CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020103, S015

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-103/S-015

AUG 26 1999

Name of Drug: Zofran (ondansetron) Tablets

Sponsor: Glaxo Wellcome, Inc.

Material Reviewed

Submission Date(s): March 29, 1999, draft labeling (unit dose blister backing, carton)
June 30, 1999, draft labeling (package insert)

Receipt Date(s): March 30, 1999
July 1, 1999

Background and Summary Description: NDA 20-103, approved December 31, 1992, provides for Zofran Tablets for the following indications:

1. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy,
2. Prevention of nausea and vomiting associated with radiotherapy, and
3. Prevention of postoperative nausea and vomiting.

Zofran is also approved in a variety of other dosage forms, including an oral solution (NDA 20-605, approved January 24, 1997). Zofran Tablets and Oral Solution share a package insert.

NDA 20-103/S-015, submitted August 27, 1998 provides for a new indication: the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m^2. A companion chemistry supplement (S-016), submitted on the same date, provides for a 24-mg tablet to be used for the new indication.

The August 27, 1998 submission contained draft labeling. However, based on the February 19, 1999 clinical review and the March 25, 1999 statistical review, a June 3, 1999 letter was sent to the firm. In this letter the firm was requested to revise the draft package insert, specifically, to modify the Chemotherapy-Induced Nausea and Vomiting subsection, Highly Emetogenic Chemotherapy subsection of the CLINICAL TRIALS section (package insert) to read as follows:

DRAFT LABELING

[redacted]

DRAFT LABELING

[redacted]

The firm was also requested to delete reference to granisetron from the table located in the

[redacted] DRAFT LABELING

Review

Package Insert:

The submitted revised draft insert (**no code; June 1999**) was compared to the currently approved insert (**4071677; RL-371; October 1996**). The following changes have been made (throughout this review new text is represented by a double underline; deleted text is represented by a strikethrough):

1. DESCRIPTION section:

The second paragraph has been revised to read, DRAFT LABELING

[redacted]

According to the February 24, 1999 chemistry review for S-016, these are acceptable revisions.

2. CLINICAL PHARMACOLOGY section, Pharmacokinetics subsection:

   a. The following sentences have been added to the end of the second paragraph: [redacted]

   DRAFT LABELING [redacted]

   According to Dr. Suliman Al-Fayoumi, biopharmaceutics reviewer, this is an acceptable revision.

   b. The following sentence has been added to the end of the fourth paragraph [redacted]

   DRAFT LABELING [redacted]

   According to Dr. Suliman Al-Fayoumi, biopharmaceutics reviewer, this is an acceptable revision.

   c. The following text has been deleted. DRAFT LABELING [redacted]

   According to Dr. Suliman Al-Fayoumi, biopharmaceutics reviewer, this is an acceptable revision.

   d. **According to Dr. Suliman Al-Fayoumi, biopharmaceutics reviewer, the following table should be inserted immediately after the table entitled "Pharmacokinetics in Normal Volunteers: Single 8-mg Tablet Dose":**

DRAFT LABELING [redacted]

DRAFT LABELING [redacted]

3. CLINICAL TRIALS section:

a. A subsection entitled "Highly Emetogenic Chemotherapy" has been added.

This is an acceptable revision

b. The new Highly Emetogenic Chemotherapy subsection reads,

DRAFT LABELING

(Note: The last sentence of the above paragraph was not requested in the June 3, 1999 letter.) According to Dr. Gallo-Torres, this paragraph is acceptable as revised.

DRAFT LABELING

(Note: The above paragraph was revised as requested in the June 3, 1999 letter, therefore, it is acceptable.)

DRAFT LABELING

(Note: The firm has editorially added the phrase DRAFT LABELING to the beginning of this paragraph. The requested wording in the June 3, 1999 letter was "In a secondary efficacy analysis..." The firm has also editorially added the word . to this paragraph.) According to Dr. Gallo-Torres, this paragraph is acceptable as revised.

DRAFT LABELING

(Note: The firm has editorially added the phrase DRAFT LABELING to the beginning of this paragraph. The have also added the word to the paragraph.) According to Dr. Gallo-Torres, this paragraph is acceptable as revised.

c. A new subsection heading entitled "Moderately Emetogenic Chemotherapy" has been added.

This is an acceptable editorial revision that increases the insert's clarity.

d. The first sentence of the Moderately Emetogenic Chemotherapy subsection has been revised as follows: DRAFT LABELING

.

According to Dr. Hugo Gallo-Torres, Medical Team Leader, this is an acceptable revision.

e. ., DRAFT LABELING

According to Dr. Hugo Gallo-Torres, this is an acceptable revision.

4. INDICATIONS AND USAGE section:

a. DRAFT LABELING

This is an acceptable revision.

b. The list of indications has been re-numbered to accommodate the new indication.

This is an acceptable revision.

5. ADVERSE REACTIONS section:

a. The first paragraph has been revised as follows:

DRAFT LABELING

According to Dr. Gallo-Torres, this is an acceptable revision.

b. The table entitled "Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN Tablets (Highly Emetogenic Chemotherapy) has been revised as requested in the June 3, 1999 letter. It has also been moved to the beginning of the ADVERSE REACTIONS section to be consistent with the other sections of the insert which describe information related to the highly emetogenic indication first

These are acceptable revisions.

c. DRAFT LABELING

These are acceptable revisions.

d. The following adverse event table heading has been revised to read DRAFT LABELING

This is an acceptable revision.

e. All adverse events which occurred at a frequency of less than 5% (abdominal pain, xerostomia, and weakness) have been deleted from the table entitled "Principal Adverse Events in US Trials: 3 Days of Therapy With 8 mg ZOFRAN Tablets (Moderately Emetogenic Chemotherapy".

According to the text that precedes it, this table is intended to describe events that occurred at a frequency of less than 5% during the clinical trials. Therefore, this revision is acceptable.

f. The following adverse event table heading has been revised to read DRAFT LABELING

This revision increases the insert's clarity, therefore it is acceptable.

6. DOSAGE AND ADMINISTRATION section: The following text has been added to the beginning of this section:

DRAFT LABELING [redacted]

a. **The firm should be requested to delete the word [redacted] in the Pediatric Use subsection and replace it with the words [redacted] in accordance with 21 CFR 201.57(f)(9)(i).**

b. **The revisions to this section are otherwise acceptable.**

7. HOW SUPPLIED section:

a. This section has been revised to include reference to the new 24-mg tablet.

b. The storage statement for the 24 mg tablet has been added, DRAFT LABELING [redacted]

i) **According to the February 24, 1999 chemistry review for S-016, these are acceptable revisions.**

ii) **According to Dr. Eric Duffy, chemistry team leader,** DRAFT LABELING [redacted] **should also be added to the storage statement.**

<u>Unit Dose Blister Backing</u>

The submitted unit dose blister backing (**coded 4098781, Rev. 3/98**) was reviewed for compliance with the applicable labeling regulations (21 CFR 201.50, 201.51(a), 201.1, 201.51, 201.100(b)(1), 201.100(b)(2), 201.55, 201.10(c), 201.100(b)(4). 201.18, 201.100(b)(6), 211.137, 211.166, 201.17, 201.15, and 201.21.

1. **The submitted unit dose blister backing does not indicate where or if the lot number and expiration date will be included, as required in 21 CFR 201.17. In an August 18, 1999 teleconference with Dr. Craig Metz, Regulatory Affairs, Glaxo Wellcome, he said that the lot number and expiration date will appear in the lower left hand portion of the blister backing.**

2. **According to Dr. Eric Duffy, chemistry team leader, DRAFT LABELING and the storage statement should also be added to the blister labeling (if space permits).**

3. **The submitted blister backing is otherwise acceptable.**

Carton Labeling:

The submitted carton labeling (**coded 4098765, Rev. 3/99**) was reviewed for compliance with the applicable labeling regulations (21 CFR 201.50, 201.51(a), 201.1, 201.51, 201.100(b)(1), 201.100(b)(2), 201.55, 201.10(c), 201.100(b)(4). 201.18, 201.100(b)(6), 211.137, 211.166, 201.17, 201.15, and 201.21.

1. **The submitted carton labeling does not indicate where or if the lot number and expiration date will be included, as required in 21 CFR 201.17. In a July 19, 1999 teleconference with Dr. Craig Metz, Regulatory Affairs, Glaxo Wellcome, he said that the lot number and expiration date will appear in the bar coded portion of the carton.**

2. **According to Dr. Eric Duffy, chemistry team leader, DRAFT LABELING should also be added to the storage statement.**

3. **The submitted carton labeling is otherwise acceptable.**

Conclusions

The submitted draft labeling is acceptable, and the application can be approved on draft labeling. However, the firm should be requested to do the following:

Package Insert:

1. Revise the Pediatric Use subsection, Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy subsection, DOSAGE AND ADMINISTRATION section to read DRAFT LABELING .

2. Revise the HOW SUPPLIED section to add DRAFT LABELING to the storage statement.

3. Revise the CLINICAL PHARMACOLOGY section to add the table as described above.

Unit Dose Blister Backing:

Include the storage statement and [redacted] if space permits.

Cartons:

Add [redacted] to the storage statement.

The above revisions should be made when FPL is printed. Also, given that Zofran Tablets and Oral Solution share a package insert, the firm should be requested to submit a labeling supplement to NDA 20-605 which provides for the revisions necessitated by the approval of this supplement.

/S/ [redacted] 8/26/99
Regulatory Health Project Manager

/S/ [redacted] 8-26-99

cc:
Original
HFD-180/Div. Files
HFD-180/McNeil

[redacted]

draft: mm/July 29, 1999/c:\mydocuments\cso\reviews\20103907-slr
r/d Initials: EDuffy 8/18/99, 8/26/99
HGallo-Torres 8/19/99
SAl-Fayoumi 8/19/99; 8/26/99
LTalarico 8/23/99
final: August 26, 1999

CSO REVIEW

EXCLUSIVITY SUMMARY FOR NDA # _20-103_____ SUPPL #_SE1-015

Trade Name _Zofran_____ Generic Name _ondansetron____

Applicant Name _Glaxo Wellcome__ HFD # _180

Approval Date If Known _____

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.) _SE1___

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.

__N/A_____

_____

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:

_____N/A_____

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

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

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

_NO_____

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? (Rx to OTC switches should be answered NO-please indicate as such)

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# __20-007_____ Zofran Injection

NDA# __20-403_____ _Zofran Premix (Inj)

NDA# ___20-605_____ Zofran Oral Solution_

NDA# __20-781_____ Zofran Orally Disintegrating Tablet

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 new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."