

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

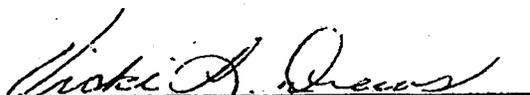
**21-915**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**1.3.5 Patent Certification and Exclusivity**

**Paragraph III Certification [21 CFR §314.94(a)(12)(3)]**

Applicant certifies that, in the applicant's opinion and to the best of applicant's knowledge, U.S. Patent Numbers 4,695,578, 4,753,789 and 5,578,628, which are listed in the current Orange Book<sup>1</sup> for ZOFTRAN® (ondansetron hydrochloride) Injection, will expire on January 25, 2005, June 24, 2006 and February 16, 2005 respectively, subject to the approved six-month pediatric exclusivity period. We request that the approval of this application be made effective immediately upon expiration of the pediatric exclusivity period for 4,753,389, which is identified to expire on December 24, 2006. ✓



Vicki Drews  
Associate Director, Global Regulatory Affairs

3/16/2005  
Date

**APPEARS THIS WAY  
ON ORIGINAL**

<sup>1</sup> U.S Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Information Technology, Division of Data Management and Services. Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book).

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

NDA NUMBER  
21-915

NAME OF APPLICANT / NDA HOLDER  
Baxter Healthcare Corporation

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)  
Ondansetron Injection, USP in PL 2408 Plastic Container

ACTIVE INGREDIENT(S)  
Ondansetron Hydrochloride, USP

STRENGTH(S)  
8 mg/50 mL and 32 mg/ 50 mL

DOSAGE FORM  
Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an Incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  Yes  No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

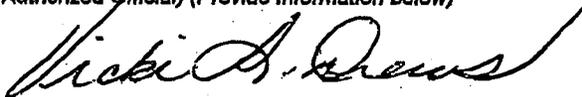
**6. Declaration Certification**

**6.1** *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning:** A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

**6.2** Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed  
5/19/2005



**NOTE:** Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Vicki Drews, Associate Director Global Regulatory Affairs	
Address 1620 Waukegan Road	City/State McGaw Park, IL
ZIP Code 60085	Telephone Number (847) 473-6296
FAX Number (if available) (847) 785-5107	E-Mail Address (if available) vicki_drews@baxter.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*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.*

## EXCLUSIVITY SUMMARY

NDA # 21-915

SUPPL #

HFD # 180

Trade Name Ondansetron Injection, USP in PL 2408 Plastic Container (32mg/50mL)

Generic Name Ondansetron

Applicant Name Baxter Healthcare Corporation

Approval Date, If Known December 25, 2006

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

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  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.

Dr. Lolita documented in her original clinical review on December 14, 2005 that no clinical studies were performed by the applicant in support of the proposed drug product. This application is based upon published literature references and the established safety of the ZOFRAN® product.

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:

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

GlaxoSmithKline (GSK) Zofran product was granted three years of Waxman-Hatch exclusivity and 6 months of pediatric exclusivity on the basis of three clinical studies performed to obtain pediatric efficacy, safety and pharmacokinetic (PK) and dosing information in response to a Written Request for Zofran® Injection. These studies extended the age range down to 1 month (for post-operative nausea and vomiting) and 6 months (for chemotherapy- induced nausea and vomiting). The Zofran® supplemental NDA (20-007/s035) was approved for prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients six to 48 months old who are receiving moderately to highly emetogenic chemotherapy, and for the prevention of post-operative nausea and vomiting in pediatric patients one to 24 months old undergoing routine surgery under general anesthesia. Based upon the pediatric studies submitted with the application, dosing was established for the age groups studied for both of these indications. This information is reflected in the labeling approved for Zofran® and Zofran Preservative Free injection and premixed injection on March 25, 2005.

It should be noted that this single dose form is not recommended in children as it is in excess of the recommended pediatric dose. The pediatric dose is available through product packaged in sterile vials for dilution.

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.**

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

YES  NO

**IF THE ANSWER TO QUESTION 2 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  NO

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

NDA# 20007	Zofran® (ondansetron hydrochloride) Injection
NDA# 20103	Zofran® (ondansetron hydrochloride) Tablets
NDA# 20403	Zofran® (ondansetron hydrochloride) Injection Premixed

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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."

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  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:

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

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

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

Investigation #1 !  
IND # YES  ! NO

! Explain:

Investigation #2

!

IND #

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

!

! NO

Explain:

! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! 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

If yes, explain:

---

Name of person completing form: Giuseppe Randazzo  
Title: Regulatory Project Manager  
Date: 12.27.06

Name of Office/Division Director signing form: Dr. Joyce Korvick  
Title: Deputy Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**APPEARS THIS WAY  
ON ORIGINAL**

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

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Joyce Korvick  
1/3/2007 02:38:07 PM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: NDA 21-915 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: 10/27/2006 (current cycle) PDUFA Goal Date: 12/27/2006

HFD-180

Trade and generic names/dosage form: Ondansetron Injection, USP in PL 2408 Plastic Container (32 mg/50 mL).

Applicant: Baxter Healthcare Corporation Therapeutic Class: Antiemetic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): \_\_\_\_\_

Indication #1: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.  
 No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

NDA 21-915  
Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**APPEARS THIS WAY  
ON ORIGINAL**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

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**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  
1/5/2007 04:47:56 PM

1.3.3 Generic Drug Enforcement Act Certification (Debarment Certification)

**Certification Per The Generic Drug Enforcement Act Of 1992**

In accordance with Section 306(k) of the Act [21 USC 355a (k)(1)], Baxter Healthcare Corporation wishes to certify that Baxter did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) and (b)], in connection with this application.

In addition, in accordance with Section 306(k) of the Act [21 USC 335a(k)(2)], Baxter wishes to certify that there are no convictions that occurred within five years of today's date, for which a person can be debarred, of the applicant and affiliated persons responsible for the development or submissions of the application.



Vicki L. Drews  
Associate Director  
Global Regulatory Affairs

8-10-05  
Date

**APPEARS THIS WAY  
ON ORIGINAL**

Acting Director Summary  
12/27/2006

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research**

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**DATE:** 12/27/06  
**FROM:** Joyce A Korvick, MD, MPH  
DGP/ODE III

**SUBJECT:** Deputy Division Director Approval Comments  
NDA 21-915

**APPLICANT:** Baxter Healthcare Corporation

**DRUG:** Ondansetron Injection USP  
Premix in INTRAVIA Plastic Container  
32 mg/50 mL

We recommend approval of this application. The October 26<sup>th</sup> section of this memo details the final review of this Class I resubmission.

**Regulatory History:**

On May 26, 2006, a 505(b)(2) NDA 21-915 for ondansetron premixed injection received a tentative approval (TA). This preparation is a 32 mg/50 mL premixed osmotic solution in single use containers. This 32 mg product may be used as a single dose in adults. Baxter responded to the TA letter on October 27, 2006 with proposed labeling. The proposed labeling does not contain any disclaimers typically associated with "carving out" of exclusivity data in generic drugs for which there is pediatric exclusivity.

Baxter lists NDA 20-007 as the reference listed product. The last pediatric exclusivity expires for the preservative free product (NDA 20-007) on September 25, 2008. In addition, there are existing exclusivities for the tablets, and orally disintegrating tablets, oral solution (see Appendix- Patent Information). The patents for the injection and premixed (NDA — are due to expire Dec 24, 2006. The PDUFA date for this product is December 27, 2006.

GlaxoSmithKline (GSK) was granted three years of Waxman-Hatch exclusivity and 6 months of pediatric exclusivity on the basis of three clinical studies performed to obtain pediatric efficacy, safety and pharmacokinetic (PK) and dosing information in response to a Written Request for Zofran® Injection. These studies extended the age range down to 1 month (for post-operative nausea and vomiting) and 6 months (for chemotherapy induced nausea and vomiting). The Zofran® supplemental NDA (20-007/s035) was approved for prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients six to 48 months old who are receiving moderately to highly emetogenic

chemotherapy, and for the prevention of post-operative nausea and vomiting in pediatric patients one to 24 months old undergoing routine surgery under general anesthesia. Based upon the pediatric studies submitted with the application, dosing was established for the age groups studied for both of these indications. This information is reflected in the labeling approved for Zofran® and Zofran Preservative Free injection and premixed injection on March 25, 2005.

**DIVISION second cycle RECOMMENDATIONS (5/26/06):**

The division recommended that a tentative approvable action for the current application. I am in concurrence with this recommendation.

The agreed upon labeling provides for approval of the 32 mg/50mL for the proposed indication:

*“Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy in adult patients, including high-dose cisplatin. Efficacy of the 32 mg single dose beyond 24 hours in these patients has not been established.”*

The tentative approval is based upon the fact that there is an existing patent exclusivity which expires December 24, 2006. Further labeling negotiations were anticipated during the Class I resubmission, especially regarding the pediatric labeling.

This supplement was in response to our approvable letter of February 1, 2006 in which the Division requested removal of the 8mg/50mL formulation. It should be noted that this formulation and dose is not approved for use in pediatric patients, and is stated as such in the label. In numerous discussions with Office of Generic Products, their aim was to have all generic products have similar labels to that of the innovator with specific “pediatric carve outs”. While this is important for the product/formulation appropriate for pediatric use (the glass vial product) it does not apply to the “minibag” 32mg, single use, and preservative free product. This product is NOT RECOMMENDED for use in pediatric patients due to the fact that this dose is far too high when compared to that calculated on a mg/kg basis as recommended in the innovator label. Because this product is only the MINI BAG formulation the division has recommended removal of pediatric dosing and inclusion of specific wording “in adults” in the label. The final regulatory comments for this label were transmitted to the division from Kim Colangelo, Office of New Drugs. This email recommended further discussions with Pediatrics for finalization of the pediatric wording. Those discussions were held between me and Lisa Mathis on Dec 22<sup>nd</sup>. It was agreed that we proceed with deletion of wording for pediatric dosing from the label and a format that differs from the current generic drug wording.

Future regulatory actions will necessitate that the division

No new clinical trials were submitted with this supplement. No new safety issues were raised by this submission.

**OCTOBER 27, 2006 Class I Resubmission:**

The label proposed by the sponsor was the same as that which the Division had requested of the sponsor in the approvable action. At that time the Division told the sponsor that labeling regarding the pediatric language would be reviewed during the final resubmission including internal conversations with the legal and pediatric departments and that further edits may be recommended.

Chemistry and Manufacturing:

The sponsor submitted information regarding clarifications of microbiology issues and a proposed label. The new CMC and labeling were reviewed in this 2 month cycle. The results of the CMC review find this product acceptable for marketing.

Final Labeling:

The outstanding issues regarding the final draft labeling surround the pediatric exclusivity and current generic labeling regarding the injection solution in vials for dilution. It is important to note that the Division agrees with the use of the vials but not the minibag due to the fact that the minibag unit dose is in excess of the recommended pediatric dosing. The innovator label contains both unit packaging forms and thus makes the issues regarding generic labeling somewhat complicated, as do the pediatric 'carve-outs'.

The Pediatric Consult Review was very informative regarding the details of the labeling issues and 'carve outs' for pediatrics. Please refer to Dr. Sachs' review.

A teleconference was held with the sponsor on Dec 26<sup>th</sup>, where the following recommendations were discussed.

1. Insert " in Adults" in all the table headings
2. Replace Zofran with Ondansetron in the label
3. Add the following under description: "Sterile, premixed solution for Intravenous Administration in Single-dose, Flexible Plastic Containers."
4. INDICATIONS and USAGE:  
*"Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy in adult patients, including high-dose cisplatin. Efficacy of the 32 mg single dose beyond 24 hours in these patients has not been established."*
5. DOSAGE and ADMINISTRATION:  
*"The ondansetron premixed formulation is not recommended for use in children. The ondansetron premixed formulation is a fixed dosage form that has*

*not been studied in the pediatric population, and is not appropriate for weight based dosing in pediatric patients.”*

The sponsor stated the second label printing would occur in February 2007. The division felt that it was reasonable to institute the above changes at that printing. These changes were felt to further clarify the recommendations against using this product in pediatric patients, but that the current wording would be satisfactory in the short term as it does contain a line warning against use in children in the PRECAUTION section.

Finally, the DMETS consult was received on Dec 22, 2006. It recommended certain minor changes. In a discussion with the sponsor it was agreed that the Overpouch Labeling would have the words “RECOMMENDED STORAGE” bolded and in capital lettering. Other recommendations regarding order of wording was not made due to consistency in labeling with other products currently on the market by this sponsor. The division felt that the current package labeling was adequate and well written.

The review team recommended a pediatric waiver for this product due to size of dose and the fact that no new additional pediatric studies of this drug are needed. I concur.

**APPEARS THIS WAY  
ON ORIGINAL**

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

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Joyce Korvick  
12/27/2006 12:04:59 PM  
MEDICAL OFFICER

D.D.D. Summary  
2nd Cycle  
5-28-2006

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research**

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**DATE:** 5/26/06  
**FROM:** Joyce A Korvick, MD, MPH  
DGP/ODE III

**SUBJECT:** Deputy Division Director Approvable Comments  
NDA 21-915

**APPLICANT:** Baxter Healthcare Corporation

**DRUG:** Ondansetron Injection USP  
Premix in INTRAVIA Plastic Container  
8 mg/50 mL or 32 mg/50 mL

**DIVISION RECOMMENDATION:**

The division recommends that a tentative approvable action for the current application. I am in concurrence with this recommendation.

The agreed upon labeling provides for approval of the 32 mg/50mL for the proposed indication:

*"Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin in adult chemotherapy patients. Efficacy of the 32 mg single dose beyond 24 hours in these patients has not been established."*

The tentative approval is based upon the fact that there is an existing patent exclusivity which expires December 24, 2006.

This supplement was in response to our approvable letter of February 1, 2006 in which the Division requested removal of the 8mg/50mL formulation. It should be noted that this formulation and dose is not approved for use in pediatric patients, and is stated as such in the label. This dose is too high for that recommended for pediatrics in the innovator label.

No new clinical trials were submitted with this supplement. No new safety issues were raised by this submission.

The label proposed by the sponsor was the same as that which the Division had requested of the sponsor prior to the approvable action.

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

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Joyce Korvick  
5/26/2006 10:50:12 AM  
MEDICAL OFFICER

## Action Package Supplement Checklist Sign-off

Application Information		
NDA # 21-915	NDA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Ondansetron Injection, USP in PL 2408 Plastic Container Established Name: Ondansetron Injection, USP Dosage Form: Injection	Applicant: Baxter Healthcare Corporation	
RPM: Giuseppe Randazzo	Division: Gastroenterology	Phone: 301-796-0980
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(2)  (A supplement can either be a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug names(s)):  NDA 20-007 Zofran® (Ondasetron) Injection  Provide a brief explanation of how this product is different from the listed drug:  The original application was submitted as a 505(b)(2) in that it was driven by their new proposed dose of 8 mg/50 mL. Subsequently, the 8 mg/50mL dose was withdrawn and the current proposed dose, 32mg/50mL, continued through the review process. The only difference between Baxter's 32mg/50mL and the RLD is the diluent.	
<p style="text-align: center;"><b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this checklist to update any information (including patent certification information) that is no longer correct.</b></p> <p><input checked="" type="checkbox"/> Confirmed Date: 12/18/06</p>		
❖ User Fee Goal Date ❖ Action Goal Date (if different)	December 27, 2006	

### Reviewers/Team Leaders Sign off

Deputy Division Director

JK



Date

12/26/09

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-915	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Ondasetron Injection, USP in PL 2408 Plastic Conntainer Established Name: Ondasetron Injection, USP Dosage Form: Injection		Applicant: Baxter Healthcare Corporation
RPM: Giuseppe Randazzo		Division: Gastroenterology      Phone # 301-796-2120
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  NDA 20-007 Zofran® (Ondasetron) Injection  Provide a brief explanation of how this product is different from the listed drug. The original application was submitted as a 505(b)(2) in that it was driven by their new proposed dose of 8 mg/50 mL. Subsequently, the 8 mg/50mL dose was withdrawn and the curent proposed dose, 32mg/50mL, continued through the review process. The only difference between Baxter's 32mg/50mL and the RLD is the diluent.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b>  <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 12/18/06
❖ User Fee Goal Date ❖ Action Goal Date (if different)		December 27, 2006
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None AE - February 01, 2006 TA - May 26, 2006
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:  Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ <b>Exclusivity</b></p>	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?             <ul style="list-style-type: none"> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></p>	
<ul style="list-style-type: none"> <li>• <b>Patent Information:</b> Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>• <b>Patent Certification [505(b)(2) applications]:</b> Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)  <input type="checkbox"/> No paragraph III certification Date patent will expire 12/24/2006
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews).</i>)</li> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified          <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<b>Summary Reviews</b>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	<p>1<sup>st</sup> cycle: Approvable - Joyce Korvick (February 01, 2006)</p> <p>MOTL: 01/08/2006</p> <p>2<sup>nd</sup> cycle: TA - Joyce Korvick (May 26, 2006)</p> <p>October 26, 2006 resubmission: Joyce Korvick (December 27, 2006)</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<b>Labeling</b>	
<b>Package Insert</b>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A - applicant label submitted is most recent label
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	October 26, 2007
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	<p>1st cycle: March 30, 2005</p> <p>RLD: Zofran recent label change approved August 22, 2006, Anzemet, Kytril, Aloxi Canadian Product Monograph for Ondansetron Injection, USP</p>
<b>Patient Package Insert</b>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	N/A
<b>Medication Guide</b>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	N/A

❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	N/A - applicant label submitted is the most recent label
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	October 26, 2007
❖ Labeling reviews and minutes of any labeling meetings ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> DMETS 11/17/2005 & 12/22/06 <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC 01/06/2006 & 12/21/2006 <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews Pediatric label review 12/18/2006 RPM label review 12/19/2006 <input checked="" type="checkbox"/> Memos of Mtgs 01/13/2006, 01/19/2006, 01/06/2006, 12/27/2006

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	Cycle 1: September 22, 2005 Appendix B revised February 1, 2006 New Action Package Checklist: complete on 12/27/2006
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	N/A Cleared 1 <sup>st</sup> and 2 <sup>nd</sup> Cycle 10/26/2006 resubmission Cleared - via email 12/05/2006
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	<input type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Incoming submission documenting commitment</li> </ul>	N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	1st Cycle: Faxed label info (01/30/2006, 01/20/2006, and 01/13/2006) Tcon 01/19/2006 Tcon 01/30/2006 IND AD letter 03/30/2004 NDA Ack letter 05/24/2005 Filing communication 6/14/2005 DMF deficiency letter 12/21/2005 Micro DR letter 12/21/2005  2 <sup>nd</sup> Cycle: Ack letter 05/10/2006  10/26/2006 Resubmission: Ack letter 12/18/2006

❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	N/A
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg      August 7, 2003
• EOP2 meeting ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>CMC/Product Quality Information</b>	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	1 <sup>st</sup> cycle: 12/23/2005 01/26/2006  2 <sup>nd</sup> cycle: 05/01/2006  10/26/2006 resubmission: 12/20/2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	1 <sup>st</sup> Cycle: December 23, 2005 pg 23 of CMC review.  2 <sup>nd</sup> cycle N/A  10/26/2006 resubmission: N/A
• <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
• <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	See under clinical review section <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents	
• Facility review ( <i>indicate date(s)</i> )	<input type="checkbox"/> Requested
• Compliance Status Check (approvals only, both original and supplemental applications) ( <i>indicate date completed, must be within 60 days prior to AP</i> )	<input type="checkbox"/> Accepted
	<input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed
	<input type="checkbox"/> Requested
	<input type="checkbox"/> Not yet requested
	<input checked="" type="checkbox"/> Not needed

<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	1 <sup>st</sup> cycle: 11/09/2005 01/19/2006  2 <sup>nd</sup> cycle: N/A  10/26/2006 resubmission: 12/19/2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

**APPEARS THIS WAY  
ON ORIGINAL**

<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	1 <sup>st</sup> cycle: MOR: DGP 12/14/2005  2nd cycle: MOR: DGP 05/08/2005  10/26/2006 resubmission MOR: DGP 12/13/2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None 1st cycle: Oncology 01/24/2006
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 1 <sup>st</sup> cycle: 12/20/2005 01/26/2006  2 <sup>nd</sup> cycle: N/A  10/26/2006 resubmission: NAI
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	1 <sup>st</sup> cycle: pg 36 of 12/14/2006 MOR  2 <sup>nd</sup> cycle: N/A  10/26/2006: N/A - no new safety information submitted
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>• Clinical Studies</li> <li>• Bioequivalence Studies</li> <li>• Clin Pharm Studies</li> </ul>	
❖ Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1 <sup>st</sup> cycle: 12/16/2006  2 <sup>nd</sup> cycle: N/A  10/26/2006 resubmission: N/A
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 10/26/2006 resubmission: 12.21.06

## Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) And no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) And all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

# NDA SUPPLEMENT ACTION PACKAGE CHECKLIST SIGN-OFF SHEET

Application Information			
NDA 21-915	Efficacy Supplement Type SE- NA	Supplement Number NA	
Drug: Ondansetron		Applicant: Baxter Healthcare Corporation	
RPM: Betsy Scroggs		HFD-180	Phone # 301-769-0991
Application Type: 505(b)(2)		Reference Listed Drug (NDA #, Drug name): 20-007 Zofran (ondansetron)	
❖ Application Classifications:			
<ul style="list-style-type: none"> <li>• Review priority</li> <li>• Chem class (NDAs only)</li> <li>• Other (e.g., orphan, OTC)</li> </ul>			(X) Standard ( ) Priority
❖ User Fee Goal Dates			February 1, 2006

## Reviewers/Team Leaders Sign Off List

CPMS  
 JD 1/17/2006 2nd cycle Melissa Hancock/Furman STATS 1/18/06  
05/23/06 SG/WOL Stella Houser

ONDQA  
 MJR/MK 2nd cycle ok per email dated 4/10/2006 from  
Mark K. - please see attached  
 MICRO consult to ONDQA email on  
 DH/SL N/A - refer to ONDQA - PM

### CLINICAL

1st cycle RH/LL RH 1/18/06  
2nd cycle [redacted] 5/2/06  
CDM may consider adding the Division proposed  
label under the section of Division proposed label  
Our labeling will be the final, not the firm's label

### BIOPHARMACEUTICS

DB/SCL Ede 1/18/06

### PHARMACOLOGY/TOXICOLOGY

JC/KZ [signature] 1/18/06

### DEPUTY DIVISION DIRECTOR

JK [signature] 5/2/06 2nd cycle  
le 2/1/06 [signature]

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-915	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: Ondansetron Injection USP in PL 2408 Plastic Container		Applicant: Baxter Healthcare Corporation
RPM: Betsy Scroggs	HFD-180	Phone # (301) 796-0991
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)                      (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input checked="" type="checkbox"/> Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):                      NDA 20-007 Zofran® (ondansetron) Injection</p>
<b>❖ Application Classifications:</b>		
Review priority	<input checked="" type="checkbox"/> Standard 1 <sup>st</sup> Cycle <input checked="" type="checkbox"/> Class 2 resubmission 2 <sup>nd</sup> Cycle	
Chem class (NDAs only)	3	
Other (e.g., orphan, OTC)	N/A	
<b>❖ User Fee Goal Dates</b>		
		1 <sup>st</sup> Cycle: February 1, 2006 2 <sup>nd</sup> Cycle: May 26, 2006
<b>❖ Special programs (indicate all that apply)</b>		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>User Fee Information</b>		
User Fee	<input checked="" type="checkbox"/> Paid 1 <sup>st</sup> Cycle and NA for 2 <sup>nd</sup> Cycle UF ID number 3006015	
User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	

❖ Application Integrity Policy (AIP)	
Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No 1 <sup>st</sup> and 2 <sup>nd</sup> Cycle
This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No 1 <sup>st</sup> and 2 <sup>nd</sup> Cycle
Exception for review (Center Director's memo)	N/A
OC clearance for approval	Cleared 1 <sup>st</sup> and 2 <sup>nd</sup> Cycle
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified
Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	This is a paragraph III certification and will be acted on as a tentative approval due to existing patent and pediatric exclusivity protection.
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	
<i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i>	
Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i>	
<i>If "No," continue with question (3).</i>	
Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	<input type="checkbox"/> Yes <input type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)

Exclusivity summary

Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

Drafted: Finalize when the application is approved.

Note:  
NDA 20-007 has pediatric exclusivity until December 24, 2006

Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

Yes, Application # \_\_\_\_\_  
 No

Administrative Reviews (Project Manager, ADRA) ( <i>indicate date of each review</i> )	Cycle 1: September 22, 2005 Appendix B revised February 1, 2006  Cycle 2: Appendix B revised May 18, 2006.
<b>General Information</b>	
❖ Actions	
Proposed action	2 <sup>nd</sup> Cycle (X) TA May 26, 2006
Previous actions (specify type and date for each action taken)	Approvable: February 1, 2006
Status of advertising (approvals only)	<b>N/A until approval.</b> ( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
Press Office notified of action (approval only)	( ) Yes (X) Not applicable
Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A: Applicant's labeling is the last labeling generated.
Most recent applicant-proposed labeling	2 <sup>nd</sup> Cycle: April 14, 2006 Package Insert
Original applicant-proposed labeling	1 <sup>st</sup> Cycle: March 30, 2005
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)</li> </ul>	1 <sup>st</sup> Cycle: DMETS – November 17, 2005 1 <sup>st</sup> Cycle: DDMAC – January 6, 2006 Labeling TCONS January 19, 20, 2006
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	Zofran, Anzemet, Kytril, Aloxi Canadian Product Monograph for Ondansetron Injection, USP
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	N/A
Applicant proposed	1 <sup>st</sup> Cycle: January 30, 2006 Carton, Container, Overwrap 2 <sup>nd</sup> Cycle: N/A
Reviews	1 <sup>st</sup> Cycle: DMETS – November 17, 2005 1 <sup>st</sup> Cycle: DDMAC – January 6, 2006 2 <sup>nd</sup> Cycle: None.
Post-marketing commitments	
Agency request for post-marketing commitments	N/A
Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
Outgoing correspondence (i.e., letters, E-mails, faxes)	1 <sup>st</sup> Cycle

	<p>IND 68,217 AD LTR: March 30, 2004 NDA ACK LTR: May 24, 2005 FG LTR: June 14, 2005 DMF LTR: December 21, 2005 MICRO DR LTR: December 22, 2005 Approvable Letter: February 1, 2006.</p> <p>2<sup>nd</sup> Cycle Acknowledgement Letter: May 10, 2006</p>
Memoranda and Telecons	<p>1<sup>st</sup> Cycle: FDA Labeling Labeling TCONs January 19, 2006 / DFS February 1, 2006 January 30, 2006/February 1, 2006</p>
Minutes of Meetings	
EOP2 meeting (indicate date)	N/A
Pre-NDA meeting (indicate date)	August 7, 2003
Pre-Approval Safety Conference (indicate date; approvals only)	N/A
Other	N/A
Advisory Committee Meeting	
Date of Meeting	N/A
48-hour alert	N/A
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary Approval Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	<p>DDD: February 1, 2006 MOTL: January 8, 2006</p>
<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	<p>1<sup>st</sup> Cycle: MOR: December 14, 2005 Oncology Review: January 24, 2006</p> <p>2<sup>nd</sup> Cycle: MOR: May 8, 2006</p>
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	<p>1<sup>st</sup> Cycle: Pg 36 of December 14, 2005 MOR</p> <p>2<sup>nd</sup> Cycle: N/A</p>
Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A

<p>Pediatric Page(separate page for each indication addressing status of all age groups)</p>	<p>1<sup>st</sup> Cycle: January 8, 2006</p> <p>2<sup>nd</sup> Cycle: N/A (see below) The following no longer applies to this application.</p> <p>“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.”</p>
<p>Demographic Worksheet (NME approvals only)</p>	<p>N/A</p>
<p>❖ Statistical review(s) (indicate date for each review)</p>	<p>1<sup>st</sup> Cycle: December 16, 2005</p> <p>2<sup>nd</sup> Cycle: N/A</p>
<p>❖ Biopharmaceutical review(s) (indicate date for each review)</p>	<p>1<sup>st</sup> Cycle: January 17, 2006</p> <p>2<sup>nd</sup> Cycle: N/A</p>
<p>❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)</p>	<p>N/A</p>
<p>❖ Clinical Inspection Review Summary (DSI)</p>	<p style="background-color: black; color: black;">[REDACTED]</p>
<p>Clinical studies</p>	<p>N/A</p>
<p>Bioequivalence studies</p>	<p>N/A</p>
<p>CMC Information</p>	
<p>❖ CMC review(s) (indicate date for each review)</p>	<p>1<sup>st</sup> Cycle: December 23, 2005 January 26, 2006</p> <p>2<sup>nd</sup> Cycle: May 1, 2006</p>
<p>Environmental Assessment</p>	
<p>Categorical Exclusion (indicate review date)</p>	<p>1<sup>st</sup> Cycle; December 23, 2005 pg 23 of the CMC review</p> <p>2<sup>nd</sup> Cycle: N/A</p>
<p>Review &amp; FONSI (indicate date of review)</p>	<p>N/A</p>
<p>Review &amp; Environmental Impact Statement (indicate date of each review)</p>	<p>N/A</p>
<p>❖ Microbiology (validation of sterilization &amp; product sterility) review(s) (indicate date for each review)</p>	<p>Cycle 1: December 20, 2005 January 26, 2006</p> <p>Cycle 2: N/A</p>
<p>❖ Facilities inspection</p>	<p>Date completed: December 30, 2005 (X) Acceptable ( ) Withhold recommendation</p>

Methods validation	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
<b>Nonclinical Pharmacokinetics</b>	
Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	1 <sup>st</sup> Cycle: November 9, 2005 January 19, 2006  2 <sup>nd</sup> Cycle: N/A
Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	N/A
❖ CAC/ECAC report	N/A

**APPEARS THIS WAY  
ON ORIGINAL**

### Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- 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)
- 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.)
- 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).

# MEMO

**To:** Brian Harvey, M.D., Ph.D.  
Director, Division of Gastroenterology Products  
HFD-180

**Through:** Denise P. Toyer, Pharm.D., Deputy Director  
Carol Holquist, R.Ph., Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Alina Mahmud, RPh., M.S., Team Leader  
Division of Medication Errors and Technical Support, HFD-420

**Date:** December 22, 2006

**Re:** Ondansetron Injection NDA# 21-915, OSE Consult 2006-803

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The Division of Gastroenterology Products submitted a request on November 9, 2006 for DMETS to assess the container label for Ondansetron Injection. DMETS previously reviewed the labels submitted on March 30, 2005 by the sponsor in OSE Consult #05-0139 and provided comments. We note that the sponsor has withdrawn the 8 mg/50 mL strength product. Thus, the following comments pertain only to the 32 mg/50 mL strength.

1. Container Label

We note the statement "protect from light until immediately prior to use" has been added at the end of the text. However, this information may be missed by the user. We recommend that it be relocated to the beginning of the text (i.e., above the Rx Only Statement).

2. Overpouch Labeling

We note that the sponsor has bolded the statement "Protect from .....Avoid excessive heat." However we recommend that the sponsor capitalize the 'Recommended Storage' statement and relocate the 'Protect from Light' statement to immediately follow. See below.

**RECOMMENDED STORAGE: PROTECT FROM LIGHT UNTIL  
IMMEDIATELY PRIOR TO USE. Store between 2°....AVOID EXCESSIVE  
HEAT.**

DMETS has no additional comments regarding the container label submitted on December 4, 2006. If you have any other questions or need clarification, please contact Sammie Beam, project manager, at 301-796-0080.

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/s/

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Alina Mahmud  
12/22/2006 01:21:12 PM  
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**Predecisional Agency Information**

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Date: December 21, 2006

From: Michael Brony, Division of Drug Marketing, Advertising, and Communications (DDMAC)

To: Giuseppe Randazzo, Division of Gastrointestinal Drug Products

Re: NDA 21-915 Ondansetron Injection, USP, 32 mg/50 mL PreMix draft label review

Page 14-15 of the draft label, states:

***“Cardiovascular***

***Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported....***

***“Neurological:***

***There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron injection and rare cases of grand mal seizure. The relationship to ondansetron injection was unclear.***

***“Other:***

***Rare cases of hypokalemia have been reported. The relationship to ondansetron injection was unclear.***

***“General:***

***Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported.”***

Understanding that the term "rare" is repeated throughout the 20-007 label, DDMAC recommends inclusion of a definitive number instead of the term, "rare." The term "rare" may minimize the adverse events associated with Ondansetron Injection therapy.

**APPEARS THIS WAY  
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/s/

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Michael Brony  
12/21/2006 06:16:07 PM  
DDMAC REVIEWER

**Division of Gastroenterology Products**  
**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 21-915 / Class 1 resubmission  
**Name of Drug:** Ondansetron Injection, USP, 32 mg/50 mL  
**Applicant:** Baxter Healthcare Corporation

**Material Reviewed:**

**Submission Date(s):** October 26, 2006  
**Receipt Date(s):** October 27, 2006

**Background and Summary**

NDA 21-915 was originally submitted March 30, 2005 and received an approvable action on February 01, 2006. Baxter resubmitted on March 27, 2006 and received a tentative approval action on May 26, 2006 due to patent expiry issues with the innovator product.

Baxter submitted a class 1 resubmission (letter date: October 26, 2006; received date: October 27, 2006) which contained no new safety or CMC information. The label included in this most recent submission is the subject of this review.

The PDUFA goal date for this class 1 resubmission is December 27, 2006.

**Review**

The May 26, 2006 tentative approval letter contained a draft label which was agreed upon by both parties. The differences between this draft label and the proposed label submitted on October 26, 2006 are outlined below:

1. The name of the company **BAXTER** was added to the top of the label above the name Ondansetron Injection, USP.
2. In the PRECAUTIONS section the following double underlined words were added:

**General:** Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

Comments: These additions are due to an approved label change for the innovator product, NDA 20-007 Zofran (ondansetron hydrochloride) injection. The additions to the innovator label was approved on August 22, 2006.

3. In the ADVERSE REACTIONS section the following double underlined words were added under the Cardiovascular subsection:

Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT interval prolongation, and ST segment depression), palpitations, and syncope.

Comments: This addition is due to an approved label change for the innovator product, NDA 20-007 Zofran (ondansetron hydrochloride) injection. The additions to the innovator label was approved on August 22, 2006.

### Conclusions

In comparing the label submitted on October 26, 2006 with the draft label attached to the May 26, 2006 TA letter the above 3 changes are the only recognizable changes.

---

Giuseppe Randazzo  
Regulatory Project Manager

Supervisory Comment/Concurrence:

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Brian Strongin, R.Ph, M.B.A  
Chief, Project Management Staff

Revised/Initialed: GR 12/19/06 BKS 12.19.06

Finalized: GR 12.19.06

Filename: C:\Data\My Documents\NDAs\21915\NDA 21915 LBL rev class 1 resub.doc

**PM LABELING REVIEW**

Pulled from DB  
on 12/27/06



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff  
Office of New Drugs, Immediate Office  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring

Tel 301-796-2200  
FAX 301-796-9744

**M E M O R A N D U M**

**Date received:** December 8, 2006  
**Date assigned:** December 8, 2006  
**Material received:** December 11, 2006  
**Date review completed:** December 18, 2006  
**Due Date requested:** December 18, 2006

**From:** Rosemary Addy, Project Manager  
Hari Cheryl Sachs, M.D., Medical Officer  
Office of New Drugs, Immediate Office  
Pediatric and Maternal Health Staff (PMHS)

**Through:** Lisa Mathis, M.D. OND Associate Director  
Office of New Drugs, Immediate Office  
Pediatric and Maternal Health Staff

**To:** Brian Harvey, MD, PhD, Director  
Division of Gastroenterology Products (DGP)

**Subject:** Ondansetron Injection, ANDA labeling question

**Sponsor:** Baxter

**NDA:** 21-915

**Innovator Approved Indication:**

Zofran® in plastic container (NDA 20-403) injection and injection premixed: Prevention of nausea and vomiting associated with emetogenic chemotherapy, including high-dose cisplatin (≥ 6 months) and prevention of post-operative nausea and vomiting (≥ 1 month)

Zofran® orally disintegrating tablets, tablets and oral solution (NDA 20-065, 20-781, 20-103) prevention of nausea and vomiting associated with highly emetogenic chemotherapy (adults only), moderately emetogenic chemotherapy ( $\geq 4$  years) and radiation therapy (adults only), and prevention of post-operative nausea and vomiting (adults only)

Zofran® preservative free injection and injection premixed (NDA 20-007): Prevention of nausea and vomiting associated with emetogenic chemotherapy, including high dose cisplatin ( $\geq 6$  months) and prevention of post-operative vomiting ( $\geq 1$  month)

**Consult question:**

What is PHMS opinion on consistency between the ANDA labeling [505(j)] and the 505(b)(2)'s labeling?

**Material Reviewed:**

Pediatric consult request

Proposed product labeling

Product labeling for Zofran®

Orange book patent information for Zofran®

Labeling consult for generic ondansetron hydrochloride injection (Lawrence Grylack, June 1, 2005)

**Background Information:**

On May 26, 2006, a 505(b)(2) NDA 21-915 for ondansetron premixed injection received a tentative approval (TA). This preparation is a 32 mg/50 mL premixed osmotic solution in single use containers. This 32 mg product may be used as a single dose in adults.. Baxter responded to the TA letter on October 27, 2006 with proposed labeling. The proposed labeling does not contain any disclaimers typically associated with "carving out" of exclusivity data in generic drugs for which there is pediatric exclusivity.

Baxter lists NDA 20-007 as the reference listed product. The last pediatric exclusivity expires for the preservative free product (NDA 20-007) on September 25, 2008. In addition, there are existing exclusivities for the tablets, and orally disintegrating tablets, oral solution (see Appendix- Patent Information). The patents for the injection and premixed (NDA ~~21-915~~) are due to expire Dec 24, 2006. The PDUFA date for this product is December 27, 2006.

GlaxoSmithKline (GSK) was granted three years of Waxman-Hatch exclusivity and 6 months of pediatric exclusivity on the basis of three clinical studies performed to obtain pediatric efficacy, safety and pharmacokinetic (PK) and dosing information in response to a Written Request for Zofran® Injection. These studies extended the age range down to 1 month (for post-operative nausea and vomiting) and 6 months (for chemotherapy-induced nausea and vomiting). The Zofran® supplemental NDA (20-007/s035) was

approved for prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients six to 48 months old who are receiving moderately to highly emetogenic chemotherapy, and for the prevention of post-operative nausea and vomiting in pediatric patients one to 24 months old undergoing routine surgery under general anesthesia. Based upon the pediatric studies submitted with the application, dosing was established for the age groups studied for both of these indications. This information is reflected in the labeling approved for Zofran® and Zofran Preservative Free injection and premixed injection on March 25, 2005.

#### **Discussion**

Signed into law on January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. BPCA section 11(a)(2) [21 USC 355a(1)(2)] states:

“(2) LABELING- ...The Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling... include--

(A) a statement that, because of marketing exclusivity for a manufacturer, ...

(i) the drug is not labeled for pediatric use; or

(ii) in the case of a drug for which there is an additional pediatric use, ... the drug is not labeled for the pediatric use ...

(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.”

New drug product exclusivity is provided by the Federal Food, Drug and Cosmetic Act under section 505(c)(3)(E) and 505(j)(5)(F). This exclusivity precludes approval of certain 505(b)(2) and 505(j) ANDA or generic applications. These applications are similar in that approval is based on data not developed by the applicant such as the agency's finding of safety and effectiveness of a previously approved drug. While the Act specifically addresses how to handle approval of drugs under 505(j) when pediatric information is added to the labeling, the Agency has interpreted this language in a way that permits approvals of applications under 505(b)(2) to utilize the same approach. Since both of these approvals rely on the approved labeling and pediatric information may be "carved out," the labeling should be consistent. Appropriate disclaimers reflecting where protected information is "carved out" should be included.

According to the PMHS generic labeling consult of June 2005, the following sections in the innovator labeling were changed due to pediatric studies for exclusivity:

**CLINICAL PHARMACOLOGY (Pharmacodynamics, Pharmacokinetics)**  
**CLINICAL TRIALS (Pediatric Studies)**  
**PRECAUTIONS (Pediatric Use)**

**ADVERSE EVENTS**  
**DOSAGE AND ADMINISTRATION (Pediatric Dosing)**  
**CLINICAL PHARMACOLOGY: Pharmacodynamics**

The dose for a child to prevent chemotherapy induced vomiting; according to the innovator labeling is 0.15 mg/kg, which equates to 8 mg for a 50 kg child. Since this 32 mg dose has not been studied in children and exceeds a typical dose, the 32 mg dose is inappropriate for children. Thus, excluding pediatric information from this label does not preclude the safe use of this 32 mg single dose product. Moreover, the 32 mg dose far exceeds the doses studied in children for chemotherapy-induced vomiting during the exclusivity studies. Consequently, most of the information from pediatric studies is not relevant for this specific product.

The proposed labeling refers to pediatric patients in three sections:

**CLINICAL PHARMACOLOGY: Pharmacokinetics (Pediatric)**  
**PRECAUTIONS (Pediatric Use)**  
**DOSAGE AND ADMINISTRATION: Pediatric Use**

**CLINICAL PHARMACOLOGY: Pharmacokinetics (Pediatric)**

Baxter has proposed to state:

“The pharmacokinetics of single dose 32 mg ondansetron pre-mixed injection have not been characterized in pediatric patients.”

*Reviewer comment: This appears to be acceptable. The pharmacokinetic information obtained from pediatric studies does not apply to this dose and this information is not derived from pediatric studies. Therefore, a disclaimer is unnecessary.*

**PRECAUTIONS: Pediatric Use**

Baxter has proposed:

“Ondansetron premixed injection has not been studied in pediatric patients and therefore is not recommended for use in children (see DOSAGE AND ADMINISTRATION section).”

*Reviewer comment: Since this premixed injection is not recommended for use in children, this appears to be acceptable. In addition, this recommendation does not refer to information derived from pediatric studies, therefore, a disclaimer is unnecessary.*

**DOSAGE AND ADMINISTRATION: Pediatric Use**

Baxter suggests:

“The ondansetron premixed formulation has not been studied in the pediatric population and therefore is not recommended for use in children. For pediatric dosing of ondansetron, the multidose regimen of three doses on a mg/kg basis is recommended. Refer to the labeling of the ondansetron

injection products used to deliver this weight based dosing for administration in the pediatric population.”

*Reviewer comment: Since this product is not recommended for use in children, this section should simply state that fact and not provide dosing information:*

*“The ondansetron premixed formulation has not been studied in the pediatric population and therefore is not recommended for use in children.”*

*If dosing information must be provided, information from pediatric studies is referenced. The information related to the pediatric studies for pediatric cancer patients 6 months to 48 months can be safely “carved out.” Therefore a disclaimer regarding the information for this subpopulation of children is recommended as follows (Note that italics are included for emphasis and should be removed):*

**Recommendation:**

In general, the labeling for a 505(b)(2) product and 505(j) product should be consistent and include the appropriate disclaimers reflecting where protected information is “carved out.”

In this case, this single dose product is not appropriate for pediatric patients. Therefore, the information obtained in pediatric studies does not apply. However, if weight-based dosing in children needs to be included, the pediatric dosing for patients ages 6 to 48 months is protected information. The dosing for these youngest patients can be safely omitted and an appropriate disclaimer should be placed.

Suggestions for labeling are attached. Note that per labeling guidance, references in labeling should be omitted unless essential.

Appendix I: Patent Information:

020403 Zofran® injection and premixed injection 2 mg base/mL (GlaxoSmithKline)

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020403	001	4695578*PED	JUL 25, 2005			
020403	001	4753789	JUN 24, 2006			<u>U-44</u>
020403	001	4753789*PED	DEC 24, 2006			
020403	001	5578628*PED	AUG 16, 2005			

020007 Zofran® preservative free injection and premixed injection 2 mg/base/mL (GlaxoSmithKline)

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Ap
Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	
020007	003	4695578*PED	JUL 25, 2005				
020007	003	4753789	JUN 24, 2006			<u>U-44</u>	
020007	003	4753789*PED	DEC 24, 2006				
020007	003	5578628*PED	AUG 16, 2005				

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020007	003	<u>D-97</u>	MAR 25, 2008
020007	003	<u>PED</u>	SEP 25, 2008
020007	003	<u>D-98</u>	MAR 25, 2008
020007	003	<u>PED</u>	SEP 25, 2008

020605 Zofran® oral solution (GlaxoSmithKline)

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020605	001	4695578*PED	JUL 25 2005			
020605	001	4753789	JUN 24 2006			<u>U-44</u>
020605	001	4753789*PED	DEC 24 2006			
020605	001	5578628*PED	AUG 16 2005			
020605	001	5854270	NOV 20 2015		Y	<u>U-44</u>
020605	001	5854270*PED	MAY 20 2016			

020103 Zofran® oral tablet 4, 8 and 24 mg base (GlaxoSmithKline)

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020103	001	4695578*PED	JUL 25 2005			
020103	001	4753789	JUN 24 2006			<u>U-44</u>
020103	001	4753789*PED	DEC 24 2006			
020103	001	5344658	SEP 06 2011			
020103	001	5344658*PED	MAR 06 2012			
020103	001	5578628*PED	AUG 16 2005			

020781 Zofran® orally disintegrating tablet 4 and 8 mg (GlaxoSmithKline)

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020781	001	4695578*PED	JUL 25 2005			
020781	001	4753789	JUN 24 2006			<u>U-330</u>
020781	001	4753789*PED	DEC 24 2006			
020781	001	5578628*PED	AUG 16 2005			
020781	001	5955488	NOV 14 2015			
020781	001	5955488*PED	MAY 14 2016			
020781	001	6063802	NOV 14 2015			
020781	001	6063802*PED	MAY 14 2016			

19 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-915

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

Dear Ms. Soo:

We acknowledge receipt on October 27, 2006 of your October 26, 2006 resubmission to your new drug application for Ondansetron Injection, USP, 32 mg/50 mL.

We consider this a complete, class 1 response to our May 26, 2006 action letter. Therefore, the user fee goal date is December 27, 2006.

We acknowledge receipt of your submission dated November 10, 2006.

If you have any questions, call me at (301) 796-0980.

Sincerely,

*{See appended electronic signature page}*

Giuseppe Randazzo  
Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Giuseppe Randazzo  
12/18/2006 11:04:40 AM

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

NDA #: 21-915

Drug Name: Ondansetron Hydrochloride Injection, USP

Revised May 12, 2006 to reflect sponsor's March 27, 2006 complete response to FDA's February 1, 2006 approvable letter.

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): (see next line)  
..... NDA 20-007 for Zofran® (ondansetron hydrochloride) Injection

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 change in diluent from 50 mL dextrose for Zofran to 50 mL Iso-osmotic sodium chloride solution for Ondansetron Injection, USP.
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): 4695578 expiry 1-25-2005  
4753789 expiry 12-24-2006 (includes 6 months of pediatric exclusivity)  
5578628 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   
The firm was granted a biowaiver.

- 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

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

YES  NO

Revised May 12, 2006  
Finalized: May 18, 2006  
Betsy Scroggs, Pharm.D.  
Regulatory Health Project Manager

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/s/

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Betsy Scroggs  
5/18/2006 02:18:58 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

*Acknowledgement Letter*

*5/10/2006*

*2nd Cycle*

NDA 21-915

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 PL2408 Plastic Container.

We acknowledge receipt on March 28, 2006 of your March 27, 2006 resubmission to your new drug application for Ondansetron Injection, USP.

We consider this a complete, class 1 response to our February 1, 2006 action letter. Therefore, the user fee goal date is Friday, May 26, 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 request for a waiver of pediatric studies for this application. Our decision will be communicated to you in our upcoming NDA action letter.

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

Sincerely,

*{See appended electronic signature page}*

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

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Betsy Scroggs  
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2/1/2006

## MEMORANDUM OF TELECON

DATE: January 19, 2006

APPLICATION NUMBER: NDA 21-915 Ondansetron Injection, USP

BETWEEN:

Amy Giertych, Senior Director, Global Regulatory Affairs  
Andrew Brugger, M.D., Medical Director  
Judy Kannenberg, Senior Manager, Global Regulatory Affairs  
Dorothy Grimm, Project Manager, R&D  
Vicki Drews, Associate Director, Global Regulatory Affairs  
Patricia Miyake, Senior Clinical Communications Manager  
Janice Troeger, Director, Clinical Planning and Operations  
Harold Sargent, Ph.D., Senior Director, Statistics, Epidemiology and Surveillance  
Lawrence Lin, Ph.D., Research Scientist, Statistics, Epidemiology and Surveillance

Representing: Baxter Healthcare Corporation

AND

Name: Division of Gastroenterology Products, HFD-180

Joyce Korvick, M.D., M.P.H., Deputy Division Director  
Ruyi He, M.D., GI Team II, Medical Team Leader  
Lolita Lopez, M.D., Medical Officer  
Marie Kowblansky, Ph.D., Pre-Market Assessment Leader, Office of New Drug Quality Management  
Suliman Al-Fayoumi, Ph.D., Biopharmacology Reviewer  
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist  
Ke Zhang, Ph.D., Pharmacology Reviewer  
Wen Jen Chen, Ph.D., Biostatistician  
Betsy Scroggs, Pharm.D., Regulatory Health Project Manager

SUBJECT: NDA 21-915 Ondansetron Injection, USP: To discuss elimination of 8 mg/50 ML premixed solution from the label

NDA 21-915 for Ondansetron Injection, USP, a 505(b)(2) application was submitted March 30, 2005 and proposes an 8 mg/50 mL and 32 mg/50 mL single intravenous doses to prevent chemotherapy related nausea and vomiting. The application relies on published literature and our findings for the original reference listed drug, NDA 20-007 Zofran® (ondansetron hydrochloride) Injection. The medical officer review dated December 14, 2005 recommends

approval for the 32 mg dose, but not the 8 mg dose citing lack of evidence to support the firm's claim for the latter dose.

We sent our Package Insert to the firm on January 13, 2006 via fax. Still pending the firm's response to the January 13, 2006 fax, the purpose of today's teleconference is to discuss our the 8 mg approvability issues with the firm.

Discussion:

Introductions were made.

The firm stated they want an understanding of why the 8 mg dose was deleted. The Medical Team Leader lead the discussion by stating that we did not find enough evidence to support the claim for the 8 mg/50 mL single dose.

The Division stated that in the FDA 1993 original review of the reference listed drug (RLD) for NDA 20-007 Zofran®, the 32 mg dose was more efficacious than the 8 mg single dose.

The Division told the firm that the literature submitted by the firm does not provide the substantial efficacy evidence to support their indication for the 8 mg/50 mL injection. They should refer to ICHE10 Guidance to further develop their hypothesis. The firm's analysis of the 1993 literature did not use the equivalent analysis described in the ICHE10 Guidance. In fact, when the Division reviewed the 1993 data again, 32 mg performed significantly better than the 8 mg dose.

The firm asked if it is acceptable to "pool" the data to perform an analysis for the three literature studies submitted in this application.

The Division responded that pooling the original 1993 literature data is not acceptable. We do not rely on pooled efficacy data for approval. We need 2 independent studies generally speaking, or 1 study with robust results. From a regulatory perspective, we do not have enough evidence to approve the 8 mg/50 mL single dose injection.

The firm asked which variable do we look at as the primary endpoint? The Division responded that we look for zero emesis and no rescue therapy.

The firm acknowledged understanding.

The firm then requested

Concluding remarks and next steps:

We have heard their requests and are not inclined to approve the 8 mg/50 mL for injection, but would reconsider their request.

The Division notes we will send additional pharmacology/toxicology comments.

The firm will send a revised label by Friday, January 24, 2006.

Betsy Scroggs, Pharm.D.  
Regulatory Health Project Manager

APPEARS THIS WAY  
ON ORIGINAL

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/s/

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Betsy Scroggs  
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## MEMORANDUM OF TELECON

DATE: January 30, 2006

APPLICATION NUMBER: NDA 21-915 Ondansetron Injection, USP

BETWEEN:

Steven Caffè, M.D., Vice President, Regulatory Affairs  
Representing: Baxter Healthcare Corporation

AND

Name: Division of Gastroenterology Products, HFD-180

Joyce Korvick, M.D., M.P.H., Deputy Division Director  
Betsy Scroggs, Pharm.D., Regulatory Health Project Manager

Telephone number: Cell Phone - ( \_\_\_\_\_ ) \_\_\_\_\_

SUBJECT: NDA 21-915 Ondansetron Injection, USP: To discuss elimination of 8 mg from the label

NDA 21-915 for Ondansetron Injection, USP, a 505(b)(2) application was submitted March 30, 2005 and proposes 8 mg/50 mL and 32 mg/50 mL single intravenous doses to prevent chemotherapy related nausea and vomiting. The application relies on published literature and our findings for the original reference listed drug, NDA 20-007 Zofran<sup>®</sup> (ondansetron hydrochloride) Injection. The medical officer review dated December 14, 2005 recommends approval for the 32 mg dose, but not the 8 mg dose citing lack of evidence to support the firm's claim for the latter dose.

We sent our Package Insert to the firm on January 13, 2006 via fax. Pending receipt of the firm's response to our January 13, 2006 fax, in a January 19, 2006 teleconference with the firm, we had discussed our approvability issues with representatives of Baxter Healthcare Corporation (see January 19, 2006 MEMORANDUM OF TELECON). The January 19, 2006 teleconference concluded with our stating that we were not inclined to approve the 8 mg/50 mL single dose for injection, but would reconsider their request \_\_\_\_\_

The firm submitted revised labeling on January 23, 2006 which was discussed with the firm January 24, 2006. During this line-by-line labeling review, the firm asserted that they want

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That labeling teleconference concluded with the understanding that the firm would weigh its options and send a labeling response on Friday, January 27, 2006.

On January 30, 2006 and pending the January 27, 2006 label from the firm, the Deputy Division Director (DDD) and Project Manager took a call from Dr. Steven Caffè, Senior Vice President of Regulatory Affairs.

Discussion: Introductions were made and Dr. Caffè explained the purpose of his call.

He explained that he started working at Baxter as of January 1, 2006 and wanted to review the issues of this application one more time to confirm what he had heard from his team.

The DDD explained that we have worked on this project for a while. Baxter team had left us on January 24, 2006 with the impression that we would have a label on January 27, 2006 and that we understood that they preferred to receive an approvable since they can't market the drug for several months.

Dr. Caffè asked to shift the topic of discussion to the firm's options of approvability versus an approval action.

The DDD expressed concern that we are very close to the action date of February 1, 2006 and we thought we would have received a label this past Friday, January 27, 2006.

Dr. Caffè asked what we need to approve the 8 mg/50 mL.

The DDD responded that we need an efficacy study for 8 mg and she outlined other emerging issues – CMC issue and OCC (lawyers) looking at label. We had expected a label and that the firm wanted an approvable action.

In conclusion:

Dr. Caffè stated that he would go to his team and discuss this issue one last time.

The DDD replied that we would need his final draft by the morning of January 31, 2006

The PM will send a Chemistry, Manufacturing, and Controls information request.

We will take action by February 1, 2006.

Betsy Scroggs, Pharm.D.  
Regulatory Health Project Manager

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ON ORIGINAL**

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CSO

Betsy Scroggs  
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CSO