M.D.
FOREIGN: # N-121-GUNNAR STAKE, OSLO, NORWAY

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 NO X

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 NO X

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

#IOH-1058A MERLYN COHEN, M.D.

#IOH-1058B RICHARD TOWN, M.D.

N-121 GUNNAR STAKE, M.D.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /X/ NO /___/ Explain: _____

Investigation #2

IND # _ YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? (50%+)

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

/S/

Signature
Title: Consumer safety officer

8-20-93
Date

/S/

Signature of Office/
Division Director

10-12-93
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac