

NDA REGULATORY FILING REVIEW
Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

*See Revised
Appendix B
dated 5/18/2006
BMS*

NDA #: 21-915

Drug Name: Ondansetron Hydrochloride Injection, USP

Revised: February 1, 2006

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 20-007 Zofran® (ondansetron hydrochloride)

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

(a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

(b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

(c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a new diluent (sodium chloride instead of dextrose) for the 32 mg and 8 mg doses. In addition the application provides for the 8 mg dose at once daily, not previously approved in the RLD.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

(Paragraph I certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s): 4,695,578 expiry 1-25-2005
4,753,789 expiry 12-24-2006 (Peds Exclusivity)
5,578,628 expiry 2-16-2005
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Betsy Scroggs
2/1/2006 01:16:13 PM
CSO



Labeling Term
1-30-06

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2006

To: Vicky Drews, RAC Associate Director Global Regulatory Affairs	From: Betsy Scroggs, Pharm.D., RHPM
Company: Baxter Healthcare Corporation	Division of Gastroenterology Products
Fax number: (847) 785-5107	Fax number: 301-796-9905
Phone number: (847) 473-6296	Phone number: 301-769-0991
Subject: NDA 21-915 - Labeling Comments post 1-30-2006 TCON with Dr. Caffey	

Total no. of pages including cover: 2

Comments: The following are the comments mentioned to Dr. Caffey in our teleconference today.

Your statement from the DESCRIPTION section of your proposed package insert submitted January 23, 2005, which reads as:

[]

would require appropriate toxicological studies to be acceptable, if such data are available. At the present time, we find that the above statement may be more appropriately replaced with the following:

“however, the plastic container materials conform to USP Biological Reactivity Testing requirements.”

We remind you of our February 1, 2006 action date. Please respond to this fax by January 31, 2006.

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/s/

Betsy Scroggs
1/30/2006 05:46:30 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 20, 2006

To: Judy Kannenburg, RAC	From: Betsy Scroggs, Pharm.D., RHPM
Company: Baxter Healthcare Corporation	Division of Gastroenterology Products
Fax number: (847) 785-5107	Fax number: 301-796-9905
Phone number: (847) 473-6309	Phone number: 301- 769-0991
Subject: NDA 21-915 – Labeling Comments	

Total no. of pages including cover: 3

Comments: NDA 21-915: January 20, 2006 FDA revisions to Container, Overwrap, carton, and Package Insert. Updated from FDA January 13, 2006 and January 19, 2006 faxed revisions.

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We have the following additional comments regarding your proposed Container, Overwrap, Carton, and Package Insert for NDA 21-915. Refer to our comments faxed on January 13, 2006 and January 19, 2006.

Please contact me if you have any questions. BHS

1. Container

Remove the following: _____

Replace with: "Premixed iso-osmotic solution with sodium chloride in single-dose INTRAVIA container"

2. Overwrap

Remove: _____

Replace with: "Premixed iso-osmotic solution with sodium chloride in single-dose container"

3. Carton

Remove: _____

Replace with: "10 x 50 mL single-dose INTRAVIA containers"

Remove: _____

Replace with: "Premixed iso-osmotic solution with sodium chloride in single-dose containers"

4. Package Insert Line 17 (Description)

Current: _____

Replace with: "A ready to use iso-osmotic formulation of Ondansetron Injection, USP in 50 mL of sodium chloride diluent..."

as follows:

"A ready to use iso-osmotic formulation of Ondansetron Injection, USP in 50 mL of sodium chloride diluent is available in the IntraVia plastic container. Each 50 mL contains 32 mg ondansetron (as Ondansetron Hydrochloride, USP); 450 mg Sodium Chloride, USP; 25 mg Citric Acid Monohydrate, USP; and 12.5 mg Sodium Citrate Dihydrate, USP. Ondansetron Injection, USP is a clear, colorless, nonpyrogenic sterile solution that contains no preservatives. The pH is 3.3 to 4.0."

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/s/

Betsy Scroggs
1/20/2006 02:27:26 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2006

To: Judy Kannenburg, RAC	From: Betsy Scroggs, Pharm.D., RHPM
Company: Baxter Healthcare Corporation	Division of Gastroenterology Products
Fax number: (847) 785-5107	Fax number: 301-796-9905
Phone number: (847) 473-6309	Phone number: 301-769-0991
Subject: NDA 21-915 – Labeling Comments post 1-19-2006 TCON	

Total no. of pages including cover: 3

Comments: These are our additional (revisions to our faxed 1-13-2006 labeling) labeling comments

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Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a 2-year oral carcinogenicity study in mice, ondansetron was not carcinogenic at doses up to 30 mg/kg/day (about 3.8 times the recommended human intravenous dose of 32 mg based on body surface area).

In a 2-year oral carcinogenicity study in rats, ondansetron was not carcinogenic at doses up to 10 mg/kg/day (about 2.5 times the recommended human intravenous dose based on body surface area).

Ondansetron was not mutagenic in standard tests for mutagenicity.

Ondansetron at oral doses up to 15 mg/kg/day (about 3.8 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B.

Reproduction studies have been performed in rats at intravenous doses up to 4 mg/kg/day (about 1 time the recommended human dose based on body surface area) and in rabbits at intravenous doses up to 4 mg/kg/day (about 2 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron.

HOW SUPPLIED

Ondansetron Injection, USP premix in IntraVia Plastic Containers is supplied as follows:

2J1421 NDC 0338-1762-41 32 mg/50 mL 10 Pack

STORAGE

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/s/

Betsy Scroggs
1/19/2006 05:38:42 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 13, 2006

To: Judy Kannenburg, RAC	From: Betsy Scroggs, Pharm.D., RHPM
Company: Baxter Healthcare Corporation	Division of Gastroenterology Products
Fax number: (847) 785-5107	Fax number: 301-796-9905
Phone number: (847) 473-6309	Phone number: 301- 769-0991
Subject: NDA 21-915 – Labeling Comments and Marked-up Package Insert	

Total no. of pages including cover: 22

Comments:

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7450. Thank you.

The Agency has the following comments regarding your proposed label for NDA 21-915:

A. GENERAL COMMENTS

We note several incidents where terminal zeros are used throughout the package insert labeling. The use of terminal zeros may result in error as often the decimals are overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeros could potentially result in a ten-fold medication dose error. The use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of terminal zeros is specially listed in the list of dangerous abbreviations, acronyms, and symbols in the 2006 National Patient Safety Goal 2b of The Joint Commission of Accreditation of Healthcare Organizations. Lastly, safety groups such as ISMP also list terminal zeros on their dangerous abbreviations and dose designations list.

Thus, we recommend deleting all terminal zeros from the labels and labeling.

B. CONTAINER LABEL

1. We recommend making the strength prominent by utilizing boxing, color shading and/or bolding (see below). Additionally, the red font may be difficult to read on a clear intravenous minibag.

Use Boxing, Color Shading, and/or Bolding to make strength prominent

2. Revise the statement "Iso-Osmotic..." to read "in Iso-Osmotic...", as ondansetron is "in" iso-osmotic sodium chloride.
3. Include the statement "protect from light until immediately prior to use". Currently, this information will be missing in the event the minibag is separated from the overpouch.

C. OVERPOUCH LABELING

1. See Container Label Comments B.1 thru B.3.
2. The orange font on the light orange background used on the 32 mg/50 mL overpouch is difficult to read. Please utilize a darker font and/or revise the color combination to improve contrast and readability. errors.
3. Increase the prominence of the statement "Protect from light...". This warning is likely to be overlooked with the current presentation.

D. CARTON LABELING

1. See Container Label Comments B.1 thru B.3.

16 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Betsy Scroggs
1/13/2006 01:41:46 PM
CSO

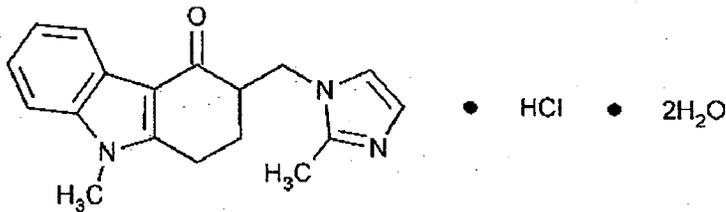
Betsy Scroggs
1/13/2006 01:45:31 PM
CSO

1-6-06

1 **Ondansetron Injection, USP**
2 **Premix in Intra Via Plastic**
3 **Container**

4 **DESCRIPTION:**

5 The active ingredient in **Ondansetron Injection, USP** is Ondansetron Hydrochloride USP, the
6 racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT₃ receptor type.
7 Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-
8 carbazol-4-one, monohydrochloride, dihydrate. It has the following structural formula:



9 The empirical formula is

10 C₁₈H₁₉N₃O•HCl•2H₂O, representing a molecular weight of 365.86

11 Ondansetron Hydrochloride, USP is a white to off-white powder that is soluble in water and
12 normal saline.

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14
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_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Debi Tran
1/6/2006 01:22:11 PM
DDMAC REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-915

DISCIPLINE REVIEW LETTER

Baxter Health Care Corporation
Attention: Vicki Drews
Regulatory Affairs
1620 Waukegan Road
McGaw Park, IL 60885-6730

Microbiology

Dear Ms. Drews:

Please refer to your March 30, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ondansetron Injection, USP in PL 2408 Plastic Containers.

Our review of the Microbiology section of your submission is complete, and we have identified the following deficiencies:

- A. The deficiencies for Drug Master File (DMF) 11,691 must be resolved before this NDA can be approved and are addressed in a separate letter.
- B. Please provide the following information regarding the production, sterilization and parametric release of Ondansetron Injection:

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We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the Prescription Drug 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 subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the User Fee Reauthorization Agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Betsy Scroggs, Pharm.D, Regulatory Health Project Manager, at 301-796-0991.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Quality Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
12/22/2005 01:36:51 PM

DMETS
17 NOV 2005

CONSULTATION RESPONSE		
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT OFFICE OF DRUG SAFETY (DMETS; WO22, M/S 4447)		
DATE RECEIVED: June 16, 2005	DESIRED COMPLETION DATE: December 1, 2005	ODS CONSULT #: 05-0139
DOCUMENT DATE: March 30, 2005	PDUFA DATE: February 1, 2006	
TO: Brian Harvey, M.D., Ph.D. Director, Division of Gastroenterology Products HFD-180		
THROUGH: Betsy Scroggs, Pharm.D. Project Manager HFD-180		
PRODUCT NAME: Ondansetron Injection, USP 8 mg/50 mL, 32 mg/50 mL		NDA SPONSOR: Baxter Healthcare
NDA#: 21-915		
SAFETY EVALUATOR: Tina M. Tezky, Pharm.D.		
RECOMMENDATIONS: 1. DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product. 2. DMETS notes that we have not received a consult for a proposed proprietary name for this product. Please allow 90 days for the review.		
APPEARS THIS WAY ON ORIGINAL		
<hr/> Denise P. Toyer, Pharm.D. Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety		<hr/> Carol Holquist, R.Ph. Division Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 796-2360 Fax: (301) 796-9865

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; WO22, 4447
Center for Drug Evaluation and Research**

LABEL AND LABELING REVIEW

DATE OF REVIEW: August 2, 2005

NDA#: 21-915

NAME OF DRUG: Ondansetron Injection, USP
8 mg/50 mL, 32 mg/50 mL

NDA HOLDER: Baxter Healthcare

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastroenterology Products (HFD-180) for a review of the container labels, carton and insert labeling of Ondansetron Injection, USP in PL 2408 Plastic Container.

PRODUCT INFORMATION

Ondansetron is an antiemetic agent indicated for the prevention of chemotherapy induced nausea and vomiting, for initial and repeat courses of emetogenic chemotherapy. The recommended dose of ondansetron injection, USP is a single 8 mg dose, a single 32 mg dose, or three 0.15 mg/kg doses. The dose is infused over 15 minutes beginning 30 minutes prior to the start of emetogenic chemotherapy. Ondansetron injection, USP will be available in 8 mg/50 mL and 32 mg/50 mL premixed plastic containers.

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

DMETS searched the FDA Adverse Event Reporting System for cases of medication errors associated with ondansetron using the preferred terms, "medication error, accidental exposure, accidental overdose, overdose, underdose, treatment noncompliance and pharmaceutical product complaint. No reports pertaining to the labels and labeling of ondansetron injection were submitted to the agency.

DMETS notes that eight reports involving the use of ondansetron injection during pregnancy have been received by the agency between April 2004 and May 2005. Ondansetron is currently labeled as pregnancy category B. In each of the eight cases received, ondansetron injection was used off-label for the treatment and/or prevention of nausea and/or vomiting associated with pregnancy and resulted in adverse events such as headache, diarrhea, constipation, lack of effect, nausea, venous occlusion, angioedema, anaphylaxis, and fetal demise. DMETS will continue to monitor for errors and complaints involving ondansetron injection.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels as well as the carton and insert labeling proposed for ondansetron injection, USP, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

DMETS notes several incidents where terminal zeros are used throughout the package insert labeling. The use of terminal zeros may result in error as often the decimals are overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeros could potentially result in a ten-fold medication dose error. The use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of terminal zeros is specially listed in the list of dangerous abbreviations, acronyms, and symbols in the 2006 National Patient Safety Goal 2b of The Joint Commission of Accreditation of Healthcare Organizations. Lastly, safety groups such as ISMP also list terminal zeros on their dangerous abbreviations and dose designations list. Thus, we recommend deleting all terminal zeros from the labels and labeling.

B. CONTAINER LABEL

1. DMETS notes the sponsor uses color to differentiate the product strengths. We recommend further differentiating the strength utilizing boxing, color shading and/or bolding (see below). Additionally, the red font may be difficult to read on a clear intravenous minibag.

LOT

EXP

Use Boxing, Color Shading, and/or Bolding to make strength prominent

EXP

NDC 0338-1762-41

2. Revise the statement "Iso-Osmotic..." to read "in Iso-Osmotic...", as ondansetron is "in" iso-osmotic sodium chloride.
3. Include the statement "protect from light until immediately prior to use". Currently, this information will be missing in the event the minibag is separated from the overpouch.

C. OVERPOUCH LABELING

1. See Container Label Comments B.1 thru B.3.
2. The orange font on the light orange background used on the 32 mg/50 mL overpouch is difficult to read. Please utilize a darker font and/or revise the color combination to improve contrast and readability. Additionally, DMETS does not recommend use of the same color scheme (i.e. blue and orange) for both strengths. Despite the reversal of the colors, the similarities may increase the potential for selection errors.
3. Increase the prominence of the statement "Protect from light...". This warning is likely to be overlooked with the current presentation.

IV. RECOMENDATIONS

- A. DMETS recommends implementation of the container label, carton, and insert labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.
- B. DMETS notes that we have not received a consult for a proposed proprietary name for this product. Please allow 90 days for the review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-827-3242.

Tina M. Tezky, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph., M.S.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tina Tezky
11/17/2005 04:28:16 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/17/2005 04:32:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/17/2005 04:35:59 PM
DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-915 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Ondanstron Injection, USP
Established Name: ondansetron hydrochloride
Strengths: 8 mg/50 mL and 32 mg/50 mL

Applicant: Baxter Healthcare Corporation
Agent for Applicant: NA

Date of Application: March 30, 2005
Date of Receipt: April 1, 2005
Date clock started after UN: NA
Date of Filing Meeting: May 24, 2005
Filing Date: May 31, 2005
Action Goal Date (optional):

User Fee Goal Date: February 1, 2006

Indication(s) requested: Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain: GSK has 0.5 years of pediatric exclusivity
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain: PREA was not addressed, however a request for waiver was received May 23, 2005. The patent form was missing, now received. Debarment certification was also missing, now received.

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? Labeling only.

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
This was not with the original submission, however has been submitted.
- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

The Debarment Certification is now received.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: PIND 68,217 and no IND opened
This Pre-IND number was administrative only. There is no corresponding IND for this application.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) August 7, 2003 YES
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 25, 2005

BACKGROUND: NDA 21-915 for Ondansetron Injection, USP in PL 2408 Plastic Container provides for the firm's seeking approval of two premixed bags of Ondansetron Injection, USP, 8 mg and 32 mg in 50 mL IntraVia flexible plastic containers. A 505(b)(2) application, the reference listed drug is Zofran (ondansetron) Injection (GSK). The proposed indication for use is for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. The 8 mg strength represents a lower dosage strength than the GSK Zofran product. The Division met with the firm on August 7, 2003 for a preNDA meeting.

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Ruyi He, Wen Jen Chen, Ke Zhange, Marie Kowblansky, Suliman Al-Fayoumi, Betsy Scroggs, Donald Hare

ASSIGNED REVIEWERS (including those not present at filing meeting) : as follows:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Lolita Lopez
Secondary Medical:	Ruyi He
Statistical:	Wen Jen Chen
Pharmacology:	Ke Zhange
Statistical Pharmacology:	NA
Chemistry:	Marie Kowblansky
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Suliman Al-Fayoumi
Microbiology, sterility:	Stephen Languille
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	NA
Regulatory Project Management:	Betsy Scroggs
Other Consults:	Shannon Benedetto, DDMAC; Sammie Beam,
DMETS, and Donald Hare from OGD	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed? YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. inspection needed?		YES <input type="checkbox"/> NO <input type="checkbox"/>
PHARMACOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP inspection needed?		YES <input type="checkbox"/> NO <input type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
	• Microbiology		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>

Although not present at meeting, the microbiologist communicated post-meeting that the application should be filed.

ELECTRONIC SUBMISSION:

Any comments: The original submission was paper, however, information requests have been made by the statistical reviewer for an electronic module 5, which has been submitted as well.

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Day 74 is June 14, 2005

Betsy Scroggs, Pharm.D.
Regulatory Project Manager, HFD-

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ON ORIGINAL**

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 20-007 Zofran
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). 8 mg IV qd is a new dose and regimen.
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s): 4,695,578 expiry 1-25-2005
4,753,789 expiry 6-24-2006 (Peds Exclusivity)
5,578,628 expiry 2-16-2005
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# N/A NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

**APPEARS THIS WAY
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**

/s/

Betsy Scroggs
9/22/2005 06:17:13 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-915

FILING COMMUNICATION

with issues

Baxter Healthcare Corporation
Attention: Vicki Drews, Associate Director, Global Regulatory Affairs
1620 Waukegan Road
McGaw Park, Illinois 60085

Dear Ms. Drews:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ondansetron Injection, USP in PL 2408 Plastic Containers. We also refer to your submissions dated May 20, 2005 and May 31, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 31, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

We have identified a potential clinical data issue. Each dosing regimen should be supported by data from adequate and well-controlled studies. Published literature alone without original data may not be adequate to support a new dosing regimen.

From the statistical perspective, in order to claim that two active drugs (Ondansetron 8mg and 32 mg) are equally effective, non-inferiority or equivalence analyses should be used, as described in "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials". Non-significant results from efficacy comparisons that involve a test of difference between the two active drugs may not be enough to demonstrate that the two drugs are equally effective.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Drug Master File (DMF) — which was referenced for ondansetron drug substance is inadequate at the present time. The DMF holder has been notified of the deficiencies.
2. You have submitted only twelve months of stability data. This may result in a shorter expiration for the product than requested in the application. You may supplement the

stability data no later than three months before the PDUFA goal date to have the additional data considered in determining expiration dating.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Betsy Scroggs, Pharm.D., Regulatory Health Project Manager at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R. Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Brian Strongin
6/14/05 11:21:00 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Acknowledgement Letter

NDA 21-915

Baxter Healthcare Corporation
Attention: Vicki Drews, Associate Director, Global Regulatory Affairs
1620 Waukegan Road
McGaw Park, Illinois 60085

Dear Ms. Drews:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ondansetron Injection, USP in PL 2408 Plastic Container
Review Priority Classification: Standard (S)
Date of Application: March 30, 2005
Date of Receipt: April 1, 2005
Our Reference Number: NDA 21-915

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 31, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 1, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your May 20, 2005 request on May 23, 2005 for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

NDA 21-915

Page 2

Dr. Brian Harvey
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:

Dr. Brian Harvey
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products
Attention: Division Document Room, HFD-180
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Betsy Scroggs
5/24/05 03:25:58 PM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Vicki Drews
Associate Director, Global Regulatory Affairs
Baxter Healthcare Corporation
1620 Waukegan Road
McGaw Park, IL 60085

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-915

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA.)

2. TELEPHONE NUMBER (Include Area Code)

(847) 473-6296

3. PRODUCT NAME

Ondansetron Injection, USP in PL 2408 Plastic Container

6. USER FEE I.D. NUMBER

3006015

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

V. Drews

TITLE

Associate Director, Global Regulatory Affairs

DATE

3/30/2005



IND Advice

letter re: cardiac
electrophysiology
studies

IND 68,217

Baxter Healthcare Corporation
Attention: Vicky Drews
Regulatory Affairs
Route 120 and Wilson Road
RLT-10
Round Lake, IL 60073-0490

Dear Ms. Drews:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ondansetron Hydrochloride Injection in IntraVia Container.

We refer to your pre-NDA meeting with the Division on August 7, 2003 in which the Division recommended that you conduct cardiac electrophysiology studies with ondansetron using the state-of-the-art *in vivo* and *in vitro* models.

We also refer to your amendment dated December 12, 2003 (serial # 001), containing a brief summary of published cardiac electrophysiology studies with ondansetron.

In this submission, you have provided a brief summary of data for the available published *in vitro* and *in vivo* cardiac electrophysiology studies with ondansetron. Further, you propose that in lieu of conducting additional studies, the available data on cardiac electrophysiology studies with ondansetron will be provided as part of the 505(b)(2) application, and have requested our opinion as to whether we are in agreement with the proposal.

We have completed the pharmacology review of your submission. Your proposal to include the reports of published *in vitro* and *in vivo* cardiac electrophysiology studies with ondansetron along with a summary in your 505(b)(2) NDA application is acceptable.

IND 68,217

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If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer,
at 301-827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joyce Korvick
3/30/04 04:09:47 PM
for Dr. Robert Justice

Pre-NDA MM
8-7-03

10/15/2003 WED 14:23 FAX 3018271305 HFD-180 DCCDP

0002/00

Memorandum of Meeting Minutes

Meeting Date: August 07, 2003
Meeting Time: 11:30 - 1:00 pm
Meeting Location: Potomac Conference Room, Parklawn Building, 3rd floor,

Application Number: Ondansetron Hydrochloride Injection in Intra Via Container
(no application number)

Type of Meeting: Pre-NDA, Industry Meeting
Meeting Chair: Dr. Hugo Gallo-Torres
Meeting Recorder: Mr. Paul E. Levine, Jr.

List of FDA Attendees

Division of Gastrointestinal and Circulation Drug Products (HFD-180)

Robert L. Justice, M.D., M.S., Division Director
Hugo Gallo-Torres, M.D., Ph.D., F.N.S., Clinical Team Leader (GI/Drugs)
Gary Della'Zanna, D.O., M.Sc., Clinical Reviewer
Ramesh Raghavachari, Ph.D., Chemistry Reviewer
Jasit Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist
Paul E. Levine, Jr., R.Ph., J.D., Regulatory Health Project Manager

Division of Pharmaceutical Evaluation, HFD-870

Suliman Al-fayoumi, Ph.D., Biopharmaceutics Reviewer

Division of Biometrics II (HFD-715)

Tom Permutt, Ph.D., Statistical Team Leader

Office of Pharmaceutical Science (HFD-604)

Don Haro, R.Ph., Project Manager

List of External Constituents:

Baxter Healthcare Corporation:

Kent Allenby, M.D., Vice President, Clinical Affairs
Patricia Barsanti, Director, Regulatory Affairs
Debra Bello, Director, Clinical Affairs
Jon Cammack, Ph.D., DABT, Research Director
Vicki Drews, Senior Manager, Regulatory Affairs
Pharmacology Consultant
Regulatory Consultant

NFC.12.03

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Pre-NDA: Ondansetron Hydrochloride Injection
Meeting Minutes: August 07, 2003
Page 2

BACKGROUND

On June 20, 2003, Baxter Healthcare Corporation (sponsor), submitted a request for a pre-NDA meeting to discuss the submission of Ondansetron Hydrochloride Injection in IntraVia Container as a 505(b)2 application. Ondansetron Hydrochloride Injection is currently marketed under the name of Zofran® (ondansetron hydrochloride) by GlaxoSmithKline for the prevention of nausea and vomiting associated with the use of emetogenic cancer chemotherapy.

On July 08, 2003, the sponsor submitted a meeting background package containing questions concerning the proposed content and format of a 505(b)2 application for Ondansetron Hydrochloride Injection in IntraVia Container.

MEETING PURPOSE

To discuss the proposed content and format of a 505(b)2 application for Ondansetron Hydrochloride Injection in IntraVia Container.

DISCUSSION

Response to Sponsor's Questions

Clinical

1. Reference is made to the *Guidance for Industry on Providing Clinical Evidence of Effectiveness*, in particular section II.C.1.d relating to different doses, regimens, or dosage forms, and sections III.A.1 and III.A.2 relating to reliance on less than usual access to clinical data or detailed study reports. Are the data and information provided adequate as a basis of support for filing a 505(b)2 application for the proposed products and dosing, in accordance with the provisions of this guidance?

FDA response: You refer to both sections III.A.1 and III.A.2 in the Guidance. Clarify if you plan to submit additional supporting documents such as those outlined in section III.A.1.

In regard to the clinical data, a preliminary review indicates that the data and information provided might not be sufficient to support dose recommendations other than those currently

¹ *Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998.*

Pre-NDA: Ondansetron Hydrochloride Injection
Meeting Minutes: August 07, 2003
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approved. Each dosing regimen should be supported by reports of adequate and well-controlled studies. We prefer that you provide the documentation requested in section III.A.1 of the guidance. If these are not available, you need to satisfy the criteria outlined in section III.A.2. A final determination of liability or approvability cannot be made until the application has been received and fully evaluated.

Additional Discussion: Baxter has investigated the possibility of obtaining the documentation cited in section III.A.1 for key studies identified in support of the new dosing. Due to varying factors () we have determined that this information was not available to us to include in a NDA submission. Consequently, we do intend on providing evidence that the studies meet the criteria detailed in Section III.A.2 of the Guidance, and would like to confirm that this approach is considered acceptable by the Agency. We would like to further discuss the level of detail needed in the published reports to support product approval.

FDA Response: We find the approach acceptable. The adequacy will depend on review of the NDA. Each dose and regimen must be adequately supported.

2. Does the use of common practice and current standards of care (e.g., Clinical Practice Guidelines and Recommendations from the American Society of Oncology², and approved non-U.S. dosing recommendations) constitute additional and appropriate basis to support the approval of the proposed products and dosing?

In general, practice guidelines and recommendations are useful but not sufficient to support approval. The final decision on approvability will be based on the Division's review of the application.

Pharmacokinetics

Ondansetron pharmacokinetics have been well characterized and documented in the literature. Does body of ondansetron PK data provide a basis for approval of the proposed dosing regimen(s)?

You should additionally characterize the PK of the proposed doses and dosing regimens of the ondansetron HCL Injection.

² "Recommendations for the Use of Anticemetics: Evidence-Based, Clinical Practice Guidelines", ASCO Special Article, *Journal of Clinical Oncology*, Vol 17, No 9 September, 1999; pp 2971-2994.

Pre-NDA: Ondansetron Hydrochloride Injection
Meeting Minutes: August 07, 2003
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Additional Discussion: We would like to better understand the Agency's request for additional PK characterization. We believe that the PK's of at least two of the proposed doses (single dose and _____) have been characterized and reported in the SBOA for 20-007 (p. 057, 064-065). Are these data appropriate support for PK characterization of these two dosing regimens?

FDA Response: We will look into the summary basis of approval and provide a response at a later date.

Pre-Clinical

Ondansetron pre-clinical data is well described in the Summary Basis for Approval for ZOFRAN and the literature. The proposed maximum dosage for ondansetron in new dosage amounts will not exceed those already approved and the Baxter formulation will not contain any new unstudied components. Does the Agency agree that no additional pre-clinical studies will be required?

Additional Discussion: We would like to better understand the Agency's rationale for this request. We have evaluated the safety information reported in the SBOA for NDA 20-007, and believe that the reported results support the proposed dosing. The following points were considered in this evaluation:

Comment: The rationale for the previous recommendation was discussed and acknowledged by the sponsor.

Pre-NDA: Ondansetron Hydrochloride Injection
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Chemistry

Is the proposed bracketing approach and stability submission data package for the proposed products adequate to support registration of this product?

They appear to be acceptable, provided a complete stability protocol including test methods, intervals, and complete specifications is included in the submission as per ICH guidelines.

General/Administrative

Does this Division concur that a 505(b)2 application is a suitable regulatory mechanism to support registration of the proposed product?

See the response to Question #1.

CONCLUSION

- 1. The Biopharm reviewer will look into the summary basis of approval and provide a response at a later date as to whether the existing body of ondansetron PK data provide a basis for approval of the proposed dosing regimen(s).**

DEC. 12. 03

11

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Betsy Scroggs

5/24/05 04:25:18 PM

Placing into DFS for administrative record for PreNDA meeting
held 8-7-2003