

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 // 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 //

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

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 / /

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:

S3AA3012

S3AA3004/3007

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.

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 # [REDACTED] YES / / NO / / Explain: _____

Investigation #2

IND # [REDACTED] YES / / 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?

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/ _____ 8/23/99
Signature Date
Title: Proj. mgr.

APPEARS THIS WAY ON ORIGINAL

/S/ _____ 8-23-99
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

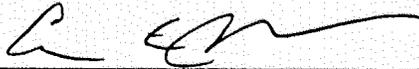
IV. Debarment Certification

NDA 20-103

Zofran (ondansetron hydrochloride) Tablets
Supplemental New Drug Application for Highly-Emetogenic
Chemotherapy

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.



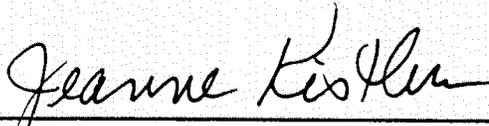
Charles E. Mueller
Head, US Clinical Compliance
World Wide Compliance

12 JUNE 98

Date

.....

The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 12Nov97 Food and Drug Administration Debarment List and the 27Apr98 Disqualified, Restricted, and Given Assurances lists.



Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

12-JUN-98

Date

III. Marketing Exclusivity

NDA 20-103

Zofran (ondansetron hydrochloride) Tablets

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of Zofran (ondansetron hydrochloride) Tablets supplemental NDA for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin.

Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigations are "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application.

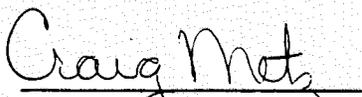
Indication – For the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin

RM1998/00122/00. A Randomized, Double-Blind Study of Oral Ondansetron, 8mg Twice Daily, 24mg Once Daily and 32mg Once Daily, in the Prevention of Nausea and Vomiting Associated with Cisplatin Chemotherapy (Study No. S3AA3012)

RD1997/04252/00. A Randomized, Double-Blind Comparison of Oral Ondansetron and Intravenous Granisetron in the Prevention of Nausea and Vomiting Associated with Moderately-High Emetogenic Chemotherapy (Study No. S3AA3004/S3AA3007)

The clinical investigations are defined as "new" as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of previously approved drug products for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

The investigations were "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application (IND 30,724) under which these investigations were conducted.


Craig Metz, Ph.D
Director, Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

II. Patent Information

NDA 20-103 (Supplement)

**Patent Information For
ZOFTRAN® (ondansetron hydrochloride) Tablets 24 mg**

Patent Information on Product
of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: ZOFTRAN® Tablets 24 mg
Active Ingredient: Ondansetron Hydrochloride
Patent Number: 4,753,789
Expiration Date: June 24, 2006
Type of Patent: Method of Use - Relief of nausea and vomiting
Name of Patent Owner: Glaxo Wellcome, Inc.
U.S. Agent: David J. Levy, Ph.D.
Vice President and Patent Counsel
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 4,753,789 covers the formulation, composition and/or method of use of ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: August 11, 1998

By: Robert T. Hrubiec
Robert T. Hrubiec, J.D., Ph.D.
Glaxo Wellcome Inc.

NDA 20-103 (Supplement)

Patent Information For
ZOFTRAN® (ondansetron hydrochloride) Tablets 24 mg

Patent Information on Product
of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: ZOFTRAN® Tablets 24 mg

Active Ingredient: Ondansetron Hydrochloride

Patent Number: 5,578,628

Expiration Date: June 24, 2006 (GATT Extended - a Certificate of Correction has been filed with the USPTO to correct the expiration date listed on the face of this patent)

Type of Patent: Method of Use in treating nausea and vomiting

Name of Patent Owner: GLAXO WELLCOME Inc.

U.S. Agent: David J. Levy, Ph.D.
Vice President and Patent Counsel
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 5,578,628 covers the formulation, composition and/or method of use of ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: August 11, 1998

By: Robert T. Hrubiec
Robert T. Hrubiec, J.D., Ph.D.
Glaxo Wellcome Inc.

NDA 20-103 (Supplement)

Patent Information For ZOFRAN® (ondansetron hydrochloride) Tablets 24 mg

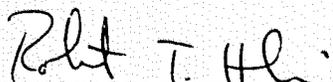
Patent Information on Product
of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZOFRAN® Tablets 24 mg
Active Ingredient:	Ondansetron Hydrochloride
Patent Number:	4,695,578
Expiration Date:	June 25, 2005
Type of Patent:	Drug Substance, Drug Product, and Method of Use
Name of Patent Owner:	GLAXO WELLCOME Inc.
U.S. Agent:	David J. Levy, Ph.D. Vice President and Patent Counsel Glaxo Wellcome Inc. 5 Moore Drive Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 4,695,578 covers the formulation, composition and/or method of use of ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: August 11, 1998

By: 
Robert T. Hrubiec, J.D., Ph.D.
Glaxo Wellcome Inc.

NDA 20-103 (Supplement)

Patent Information For ZOFRAN® (ondansetron hydrochloride) Tablets 24 mg

Patent Information on Product
of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	ZOFRAN® Tablets 24 mg
Active Ingredient:	Ondansetron Hydrochloride
Patent Number:	5,344,658
Expiration Date:	September 6, 2011
Type of Patent:	Drug Substance and Drug Product - Crystalline Ondansetron hydrochloride dihydrate
Name of Patent Owner:	GLAXO WELLCOME Inc.
U.S. Agent:	David J. Levy, Ph.D. Vice President and Patent Counsel Glaxo Wellcome Inc. 5 Moore Drive Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 5,578,658 covers the formulation, composition and/or method of use of ondansetron in treating nausea and vomiting. This product is the subject of this application for which approval is being sought.

Date: August 11, 1998

By: Robert T. Hrubiec
Robert T. Hrubiec, J.D., Ph.D.
Glaxo Wellcome Inc.

McNeil

NDA 20-103/S-015

Glaxo Wellcome Inc.
Attention: Craig Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

JUN 3 1999

Dear Dr. Metz:

Please refer to your pending August 27, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron HCL) Tablets.

The supplemental application provides for the addition of "Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin" as an indication.

Studies S3AA3004/3007, entitled "A Randomized, Double-Blind Comparison of Oral Ondansetron and Intravenous Granisetron in the Prevention of Nausea and Vomiting Associated with Moderately-High Emetogenic Chemotherapy," and S3AA3012, entitled "A Randomized, Double-Blind Study of Oral Ondansetron, 8 mg Twice Daily, 24mg Once Daily and 32mg Once Daily, in the Prevention of Nausea and Vomiting Associated with Cisplatin Chemotherapy," provided the primary support of this indication. Note: Studies S3AA3004 and S3AA3007 were initiated as separate studies using the identical protocol. However, due to the slow accrual of patients, the data from both trials were combined and they were analyzed as a single study.

An analysis of the Intent-To-Treat population from Study S3AA3004/3007 revealed no significant differences between the two treatment arms (oral ondansetron 24 mg QD and intravenous granisetron 10 mcg/kg) for the primary efficacy variable, defined as the number of patients with zero emetic episodes who completed the trial without rescue over the 24-hour study period. This study was designed as a superiority trial, with an expected 15% difference between treatment arms; neither non-inferiority nor equivalence hypotheses were specified in the study protocol. Further, the sample size was insufficient for either a non-inferiority trial or an equivalence trial.

We do not concur, therefore, with your conclusion, based on the results of Study S3AA3004/3007, that a single dose of ondansetron (24 mg) is therapeutically equivalent to a single intravenous dose of granisetron (10 mcg/kg) for the prevention of nausea and vomiting in subjects administered highly emetogenic chemotherapy. However, for both studies (S3AA3004/3007 and S3AA3012) the ondansetron 24 mg QD treatment group was shown to be statistically superior to a relevant historical placebo control.

The Biopharmaceutics review of this application is ongoing. However, we have completed our review of the Clinical and Statistical sections of your submission and request that you make the

following revisions to the cited portions of the package insert:

1. Please modify the Chemotherapy-Induced Nausea and Vomiting subsection, Highly Emetogenic Chemotherapy subsection of the CLINICAL TRIALS section to read as follows:

“In two randomized, double-blind, monotherapy trials, a single 24-mg ZOFTRAN Tablet was superior to a relevant historical placebo control in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m². Steroid administration was excluded from these clinical trials.

The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day, and 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥ 50 mg/m². A total of 66% of patients in the ondansetron 24 mg once a day group, 55% in the ondansetron 8 mg twice a day group, and 55% in the ondansetron 32 mg once a day group completed the 24-hour study period with zero emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the three treatment groups was shown to be statistically significantly superior to a historical placebo control.

In a secondary efficacy analysis, 56% of patients receiving ondansetron 24 mg once a day experienced no nausea during the 24-hour study period, compared with 36% of patients in the ondansetron 8 mg twice a day group ($p = 0.001$) and 50% in the ondansetron 32 mg once a day group.

Efficacy of the ondansetron 24 mg once a day regimen in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m², was confirmed in a second study.”

2. Please delete reference to granisetron from the table located in the ADVERSE REACTIONS section, entitled “Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFTRAN Tablets (Highly Emetogenic Chemotherapy).

Additional labeling comments may be forthcoming upon finalization of the Biopharmaceutics review. Please submit revised marked-up draft labeling which includes the revisions requested above, but is otherwise identical to the marked-up draft labeling that was included in the August 27, 1998 supplemental application.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject

to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager at (301) 827-7310.

Sincerely,



6/3/99

mm 6/2/99

Kati Johnson
Supervisor, Project Management Staff
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-103
HFD-180/Div. Files
HFD-180/M.McNeil
HFD-180/Talarico
HFD-180/Gallo-Torres
HFD-715/Fan
HFD-715/Al-Osh
HFD-870/Lee
HFD-870/Al-Fayoumi
DISTRICT OFFICE

APPEARS THIS WAY ON ORIGINAL

Drafted by: mm/April 13, 1999
Initialed by: KJohnson 4/27/99, 5/12/99
HGallo-Torres 5/25/99
final: June 2, 1999
filename: c:\mydocuments\cso\n\20103904-s015-ir.doc

INFORMATION REQUEST (IR)

Craig Johnson

NDA 20-103/S-015

GlaxoWellcome Inc.
Attention: Craig Metz, PhD
Director, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

SEP - 3 1998

Dear Dr. Metz:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zofran (ondansetron HCL) Tablets

NDA Number: 20-103

Supplement Number: S-015

Therapeutic Classification: Standard (S)

Date of Supplement: August 27, 1998

Date of Receipt: August 28, 1998

This supplement proposes the following change: The addition of "Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin" as an indication.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 27, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 28, 1999.

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-103/S-015

Page 2

If you have any questions, contact me at (301) 443-0487.

Sincerely,

/s/ [Redacted]

9/2/98

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-103/S-015
HFD-180/Div. Files
HFD-180/K.Johnson
DISTRICT OFFICE

Drafted by: kj/September 2, 1998
filename: 20103809.S15

SUPPLEMENT ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20103</u>	Trade Name:	<u>ZOFRAN (ONDANSETRON HCL) TABLETS</u>
Supplement Number:	<u>15</u>	Generic Name:	<u>ONDANSETRON HYDROCHLORIDE</u>
Supplement Type:	<u>SE1</u>	Dosage Form:	<u>TAB</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Adequate for SOME pediatric age groups
Formulation Status _____
Studies Needed _____
Study Status _____

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELODI MCNEIL

/s/ [REDACTED] _____
 Signature

 Date 8/16/99

/s/ [REDACTED] 8-23-99