

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020007/S022**

**ADMINISTRATIVE DOCUMENTS**

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number and Name of Drug :

JEU - 8 1997

NDA 20-007/S-022: Zofran (ondansetron Hcl) Injection

NDA 20-403/S-005: Zofran (ondansetron HcL) Injection Premixed

Sponsor: GlaxoWellcome Inc.

Material Reviewed

Submission Date(s): November 25, 1997

Receipt Date(s): November 26, 1997

Background and Summary Description:

Review

NDA 20-007/S-017 was submitted 6/30/94 to provide for intramuscular administration as an alternative to intravenous administration in the prevention of postoperative nausea and vomiting. As the basis for approval, the firm submitted results from Study W91-016. In this study, as expected, the pharmacokinetic parameters generally used to determine bioequivalence (Cmax, Tmax, AUC) were not the same for both routes of administration. After meeting with the Agency on 8/17/94, and being notified of the information required to obtain approval for the alternative route of administration, the firm withdrew the supplement on 8/26/94.

NDA 20-007/S-022 was submitted 5/6/96 to provide for this alternative route of administration. In support of the application, the firm included the previously submitted Study W91-016, and Study S3AA1001, which compared the efficacy of ondansetron by both routes of administration in patients taking ipecac. The application was approvable (AE) 5/6/97 pending revised labeling. In addition to providing some wording we were requesting be included in the CLINICAL PHARMACOLOGY section, we asked that the firm clarify why pharmacokinetic data from Study W91-016 was included in the labeling when Study S3AA1001 was required for approval of the application, and which also contained pharmacokinetic information. The issue was raised because of the very different pharmacokinetic values reported for the respective studies.

In their submission dated 7/25/97, the firm provided final printed labeling which contains pharmacokinetic information from both Studies W91-016 and S3AA1001. Since the Injection and Injection Premixed formulations share a common package insert, the firm submitted, on July 25, 1997, a duplicate submission to NDA 20-403, which was acknowledged as labeling

NDA 20-007/S-022

NDA 20-403/S-005

Page 2

supplement -005. Following a meeting on 10/2/97 between Dr. Lilia Talarico (Acting Division Director), Dr. Raj Pradhan (Biopharmaceutics Reviewer), and Ms. Kati Johnson (Supervisor, Project Management Staff), the firm was given two options to pursue. Either they could only include the pharmacokinetic information from Study S3AA1001, or include pharmacokinetic data from both studies and clarify that efficacy in preventing nausea and vomiting has not been linked to any particular pharmacokinetic parameter value. In their submission dated October 10, 1997, they chose the former option, and revised the CLINICAL PHARMACOLOGY section accordingly. The applications were approved on draft labeling on 10/31/97 and the firm was requested to submit final printed labeling identical in content to that submitted on 7/25/97, modified slightly (see CSO labeling review dated 10/31/97).

The firm has submitted final printed labeling.

#### Conclusions

The submitted labeling (RL-502, October 1997) was identical in content to that submitted 7/25/97 with the following exceptions:

1. As stated in the cover letter, the paragraph under CLINICAL PHARMACOLOGY, Pharmacokinetics, which describes pharmacokinetic results from Study S3AA1001, has been revised as requested in the AP letter. In addition, the numerical values in the paragraph have been revised to reflect the geometric mean, rather than the arithmetic mean because the confidence intervals are calculated using the geometric mean.
2. In the Pediatric Studies subsection (Prevention of Further Post-operative Nausea and Vomiting) of the CLINICAL TRIALS section, "children" has been replaced with "pediatric patients".

These are acceptable editorial revisions which do not alter the content of the package insert. An Acknowledge and Retain letter should be drafted.

*/s/*  
Consumer Safety Officer

12/8/97

APPEARS THIS WAY  
ON ORIGINAL

cc:

Original

HFD-180/Div. Files

HFD-180/KJohnson

draft: kj/December 8, 1997/c/wpfiles\cso\n\20007s22.rkj

APPEARS THIS WAY  
ON ORIGINAL

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

OCT 30 1997

Application Number, Name of Drug, Submission Dates:

**NDA 20-007/S-022**, Zofran (ondansetron HCL) Injection  
Submitted July 27, 1997, Received July 28, 1997  
Amended October 10, 1997

**NDA 20-403/S-005**, Zofran (ondansetron HCL) Injection Premixed  
Submitted July 25, 1997, Received July 28, 1997  
Amended October 10, 1997

Sponsor: GlaxoWellcome Inc.

Material Reviewed

**Background and Summary Description:**

NDA 20-007/S-017 was submitted June 30, 1994 to provide for intramuscular administration as an alternative to intravenous administration in the prevention of postoperative nausea and vomiting. As the basis for approval, the firm submitted results from Study W91-016. In this study, as expected, the pharmacokinetic parameters generally used to determine bioequivalence (Cmax, Tmax, AUC) were not the same for both routes of administration. After meeting with the Agency on August 17, 1994, and being notified of the information required to obtain approval for the alternative route of administration, the firm withdrew the supplement on August 26, 1994.

NDA 20-007/S-022 was submitted May 6, 1996 to provide for this alternative route of administration. In support of the application, the firm included the previously submitted Study W91-016, and Study S3AA1001, which compared the efficacy of ondansetron by both routes of administration in patients taking ipecac. The application was approvable (AE) May 6, 1997 pending revised labeling. In addition to providing some wording we were requesting be included in the CLINICAL PHARMACOLOGY section, we asked that the firm clarify why pharmacokinetic data from Study W91-016 was included in the labeling when Study S3AA1001 was required for approval of the application, and which also contained pharmacokinetic information. The issue was raised because of the very different pharmacokinetic values reported for the respective studies.

In their submission dated July 25, 1997, the firm provided final printed labeling which contains pharmacokinetic information from both Studies W91-016 and S3AA1001. Following a meeting on October 2, 1997 between Dr. Lilia Talarico (Acting Division Director), Dr. Raj Pradhan (Biopharmaceutics Reviewer), and Ms. Kati Johnson (Supervisor, Project Management Staff), the firm was given two options to pursue. Either they could only include

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### Review

The final printed labeling submitted July 25, 1997 (July 1997, RL-438), in conjunction with the revised CLINICAL PHARMACOLOGY section that was submitted October 10, 1997, was compared to the currently approved labeling (March 1997, RL-402, approved with NDA 20-007/S-023 and NDA 20-403/S-004 on April 2, 1997). The labeling did not contain any revisions other than those described by the firm. I did note, however, that in the revised CLINICAL PHARMACOLOGY section, the pharmacokinetic parameter values in the firm's submission varied slightly with those contained in the April 3, 1997 Biopharmaceutics review. I spoke with Lydia Kaus, PhD, Biopharmaceutics Team Leader, and the difference was due to a log transformation of the data by the reviewer. According to Dr. Kaus, use of the firm's values are acceptable, but suggested that the values include the 95% CI to indicate the variability of the parameter estimates. The firm should also be requested to revise the number of patients included in the study from which the pharmacokinetic information was derived. Although the proposed labeling states "n=28", the correct number is "56".

### Conclusions

An approval letter (on draft labeling) should be issued. The final printed labeling to be submitted should be identical to that submitted July 25, 1997 and October 10, 1997 with the CLINICAL PHARMACOLOGY section revised as follows:

1. Correct the number of patients included in the study from "28" to "56".
2. Revise the pharmacokinetic values to include the 95% CI to indicate the variability of the parameter estimates.

*/S/*  
\_\_\_\_\_  
Consumer Safety Officer *10/30/97*

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ON ORIGINAL

*/S/ 10-30-97*

NDA 20-007/S-022

NDA 20-403/S-005

Page 3

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CC:

Original NDA 20-007/S-022, NDA 20-403/S-005

HFD-180/Div. Files

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draft: kj/October 28, 1997/c:\wpfiles\cso\n\20007rkj.s22

CSO REVIEW

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# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # NDA 20-007 Supplement # 022 Circle one: SE1 SE2 **SE3** SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Zofran (ondansetron) Inj Action: **AP** AE NA

Applicant GlaxoWellcome Therapeutic Class antiemetic

Indication(s) previously approved prevention of (1) chemotherapy-induced emesis (2) postoperative nausea & vomiting  
Pediatric information in labeling of approved indication(s) is adequate  inadequate

Indication in this application IM as an alternate to IV admin for chemo-induced emesis (For emesis)  
supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing,
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

ISJ  
Signature of Preparer and Title SCSD

10/30/97  
Date

cc: Orig NDA/PLA/PMA # 20-007/S-022  
HFD-180 /Div File  
NDA/PLA Action Package  
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

2000  
DIF

EXCLUSIVITY SUMMARY for NDA # 20-007 SUPPL # 022

Trade Name Zofran Injection Generic Name ondansetron hydrochloride  
Applicant Name GlaxoWellcome HFD-180

Approval Date 10/31/97

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

a) Is it an original NDA?  
YES /    / NO /   X   /

b) Is it an effectiveness supplement?  
YES /   X   / NO /    /

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

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

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

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

Form OGD-011347 Revised 8/7/95; edited 8/8/95  
cc: Original NDA Division File HFD-85 Mary Ann Holovac

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d) Did the applicant request exclusivity?

YES /  / NO /  /

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

\_\_\_\_\_

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

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

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

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

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

YES /  / NO /  /

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

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**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES / X / NO /    /

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

NDA # 20-007 \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

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2. Combination product.

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

YES /    / NO /    /

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

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

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

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

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

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 /  /

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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:

Investigation #1, Study # \_\_\_\_\_

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

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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 / ___ /
Investigation #3	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:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

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 / ___ /
Investigation #3	YES / ___ /	NO / ___ /

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

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

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ON ORIGINAL**

- 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"):

Investigation #\_, Study # \_\_\_\_\_

Investigation #\_, Study # \_\_\_\_\_

Investigation #\_, Study # \_\_\_\_\_

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 / \_\_ / Explain \_\_\_\_ ! NO / \_\_ / Explain \_\_\_\_  
 ! \_\_\_\_\_  
 ! \_\_\_\_\_  
 ! \_\_\_\_\_

Investigation #2

YES / \_\_\_ / Explain \_\_\_\_\_

NO / \_\_\_ / Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

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

YES / \_\_\_ /

NO / \_\_\_ /

If yes, explain: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

MSI  
 Signature \_\_\_\_\_ - 10/30/97  
 Title: JSCSD Date

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ON ORIGINAL

MSI AM 10-30-97  
 Signature of Division Director Date

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ON ORIGINAL

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number and Name of Drug: :

DEC - 8 1997

NDA 20-007/S-022: Zofran (ondansetron Hcl) Injection

NDA 20-403/S-005: Zofran (ondansetron HcL) Injection Premixed

Sponsor: GlaxoWellcome Inc.

Material Reviewed

Submission Date(s): November 25, 1997

Receipt Date(s): November 26, 1997

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cc:

Original  
HFD-180/Div. Files  
HFD-180/KJohnson

draft: kj/December 8, 1997/c:\wpfiles\cso\n\20007s22.rkj

CSO REVIEW

APPEARS THIS WAY  
ON ORIGINAL

/S/ 12/8/97  
Consumer/Safety Officer

APPEARS THIS WAY

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # NDA 20-007 Supplement # 022 Circle one: SE1 SE2 **SE3** SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Zofran (ondansetron) Inj Action: **AP** AE NA

Applicant GlaxoWellcome Therapeutic Class antiemetic

Indication(s) previously approved prevention of (1) chemotherapy-induced emesis (2) postoperative nausea & vomiting  
Pediatric information in labeling of approved indication(s) is adequate  inadequate

Indication in this application IM as an alternate to IV admin for chemo-induced emesis (For emesis supplements, answer the following questions in relation to the proposed indication.)

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/S/ SCSD 10/30/97  
Signature of Preparer and Title Date

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HFD-180 /Div File  
NDA/PLA Action Package  
HFD-006/ SOLmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)**

**APPEARS THIS WAY  
ON ORIGINAL**