

### ***Single-Dose Ondansetron for the Prevention of Cisplatin-Induced Emesis: Efficacy Results***

**Study Dates:** Not provided in the publication

**Study Centers:** Patients were recruited from 26 different centers in the United States.

#### **Ethics**

The publication states that the protocol was reviewed and approved by the institutional review board at each institution and written informed consent was obtained from each patient.

#### **Study Design and Treatment**

This was a randomized, double-blind, active-controlled, multi-center, parallel group, multiple and single-dose study. The purpose of this study was to evaluate the efficacy of two fixed single-dose ondansetron regimens (8 mg and 32 mg) to the approved divided dose regimen (0.15 mg/kg x 3).

Patients were stratified according to their dose of cisplatin and then randomized (1:1:1) to receive either:

- three 0.15 mg/kg IV doses (predose and 4 and 8 hours postdose)
- a single 8 mg IV dose 30 minutes prior to cisplatin followed by saline at 4 and 8 hours postdose
- a single 32 mg IV dose 30 minutes prior to cisplatin followed by saline at 4 and 8 hours postdose

Cisplatin was administered as a single IV infusion during a period of three hours or less.

#### **Study Population**

Recruited were chemotherapy-naïve adult cancer patients 18 years and older with a Karnofsky performance status of at least 60%. scheduled to receive moderate-dose (50 to 70 mg/m<sup>2</sup>) or high-dose (≥100 mg/m<sup>2</sup>) cisplatin. Other concomitant chemotherapy was allowed with the exception of the following: cyclophosphamide (>500 mg/m<sup>2</sup>), nitrogen mustard (mechlorethamine), dacarbazine (DTIC), procarbazine, carmustine (BCNU), ifosfamide (>1.5 g/m<sup>2</sup>), or carboplatin.

The exclusion criteria were:

- Patients were excluded if they had impaired renal function (serum creatinine >2 mg/dL or creatinine clearance ≤ 50 mL/min).
- ALT >2x the upper limit of normal.
- Vomited or retched within 24 hours prior to the study.

Patients could not have received any anti-emetic medication 24 hours prior to, or during

the study period, or radiation therapy to the abdominal or pelvic region 48 hours prior to, or during the study period.

*Medical Officer Comments: The antiemetic therapy prohibited was not specified. There was no statement regarding the disposition of females who are lactating, pregnant or of child bearing potential. The source data is not available regarding concomitant medication use to verify information regarding this population.*

#### **Efficacy Assessment**

The primary efficacy parameter was the number of emetic episodes that occurred during the 24 – hour study period. An emetic episode was defined as a single episode of vomiting, a single episode of retching, or any number of continuous vomits and/or retches. Emetic episodes by definition were separated by at least a one minute absence of both vomiting and retching.

Emesis control during the first 24 hours was scored as follows:

- complete response = 0 episode
- major response = 1-2 episodes
- minor response = 3-5 episodes
- failure = >5 episodes, requirement for rescue anti-emetic therapy, or withdrawal from the study.

Nausea was evaluated at 24 hours following chemotherapy and was graded using a visual analog scale (0 = no nausea; 100 = nausea as bad as it could be).

Complete blood cell counts and biochemistry evaluation were obtained 48 hours before the first dose of study drug and at the end of the 24-hour study period. Abnormal values considered related to ondansetron were followed up until they returned to normal or were otherwise explained.

#### **Statistical Analysis**

The determination of sample size was not specified in either of the study reports. The authors stratified the analyses based on the dose of cisplatin received. Treatment groups were compared with regard to the number of emetic episodes experienced during the 24-hour study period using the Wilcoxon rank-sum test. Patients who reported > 5 emetic episodes or who were rescued or withdrawn for any reason were assigned the same arbitrarily high value (> 5) for number of emetic episodes.

Treatments were also compared with respect to the proportion of patients with a CR, those who were considered to have undergone unsuccessful treatment (Mantel-Haenszel test); time to first emetic episode (Wilcoxon rank-sum test); severity of nausea (Wilcoxon rank-sum test); and food intake (Mantel-Haenszel test). Patients with no emetic episodes were assigned the same arbitrary time (> 24 hours).

## Results

### Patient Accounting

A total of 773 patients were enrolled, and 699 patients received active medication:

- 234 received the weight-based dose (0.15 mg/kg x 3 doses)
- 245 received a single 8 mg dose
- 220 received a single 32 mg dose.

In the efficacy analyses, 618 patients were included (317 receiving high-dose cisplatin and 301 receiving low dose cisplatin). A total of 699 patients who received the study drug were included in the ITT analysis.

A total of 15 patients with violations of the inclusion/exclusion criteria and 66 patients with protocol violations were excluded from the analysis. See the table below.

No information concerning the number of patients who completed the study was available.

**Table A10: Protocol Deviations Resulting in Patient Exclusion from Efficacy Evaluation**

Deviation	No. of Patients (N = 699)*
<b>No. of ineligible patients (%)</b>	<b>15 (2)</b>
Received antiemetic within 24 hours before the study	8
Vomited within 24 hours before the study	4
Previously received chemotherapy	2
Abdominal radiation before or during study	1
<b>Deviations during study (%)</b>	<b>66 (9)</b>
Received excluded concomitant medication	30
Ondansetron dosing error	24
Cisplatin dosing error	16
Withdrawn due to administrative error	7
Received alternate antiemetic by mistake	5
Blind broken by study staff	3
Received cyclophosphamide dose > 550 mg/m <sup>2</sup>	3
Missing dosing and efficacy data	1

Table from Beck, et al

*Medical Officer Comments: From the table above, it is not specified how much ondansetron was received by patients included in the dosing error item. For both the ITT and efficacy analysis, it is not stated if patients were included in the analysis if they are in the multidose regimen (x3 doses) but did not receive the three doses of ondansetron.*

**Patient Characteristics**

**Table A11: Patient Characteristics**

Ondansetron Dose	0.15 mg/kg x 3	8 mg IV SD	32 mg IV SD
No of Patients	N=234	N=245	N=220
Gender (N, %)			
Male	157 (67%)	160 (65%)	148 (67%)
Female	77 (33%)	85 (35%)	72 (33%)
Age (yr)			
Median	61	62	62
Range	20-87	21-82	21-82
Alcohol Use (N, %)			
None/Occasional	162 (69%)	160 (65%)	158 (72%)
Moderate	19 (8%)	31 (13%)	16 (7%)
Heavy	53 (23%)	52 (21%)	46 (21%)
Chemotherapy			
Cisplatin alone	47 (20%)	55 (22%)	57 (26%)
Cisplatin combination	187 (80%)	190 (78%)	163 (74%)
Cancer Type (N, %)			
Lung	107 (46%)	117 (48%)	108 (49%)
Head and Neck	41 (18%)	45 (18%)	41 (19%)
Gastrointestinal	23 (10%)	34 (14%)	13 (6%)
Genitourinary	20 (9%)	16 (7%)	21 (10%)
Gynecologic	14 (6%)	14 (6%)	12 (5%)
Bone and Soft Tissue	8 (3%)	2 (1%)	4 (2%)
Other	21 (9%)	17 (7%)	21 (10%)
Chemotherapy			
cisplatin alone	47 (20%)	55 (22%)	57 (26%)
cisplatin + other agents	187 (80%)	190 (78%)	163 (74%)

*Sponsor's Table*

The three treatment groups were similar with regard to sex and age distribution; two thirds of the patients in each treatment group were male (67%) and one-third were female (33%). Lung cancer was the most common malignancy (~48%), followed by head and neck cancer (18%) and gastrointestinal malignancies (10%). Twenty-three percent (23%) of patients received cisplatin alone, whereas 77% received cisplatin in combination with other chemotherapeutic agents. The agents most frequently used in combination were etoposide (32%) and fluorouracil (26%).

*Medical Officer Comments: The dose of cisplatin was not included in the table that illustrates the patients' baseline characteristics. A table on antiemetic efficacy shows that the following number of patients received high-dose cisplatin (>100 mg/m<sup>2</sup>) and medium dose cisplatin(50-70 mg/m<sup>2</sup>). See table A12 below:*

**Table A12: Patients who Received Medium and High-dose Cisplatin**

Ondansetron dose	0.15 mg/kg x 3	8 mg x 1	32 mg x 1
High-dose cisplatin (>100 mg/m <sup>2</sup> )	100	115	102
Medium dose cisplatin(50-70 mg/m <sup>2</sup> )	101	107	93

**Efficacy**

The authors stratified the analyses based on the dose of cisplatin received. The publication presents efficacy data for an evaluable population of 618 patients. The investigator indicated analyses were also performed for the 699 Intent-to-Treat patients, and that similar reports were found; however, this was not presented in the publication. The tables below compares the efficacy of the three dose schedules.

**Table A14: Antiemetic Efficacy in the High-Dose Cisplatin Stratum (> 100 mg/m<sup>2</sup>): Primary Efficacy Variables**

	Ondansetron Dose					
	0.15 mg/kg x 3		8 mg x 1		32 mg x 1	
	No.	%	No.	%	No.	%
<b>No. of patients*</b>	100	100	115	100	102	100
<b>Complete response</b>						
0 EE	41	41	40	35	49	48
<b>Major response</b>						
1 EE	14	14	16	14	14	14
2 EE	5	5	9	8	11	11
<b>Minor response</b>						
3-5 EE	4	4	11	10	8	8
<b>Failure</b>						
> 5 EE or withdrawn/rescued	36	36	39	34	20	20

Abbreviation: EE, emetic episode.

\*Number of patients assessable for antiemetic efficacy.

Table from publication

**Table 15. Antiemetic Efficacy in the High-Dose Cisplatin Stratum (>100 mg/m<sup>2</sup>) Statistical Test Results**

	CR	EE	FR
32 mg x 1 v 8 mg x 1	0.048*	0.015*	0.018*
32 mg x 1 v 0.15 mg/kg x 3	0.315	0.095	0.009*
8 mg x 1 v 0.15 mg/kg x 3	0.349	0.590	0.749

Abbreviation: FR, failure (> 5 EE, rescue, or withdrawal).

\*P < .05.

Table from publication

**Table 16. Antiemetic Efficacy in the Medium-Dose Cisplatin Stratum (50 to 70 mg/m<sup>2</sup>): Primary Efficacy Variables**

	Ondansetron Dose					
	0.15 mg/kg x 3		8 mg x 1		32 mg x 1	
	No.	%	No.	%	No.	%
<b>No. of patients*</b>	<b>101</b>	<b>100</b>	<b>107</b>	<b>100</b>	<b>93</b>	<b>100</b>
<b>Complete response</b>						
<b>0 EE</b>	62	61	54	50	68	73
<b>Major response</b>						
<b>1 EE</b>	7	7	12	11	10	11
<b>2 EE</b>	4	4	8	7	4	4
<b>Minor response</b>						
<b>3-5 EE</b>	6	6	8	7	3	3
<b>Failure</b>						
<b>&gt; 5 EE or withdrawn/rescued</b>	22	22	25	23	8	9

\*Number of patients assessable for antiemetic efficacy.

Table from publication

**Table 4. Antiemetic Efficacy in the Medium-Dose Cisplatin Stratum (50 to 70 mg/m<sup>2</sup>) Statistical Test Results**

	CR	EE	FR
<b>32 mg x 1 v 8 mg x 1</b>	<b>0.001*</b>	<b>0.001*</b>	<b>0.005*</b>
<b>32 mg x 1 v 0.15 mg/kg x 3</b>	<b>0.083</b>	<b>0.033*</b>	<b>0.011*</b>
<b>8 mg x 1 v 0.015 mg/kg x 3</b>	<b>0.114</b>	<b>0.201</b>	<b>0.786</b>

Abbreviation: CR, complete response.  
 \*P < .05.

As shown in tables above, with regard to the complete response rates (0 emetic episodes), the single 32-mg dose was numerically superior to the standard three-dose schedule (0.15 mg/kg x 3 doses) in both the high and moderate dose cisplatin groups:

In the moderate dose cisplatin group, the single 32-mg dose was statistically superior to the standard three-dose schedule with respect to failure rate (p=.011), food intake (p=.029), and total emetic episodes (p=.033).

In the high-dose cisplatin group, the single 32-mg dose was again superior to the standard three-dose schedule with respect to failure rate (p=.009); in this group of patients, the single 32-mg dose was also superior to the standard dose with respect to nausea score (p=.036).

The single 32-mg dose was not inferior to the standard three dose schedule in any comparison for either cisplatin-dose group. It is also reported in the publication that there were no statistically significant differences between the standard three-dose regimen and the single 8-mg ondansetron dose.

*Medical Officer Comments: This study has shown that the single 32-mg dose was superior to the single 8-mg dose in multiple comparisons, including number of emetic episodes, complete response rate, failure rate, time to first emetic episode, severity of nausea, and food intake for both the moderate and high-dose cisplatin groups.*

*Although it is reported in the publication that there were no statistically significant differences between the standard three-dose regimen and the single 8-mg ondansetron dose, one should be very careful in interpreting this statement because having no statistical difference between these two groups does not mean that they are of the same efficacy. This could simply mean that there is not enough information to show that they are different. Moreover, although the data failed to show a difference between the 8 mg SD & the 0.15 mg/kg x 3 dosing, the effectiveness of the latter regimen has been established in previous trials & has been previously approved by the FDA."*

### **Safety**

All 699 patients who received active study medication were included in the safety evaluation. The most common adverse events reported were headache, fever, and diarrhea (see table below). Headache was reported in 25% of patients in the 32 mg dose group, 18% of patients in both the single 8mg dose and the standard 3 dose groups. Headaches was reported to be generally mild or moderate in nature and treatable with nonnarcotic analgesics. Otherwise, no differences were noted between the treatment groups.

No significant differences were observed between the three treatment groups with respect to laboratory indices of safety, which included transaminase elevations. However, there was an approximate 10-fold increase in the incidence of clinically significant transaminase elevations when high-dose cisplatin was administered compared to medium-dose cisplatin.

**Table A17. Adverse Events (Beck/Hainsworth, et al)**

	Ondansetron 0.15 mg/kg x 3 N = 234	Ondansetron 8 mg IV SD N = 245	Ondansetron 32 mg IV SD N = 220
Headache	43 (18%)	44 (18%)	55 (25%)
Fever	26 (11%)	19 (8%)	16 (7%)
Diarrhea	25 (11%)	16 (7%)	18 (8%)
AST/SGOT (>2XULN) (a)			
High-dose Cisplatin	8/106 (8%)	6/112 (5%)	7/105 (7%)
Medium-dose Cisplatin	1/97 (1%)	1/98 (1%)	0/91 (0%)
ALT/SGPT (>2XULN) (a)			
High-dose Cisplatin	4/105 (4%)	5/110 (5%)	7/102 (7%)
Medium-dose Cisplatin	1/100 (1%)	0/99 (0%)	0/91 (0%)

(a) In patients who had normal or below-normal Baseline values.

**Medical Officer Comments:**

*This study has been reviewed by the Agency in 1993 for the approval of Ondansetron 32 mg single dose I.V. for the prevention of chemotherapy induced nausea and vomiting under NDA 20-007/S-003. The Medical Reviewer, Dr. Hugo Gallo-Torres concluded in his review:*

**“For the prevention of CINV:**

- A SD 32 mg OND provides superior efficacy vs. SD 8 mg
- A SD 32 mg provides equivalent, if not superior efficacy vs. 0.15 mg/kg x 3
- The data failed to show a difference between the 0.15 mg/kg x 3 vs. the SD 8 mg

*Although the data failed to show a difference between the 8 mg SD & the 0.15 mg/kg x 3 dosing, the effectiveness of the latter regimen has been established in previous trials & has been previously approved by the FDA.”*

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*Oncology  
Review  
1/24/2006*

**Oncology Consult for NDA 21915**

Consult NDA: 21915  
Type of NDA 505(b)(2)  
NDA primary reviewer: Lolita Lopez, MD  
Consult requestor: Besty Scroggs, Pharm D, RHPM  
Request Division: Gastroenterology Products  
Consult receiving date: October 25, 2005  
Consult complete date: 1-20-2006  
Medical Reviewer: Qin Ryan, MD, PHD  
Medical Team Leader: Amna Ibrahim, MD

**Summary of the Consult Issues:**

NDA 21-915 for Ondansetron Injection, USP in PL 2408 Plastic Container provides for the firm's seeking approval of two premixed bags of Ondansetron Injection, USP, 8 mg and 32 mg in 50 mL IntraVia flexible plastic containers. A 505(b)(2) application, the reference listed drug is NDA 20-007 for Zofran (ondansetron) Injection (GSK). The firm has not conducted studies for this application. The application is mostly paper with electronic labeling and a requested module 5 in the EDR. The Gastroenterology Division filed the application with issues noted in the 74-day filing letter (in DFS). Other relevant paper jackets were delivered to the Oncology consultant.

As per Zofran label, the approved indication is "Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin." The approved dose and administration for Zofran is "a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy."

The NDA21-915 proposed indication is, same as Zofran, for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. However, the proposed dose and administration included both 32 mg single dose and 8 mg single dose. The 8 mg strength represents a lower dosage strength than the GSK Zofran product. The medical reviewer of Gastroenterology Division does not recommend the approval of the proposed new lower single dose ondansetron 8 mg I. V. for the above indication due to lack of substantial evidence of the effectiveness of this dose for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin in adult chemotherapy patients.

The Division met with the firm on August 7, 2003 for a preNDA meeting under PIND 68,217. The sponsor states that according to the guidelines issued by the American Society of Clinical Oncology (ASCO), the optimal dose recommended for IV ondansetron is 8 mg or 0.15 mg/kg for the indication of chemotherapy-induced nausea and vomiting (including high-dose cisplatin). In order to clarify the view of oncology

community on this issue, the Gastroenterology Division consulted the Oncology Division with 3 specific questions.

### Problem Oriented Literature Review

Antiemetic agents are the most common intervention in the management of treatment-related nausea and vomiting. The basis for antiemetic therapy is the neurochemical control of vomiting. Although the exact mechanism is not well understood, peripheral neuroreceptors and the chemoreceptor trigger zone (CTZ) are known to contain receptors for serotonin, histamine (H1 and H2), dopamine, acetylcholine, opioids, and numerous other endogenous neurotransmitters.<sup>1,2</sup> Many antiemetics act by competitively blocking receptors for these substances, thereby inhibiting stimulation of peripheral nerves at the CTZ, and perhaps at the vomiting center. Most drugs with proven antiemetic activity can be categorized into 1 of the following groups:

Competitive antagonists at dopaminergic (D2 subtype) receptors:

Phenothiazines.

Substituted benzamides.

Butyrophenones.

Competitive antagonists at serotonergic (5-hydroxytryptamine-3 or 5-HT3 subtype) receptors.

Corticosteroids.

Cannabinoids.

Ondansetron is one of the serotonin receptor (5-HT3) antagonists. Agents in this class are thought to prevent nausea and vomiting by preventing serotonin, which is released from enterochromaffin cells in the gastrointestinal (GI) mucosa, from initiating afferent transmission to the CNS via vagal and spinal sympathetic nerves.<sup>3</sup> The 5-HT3 antagonists may also block serotonin stimulation at the CTZ and other CNS structures. The most recent NCI, NCCN and ASCO guidelines on using Ondansetron as antiemetic agent during chemotherapy are summarized in the table below.

**Table 1: Guidelines for Ondansetron IV Dosing for Emesis Prevention**

Guidelines	Most Recent Version Date	Ondansetron IV Single Dose Regimens
NCI <sup>4</sup>	Nov 21, 2005	32 mg IV single dose is superior than 8 mg IV <sup>a</sup>
NCCN <sup>5</sup>	2006	8-12 mg (maximum 32 mg) IV <sup>b</sup>
ASCO <sup>6</sup>	September 1999	8 mg x 1 before chemotherapy <sup>c</sup>

- a. For hepatic insufficiency patients, a single IV or oral dose should not exceed 8 mg.
- b. For break through emesis treatment is recommended 16 mg PO or 8 mg IV daily.
- c. Level II evidence (Evidence is obtained from at least one well-designed experimental study. Randomized trials have high false-positive and/or -negative errors, such as low power or in suboptimal control).

Several studies have demonstrated that ondansetron produces an antiemetic response that equals or is superior to high doses of metoclopramide, but ondansetron has a worse toxicity profile compared with dopaminergic antagonist agents.<sup>7-17</sup> Ondansetron (0.15

mg/kg) is given IV 15 to 30 minutes prior to chemotherapy and is repeated every 4 hours for 2 additional doses. Although ASCO (1999)<sup>6</sup> and NCCN (2006)<sup>5</sup> guidelines has listed 8 mg, 12 mg and 32 mg IV doses, the relative efficacy between the different doses was not clarified in these two guidelines. For patients older than 18 years of age, a multicenter randomized double blind study (n = 699) determined that a single 32 mg dose of ondansetron is more effective in treating cisplatin-induced nausea and vomiting than a single 8 mg dose, and is as effective as the standard regimen of 3 doses at 0.15 mg/kg given every 4 hours starting 30 minutes before chemotherapy<sup>18</sup>. This statement is supported by NCI (2006) guideline<sup>4</sup> and approved ordanstron label. The 32 mg dose is considered to have level I evidence and the 8 mg dose is considered to have level II evidence.

Studies suggest that there are no major differences in efficacy or toxicity of the 3 first-generation 5-HT<sub>3</sub> receptor antagonists (dolasetron, granisetron, ondansetron) in the treatment of chemotherapy-induced acute nausea and vomiting. These 3 agents are equivalent in efficacy and toxicity when used in appropriate doses.<sup>19</sup> The Ondansetron dose used in these trials for efficacy and safety comparison were 32 mg or the sum of 24 hour doses approximately equal to 32 mg<sup>20, 21</sup>.

**Table 2: Ondansetron dose used in Randomized Studies to Compare with Other First Generation 5-HT<sub>3</sub> Antagnist.**

Study	Design	N	Dolasetron (mg/kg)		Ondansetron
Hesketh <sup>20</sup>	Double blind, randomized to 3 treatments, in prevention of first course cicplatin induced emesis.	609	1.8	2.4	32 mg
Navari <sup>21</sup>	Double blind, randomized, chemonaive patients receive cisplatin.	987	Granisetron (ug/kg)		0.15 mg/kg x3
			10	40	

Although these agents have been shown to be effective in the first 24 hours post-chemotherapy (acute phase), they have not been demonstrated to be effective in days 2 to 5 post-chemotherapy (delayed phase).<sup>22-24</sup>

Currently, the oral and injectable ondansetron formulations are approved for use without dosage modification in patients older than 4 years, including the elderly and patients with renal insufficiency. Oral ondansetron is given 3 times daily starting 30 minutes before chemotherapy and continuing for up to 2 days after chemotherapy is completed. Patients older than 12 years should receive 4 mg/dose. Ondansetron is not approved for use in children younger than 4 years. Ondansetron clearance is diminished in patients with severe hepatic insufficiency; therefore, such patients should receive a single injectable or oral dose no greater than 8 mg. There is currently no information available evaluating the safety of repeated daily ondansetron doses in patients with hepatic insufficiency.

Other effective dosing schedules, such as a continuous IV infusion (e.g., 1 mg/hr for 24 hours) or oral administration have also been evaluated.<sup>18</sup> The major adverse effects

include headache (which can be treated with mild analgesics), constipation or diarrhea, fatigue, dry mouth, and transient asymptomatic elevations in liver function tests (ALT and AST), which may be related to concurrent cisplatin administration.<sup>25</sup> Ondansetron has been etiologically implicated in a few case studies involving thrombocytopenia, renal insufficiency, and thrombotic events.<sup>26</sup> Nevertheless, the greatest advantage of serotonin receptor antagonists over dopaminergic receptor antagonists is that they have fewer adverse effects. Despite prophylaxis with ondansetron, many patients receiving doxorubicin, cisplatin, or carboplatin will experience acute and delayed-phase nausea and vomiting.<sup>27</sup> A randomized, double-blind, placebo-controlled trial suggests that the addition of aprepitant, a neurokinin-1 (NK1) antagonist, may mitigate nausea and vomiting.<sup>28</sup> The optimal dose of aprepitant may be 125 mg on day 1 followed by 80 mg on days 2 to 5.<sup>29</sup>

### **Consult Questions and Answers**

1) From a clinical oncology perspective, how valid is their recommendation for IV ondansetron 8 mg as a single dose?

In randomized comparative studies, the efficacy dose of Ondansetron considered equivalent to other first generation 5-HT<sub>3</sub> antagonists is 32 mg or 0.15 mg/kg every 4 hours x 3. The data for the 8 mg single dose is considered as level II evidence (Evidence is obtained from at least one well-designed experimental study. Randomized trials included may have high false-positive and/or -negative errors, such as low power or a suboptimal control). The efficacy of 8 mg single dose was only demonstrated in comparison to metoclopramide, or in a nonrandomized setting. In randomized setting, 32 mg single dose or 0.15 mg/kg q4 hrs x 3 regimen was equivalent to other 5-HT<sub>3</sub> antagonist and superior to 8 mg single dose.

2) On what data did they base their recommendations?

Both ASCO and NCCN listed 8 mg dose, with level II evidence, as an alternative for off label use in case by case base. The oncology community recognizes the superior efficacy of 32 mg IV single dose of Ondansetron.

3) Is this the standard of practice in the community?

The 32 mg IV single dose IV at Day 1 (pre-chemotherapy) is standard practice among oncologists. 8 mg dose is used on a case by case basis. It can be used when the concern for Ondansetron toxicity outweighs that for efficacy and because of its cost. In addition, 8 mg dose is also used for hepatic function impaired patients and break through (delayed phase) vomiting.

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## MEMORANDUM TO THE FILE

Date: December 12, 2006

Subject: NDA 21-915  
Ondansetron Injection USP

From: Dr. Nancy F. Snow  
Medical Officer  
HFD-180

Through: Dr. Hugo Gallo-Torres  
Medical Team Leader  
HFD-180

### BACKGROUND:

On 5/26/06 Baxter Healthcare Corporation was given a tentative approvable action for NDA 21-915, Ondansetron Injection Premix in INTRAVIA Plastic Container. The tentative approval was based upon the fact that there is an existing patent exclusivity, which will expire on 12/24/06.

The sponsor has submitted a revised label in which they incorporate FDA recommendations. **The purpose of this document is to comment on the revised label changes proposed by the sponsor.** No new safety information has been submitted since the original NDA, and this memorandum will not address safety issues.

### DISCUSSION:

The sponsor has submitted a label in which they have highlighted sections that have been changed. The Table below illustrates the sponsor's proposed label on the left, and the FDA recommended label on the right.

Additions to the label are underlined on the left, with the final recommended version (without underlining) on the right.

**Table 1**  
**NDA 21,915**  
**Comparison of Sponsor's Label and FDA Label**  
**(For sponsor identified changes only)**

Sponsor's Label	FDA Label
<p><b>PRECAUTIONS</b></p> <p><b>General:</b> 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.</p> <p><u>Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.</u></p>	<p><b>Precautions</b></p> <p><b>General:</b> 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.</p> <p>Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported</p>
<p><b>ADVERSE REACTIONS</b></p> <p><b>Observed During Clinical Practice:</b></p> <p><b>Cardiovascular:</b></p> <p>Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, <u>QT interval prolongation</u>, and ST segment depression), palpitations, and syncope.</p>	<p><b>ADVERSE REACTIONS</b></p> <p><b>Observed During Clinical Practice:</b></p> <p><b>Cardiovascular:</b></p> <p>Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block and ST segment depression), palpitations, and syncope.</p>

**CONCLUSIONS:**

The sponsor highlights two sections of the label to which modifications have been made. The modifications specifically refer to ECG changes and QT prolongation. These proposed revisions are acceptable. They are intended to alert the practitioner to be attentive to these possible effects of the drug.

**RECOMMENDATIONS FOR REGULATORY ACTION:**

*Acceptance of these few labeling revisions, as outlined by the sponsor, is recommended.*

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Nancy Snow  
12/13/2006 09:29:53 AM  
MEDICAL OFFICER

Hugo Gallo Torres  
12/13/2006 11:58:38 AM  
MEDICAL OFFICER

5/8/2006 MTL  
Review

**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:** 5/8/2006

**FROM:** Ruyi He, MD  
Medical Team Leader  
Division of Gastroenterology Products/ODE III

**SUBJECT:** GI Team Leader AP Comments  
NDA 21-915/000BL

**APPLICANT:** Baxter Healthcare Corporation

**DRUG:** NDA 21-915/AL Submitted on 3/29/06  
Ondansetron Hydrochloride (Ondansetron Injection, USP)  
Premixed 32 mg Solution

**I. BACKGROUND:**

Ondansetron is a selective 5-HT<sub>3</sub> antagonist available as an oral and parenteral antiemetic agent. It preferentially blocks the serotonin 5-HT<sub>3</sub> receptors found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines. Ondansetron (Zofran®) was developed by GlaxoSmithKline. It is currently approved for the prevention of chemotherapy, postoperative and radiotherapy induced nausea and vomiting. The recommended intravenous (I.V.) dosing regimen for prevention of chemotherapy-induced (CINV) emesis in adults is a single 32 mg dose administered 30 minutes before the start of emetogenic chemotherapy; or three 0.15 mg/kg doses, the first dose administered 30 minutes prior to chemotherapy with subsequent doses at 4 and 8 hours after the first dose.

On April 1, 2005 Baxter Healthcare Corporation submitted a 505(b)(2) application and proposed the use of an already approved single dose of ondansetron 32 mg I.V. premixed bag and an alternate new lower single dose ondansetron 8 mg I.V. premixed formulation for the indication of prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

Based on Dr. Lolita Lopez's review, intravenous ondansetron hydrochloride of 32 mg I.V. single dose in a 0.9% saline diluent in 50 mL intravia flexible plastic container was recommended for the proposed indication. However, the proposed new lower single dose

ondansetron 8 mg I.V. was not recommended, because Beck/Hainsworth study presented in the NDA 21-915 and in the original NDA for GSK 32 mg Zofran clearly indicates that the 8 mg single dose ondansetron did not provide optimal efficacy when compared to the 32 mg single dose in the prevention of chemotherapy induced nausea and vomiting. In February 2006, the Division issued an Approvable Letter in which it states that the sponsor should conduct a prospective, randomized, double-blind clinical trial to demonstrate efficacy for 8 mg dose before the application may be approved.

In the current submission, in response to the Approvable Letter, the sponsor is requesting that 8 mg dose be withdrawn from Agency consideration for approval under this original application.

**RECOMMENDATION:**

Based on Dr. Lolita Lopez's original NDA review and my previous medical team leader's memorandum for NDA 21-915, the sponsor's proposal to withdraw 8 mg dose from the NDA is acceptable.

I recommend that intravenous ondansetron hydrochloride of 32 mg I.V. single dose in a 0.9% saline diluent in 50 mL intravia flexible plastic container be approved for the indication of 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. This is already an approved dose of ondansetron and the formulation is essentially the same as the 32 mg premixed Zofran® product currently marketed by GSK except for the use of saline instead of a dextrose vehicle. To get approval, the sponsor should incorporate the Division's labeling recommendations and there should be no unexpired patent for the Zofran® 32 mg premixed injection at the time of approval of this NDA.

The sponsor requested a waiver for pediatric studies in the original NDA submission. I recommend that this request be granted for the use of single dose ondansetron 32 mg I.V.

There are no Phase 4 commitment, request or risk management steps recommended.

I concur with Dr. Lolita Lopez's labeling recommendations listed in her original NDA review. In general, any descriptions related to 8 mg ondansetron should be deleted from the labeling. In addition, the ondansetron 32 mg premixed formulation has not been studied in the pediatric population and it is not recommended for use in children. Therefore, the information related to use in children should be deleted from the labeling.

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Ruyi He  
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MEDICAL OFFICER

**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:** 1/8/2006

**FROM:** Ruyi He, MD  
Medical Team Leader  
Division of Gastroenterology Products/ODE III

**SUBJECT:** GI Team Leader AP Comments  
NDA 21-915

**APPLICANT:** Baxter Healthcare Corporation

**DRUG:** Ondansetron Hydrochloride (Ondansetron Injection, USP)  
Premixed 8 mg and 32 mg Solution

**RECOMMENDATION:**

I concur with Dr. Lolita Lopez's recommendations that intravenous ondansetron hydrochloride of 32 mg I.V. single dose (SD) in a 0.9% saline diluent in 50 mL intravenous flexible plastic container be approved for the indication of 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. Intravenous ondansetron hydrochloride of 32 mg SD is already an approved dose of ondansetron and the formulation is essentially the same as the 32 mg premixed Zofran® product currently marketed by GSK except for the use of saline instead of a dextrose vehicle. To get approval, the sponsor should incorporate the Division's labeling recommendations and there should be no unexpired patent for the Zofran® 32 mg premixed injection at the time of approval of this NDA.

I concur with Dr. Lolita Lopez's recommendations that the proposed new lower single dose ondansetron 8 mg I.V. for the same above indication not be approved because Beck/Hainsworth study presented in this NDA and in the original NDA for GSK 32mg Zofran clearly indicates that the 8 mg SD ondansetron did not provide optimal efficacy

when compared to the 32 mg SD in the prevention of chemotherapy induced nausea and vomiting.

The sponsor is requesting a waiver for pediatric studies. I recommend that this request be granted for the use of single dose ondansetron 32 mg I.V.

There are no Phase 4 commitment, request or risk management steps recommended.

## **I. BACKGROUND:**

Ondansetron is a selective 5-HT<sub>3</sub> antagonist available as an oral and parenteral antiemetic agent. It preferentially blocks the serotonin 5-HT<sub>3</sub> receptors found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines. Emesis during chemotherapy and radiation therapy appears to be associated with the release of serotonin from enterochromaffin cells in the small intestine. Ondansetron (Zofran®) was developed by GlaxoSmithKline and has been approved for use in the United States for almost 15 years now. It is currently approved for the prevention of chemotherapy, postoperative and radiotherapy induced nausea and vomiting. The recommended intravenous (I.V.) dosing regimen for prevention of chemotherapy-induced (CINV) emesis in adults is a single 32 mg dose administered 30 minutes before the start of emetogenic chemotherapy; or three 0.15 mg/kg doses, the first dose administered 30 minutes prior to chemotherapy with subsequent doses at 4 and 8 hours after the first dose.

Ondansetron has been marketed worldwide since 1990 and in the U.S. since 1991. It has not known to be withdrawn from the market due to safety reasons. The safety profile of ondansetron use in both adults and children is well-characterized.

The applicant of this NDA, Baxter Healthcare Corporation, submitted a 505(b)(2) application relying on the Agency's finding of safety and efficacy for Zofran® I.V. The applicant is proposing the use of an already approved single dose of ondansetron 32 mg I.V. premixed bag which is essentially the same formulation as the Zofran® 32 mg premixed product currently marketed by Glaxo Smith Kline (GSK) except for the use of 0.9% saline diluent rather than a 5% dextrose diluent in the latter product to reflect current clinical preference. The use of either diluent is reflected in the current Zofran vial product. In addition, an alternate new lower single dose ondansetron 8 mg I.V. premixed formulation is also being proposed. The sponsor is seeking only for the indication of prevention of chemotherapy induced nausea and vomiting for both doses. The indication for the prevention postoperative nausea and vomiting (PONV) is not being sought in this submission.

There were no clinical studies performed by the applicant in support of the proposed drug product. The submission is based upon published literature references and the established safety and efficacy of the Zofran® product.

## **II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:**

### **A. OPDRA/DDMAC/DMETS:**

DMETS notes several incidents where terminal zeros are used throughout the package insert labeling. The use of terminal zeros may result in error as often the decimals are overlooked. As evidenced by post-marketing surveillance, the use of terminal zeros could potentially result in a ten-fold medication dose error. Thus, DMETS recommend deleting all terminal zeros from the labels and labeling.

In the Dosage and Administration Section, DMETS does not recommend use of the abbreviation "I.V.". Please revise by spelling out the word "intravenous".

I concur with above recommendations.

### **B. Chemistry and Manufacturing/Microbiology:**

Based on Dr. Stephen Langille, Microbiology reviewer, the applicant failed to provide adequate information regarding:

- The WFI system
- Historical sterility data for products manufactured in the 50 mL PL 2408 containers
- Sterilization validation information
- Biological indicator data

Failure to address the microbiology deficiencies listed above could result in endotoxin and/or microbial contamination of the drug product. Therefore, Dr. Langille recommended that NDA 21-915 is approvable pending the resolution of product quality microbiology deficiencies.

From the CMC perspective, both proposed strengths may be approved with a 24-month expiration date (with room temperature storage), pending satisfactory resolution of the deficiencies cited in the Microbiology review and a recommendation from the Office of Compliance that the manufacturing facilities are Acceptable. Please see Dr. Marie Kowblansky's review in details.

The deficiencies cited in the Microbiology review have been forwarded to the sponsor and responses are currently pending.

### **C. Pre-Clinical Pharmacology/Toxicology:**

Pharmacology Reviewer, Dr. Ke Zhang, recommended that pre-mixed intravenous product of Zofran be approved for the proposed indication. There is no recommendation for further nonclinical studies.

**D. Biopharmaceutics:**

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, the bio-equivalence study was waived by the agency because of intravenous formulation and NDA 21-915 is acceptable provided that a satisfactory agreement is reached between the Agency and the sponsor regarding the proposed language in the package insert. Please see Dr. Suliman Al-Fayoumi's review in details.

**E. Clinical/Statistical:**

**Efficacy:**

To support the efficacy of the new lower single dose ondansetron 8 mg injection for the proposed indication, the applicant mainly submitted four studies from published literature written by the following authors: Italian Group for Anti-emetic Research (IGAR), Seynaeve, Ruff, and Beck/Hainsworth. Study design and number of patients enrolled in those 4 studies are summarized below.

**Table 1: Study Design and Number of Subjects Enrolled**

Author	Design	Treatment	N
IGAR 12/92 - 7/94	R, DB, AC, MC, Parallel, SD	OND 8 mg + DXM on D1;	483
		MCP + DXM on D 2-4 Gran 3 mg + DXM on D1; MCP + DXM on D 2-4	483
Seynaeve C, 9/89 - 6/90	R, DB, AC, MC, Parallel, SD, MD	OND 8 mg + 1 mg/hr	182
		OND 32 mg + PL x 24 hr	180
		OND 8 mg + PL x 24 hr	173
Ruff P, et al 12/91-11/92	R, DB, AC, MC, Parallel, SD	OND 8 mg	165
		OND 32 mg	162
		Granisetron 3 mg	169
Beck/ Hw et. al. 1991?	R, DB, AC, MC, Parallel, SD, MD	OND 0.15 mg/kg x 3 doses	234
		OND 8 mg then PL 4 & 8 hrs	245
		OND 32 mg then PL 4 & 8 hr	220

R= randomized; DB= double blind; AC= active control; MC= multicenter; SD=single dose; MD=multi-dose; D=day; PL=placebo

One of the major limitations of those studies is the statistical analysis. The studies treated the non-significance results for the efficacy comparisons between the different treatment groups as the efficacy equivalence for these different treatment groups; this is not an

acceptable statistical analysis. In the current statistical guideline (ICH E10), the margin of equivalence should be pre-specified before conducting the trials.

Two of the studies, Ruff and Saynaeve used complete plus major response as their primary endpoint which is considered as inadequate primary endpoint; complete response or no emetic episode is the most clinically meaningful primary endpoint and which has also been used for the approval of several other 5HT3s in the past. The sponsor did not provide any raw data to allow the reviewers to do any further efficacy evaluation for those studies.

The IGAR study, ondansetron was administered in combination with dexamethasone (DXM). The use of DXM can be a potential confounder in this study. Therefore, the IGAR study may not be useful for the efficacy assessment for ondansetron 8 mg single dose. In addition, the sponsor did not provide any raw data to allow the reviewers to do any further efficacy evaluation for this study.

Beck/Hainsworth study was the pivotal study submitted by Glaxo-Smith Kline for the approval of single dose Zofran 32 mg I.V. for the prevention of CINV in 1993 (NDA 20-007/S-003). The Beck and Hainsworth study has shown that a 32 mg single dose (SD) ondansetron I.V. is significantly more efficacious than an 8 mg SD ondansetron I.V. The efficacy results are summarized in the tables below.

**Table 2: Beck/Hainsworth-Antiemetic Efficacy in the High-Dose Cisplatin Stratum (> 100 mg/m<sup>2</sup>) Efficacy Variables**

	Ondansetron Dose					
	0.15 mg/kg × 3		8 mg × 1		32 mg × 1	
	No.	%	No.	%	No.	%
<b>No. of patients*</b>	100	100	115	100	102	100
<b>Complete response</b>						
0 EE	41	41	40	35	49	48
<b>Major response</b>						
1 EE	14	14	16	14	14	14
2 EE	5	5	9	8	11	11
<b>Minor response</b>						
3-5 EE	4	4	11	10	8	8
<b>Failure</b>						
> 5 EE or withdrawn/rescued	36	36	39	34	20	20

Abbreviation: EE, emetic episode.

\*Number of patients assessable for antiemetic efficacy.

For patients receiving high dose cisplatin, the complete response rate (0 emetic episode) was significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (48% vs. 35%, p=0.048).

For patients receiving medium dose cisplatin, the complete response rate (0 emetic episode) was also significantly higher in patients who received a 32 mg SD ondansetron compared to those who received an 8 mg SD ondansetron (73% vs. 50%, p=0.001). Please see the table below.

**Table 3: Beck/Hainsworth - Antiemetic Efficacy in the Medium-Dose Cisplatin Stratum (50 to 70 mg/m<sup>2</sup>): Efficacy Variables**

	Ondansetron Dose					
	0.15 mg/kg × 3		8 mg × 1		32 mg × 1	
	No.	%	No.	%	No.	%
<b>No. of patients*</b>	101	100	107	100	93	100
<b>Complete response</b>						
0 EE	62	61	54	50	68	73
<b>Major response</b>						
1 EE	7	7	12	11	10	11
2 EE	4	4	8	7	4	4
<b>Minor response</b>						
3-5 EE	6	6	8	7	3	3
<b>Failure</b>						
> 5 EE or withdrawn/rescued	22	22	25	23	8	9

\*Number of patients assessable for antiemetic efficacy.

This study clearly indicates that the 8 mg SD ondansetron did not provide optimal efficacy when compared to the 32 mg SD in the prevention of chemotherapy induced nausea and vomiting.

**Safety:**

In general, both the 8 mg and 32 mg single dose of ondansetron were well tolerated by patients receiving moderately to highly emetogenic chemotherapy. There were no new safety concerns identified in this submission. The type and incidence of adverse events were similar among the treatment arms in each study. Since the submission includes published articles and the sponsor had no access to the source data, there were neither narratives nor case report forms available for review.

In the IGAR study, one death was reported, this patient was on granisetron plus dexamethasone; no further information was provided in the publication about this death. In the Seynaeve study, one patient was withdrawn due to an adverse event regarded by the investigator to be unrelated to ondansetron treatment. In addition, two major adverse events were reported: one case of severe constipation and one case of pseudomembranous colitis which resolved spontaneously; no further information was provided regarding these events. No other serious adverse events were reported from the publications.

The most common adverse event consistently reported in patients who received ondansetron in all four studies was headache (9% to 18%); followed by diarrhea, fever and hiccup. In the previous trials with ondansetron, headache was the most common adverse event reported among patients who received ondansetron prior to surgery; while diarrhea (8 to 16%) and headache (17% to 25%) were the most commonly reported in patients receiving chemotherapy. Headache was reported to be generally mild and responded to non-narcotic analgesic. The adverse events reported in this submission were generally consistent with the already known adverse events for ondansetron.

The overall clinical experience for ondansetron is adequate for up to 32 mg single dose injection per day. Ondansetron is an established drug for up to 32 mg single dose injection per day and the dose of 8 mg single dose being proposed is lower than the already approved dose. Because of this, there should not be any specific safety concern with either proposed dose.

#### **F. Pediatric Use:**

Ondansetron is currently labeled for use in children as young as 6 months old undergoing chemotherapy at a dose of 0.15 mg/kg x 3 doses and in patients as young as 1 month old undergoing surgery at a dose of 0.1 mg/kg single dose. In addition, there are already existing age appropriate formulations available for pediatric use.

The sponsor is requesting a waiver for pediatric studies. I recommend that this request be granted for the use of single dose ondansetron 32 mg I.V. because it is not considered as an appropriate pediatric formulation. Body weight based formulation is more age appropriate formulations for pediatric use. Therefore, single dose ondansetron 32 mg premixed formulation is not recommended for use in the pediatric population.

#### **III. Labeling Recommendations:**

I concur with Dr. Lolita Lopez's labeling recommendations listed in her review. In general, any descriptions related to 8 mg ondansetron should be deleted from the labeling. In addition, the ondansetron 32 mg premixed formulation has not been studied in the pediatric population and it is not recommended for use in children. Therefore, the information related to use in children should be deleted from the label.

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Ruyi He  
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MEDICAL OFFICER

Executive Summary  
2/1/2006

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:** 1/30/06

**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 an approvable action for the current application. I am in concurrence with this recommendation.

The medical reviewer and Team Leader recommended 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."*

This single 32 mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. This is the approved dose for the 32 mg premixed Zofran® product currently marketed by GSK. Baxter's new formulation utilized saline instead of a dextrose vehicle. This dose is known to be safe and effective for its intended use based upon FDA's previous findings. However, there are unexpired patents for Zofran® 32 mg/50mL premixed injection, thus only a tentative approval could be granted at this time.

The medical reviewer, team leader and statistical team did not recommend the approval of the proposed new lower single dose ondansetron 8 mg I.V. for the above indication due to lack of substantial evidence of the effectiveness for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin in adult chemotherapy patients. In addition, the innovator product, Zofran®, is not labeled for the 8 mg single dose and the findings of the original

medical reviewer recommended against approval of this lower dose citing lack of efficacy.

**Current Submission:**

This submission qualifies as a 505(b)(2) and not an ANDA for two reasons: 1.) it proposes a new lower dose; 2.) it is a new formulation.

**Efficacy:**

There were no clinical studies performed by Baxter in support of the proposed drug product since they believe that sufficient data are available for the proposed dosing. Their submission is based upon published literature references and the established efficacy and safety of the Zofran® product.

To support the efficacy of the new lower single dose ondansetron 8 mg injection for the proposed indication, the Baxter relied on four studies from published literature written by the following authors: Italian Group for Anti-emetic Research (IGAR), Seynaeve, Ruff, and Beck/Hainsworth. In these studies, ondansetron 8 mg was administered as a single dose prior to chemotherapy, with no follow-up doses for 24 hours; all were designed as randomized, double-blind, active-controlled, multi-center, parallel-group studies. Patients enrolled were naïve to cisplatin and were scheduled to receive cisplatin-containing chemotherapy ( $\geq 50$  mg/m<sup>2</sup>). The sponsor also supports this submission with the practice guidelines and recommendations issued by the American Society of Clinical Oncologists (ASCO).

The division did review the Beck and Hainsworth study as part of the original 32 mg single dose ondansetron NDA 20-007/S-003 in 1993. The Medical Reviewer concluded that a 32 mg SD ondansetron is significantly more efficacious than an 8 mg single dose (SD) ondansetron and that the 32 mg SD is more efficacious, or at least as efficacious as the standard regimen of 0.15 mg/kg x 3 doses in preventing cisplatin-induced emesis. Although the data failed to show a difference between the ondansetron the single dose 8 mg and the 0.15 mg/kg x 3 doses, the effectiveness of the latter regimen has been established in previously conducted clinical trials and has been approved by the FDA to be an efficacious dose. Moreover, failing to show a difference between the two treatment groups only indicates that there is no sufficient power to reject the null hypothesis of no treatment difference but does not provide evidence to support the equivalence of the two drugs. Thus, the only clinical data that the division has to review is from this study and dose not sufficient to demonstrate efficacy of this dosing regimen by itself.

The other literature studies submitted by the sponsor did not have source data to review and the designs raised several issues. These studies are reviewed in detail in the Medical Officer, MO Team Leader and Statistical Reviews. I agree with their review of the issues and the conclusion that they are not sufficient evidence to support efficacy of the low dose.

**Safety:**

There are no new safety issues.

**Labeling:**

In labeling negotiations with the sponsor several issues were raised. The Baxter agreed to removal of the 8 mg indication in the "CLINICAL TRIALS", "INDICATIONS AND USAGE", ADVERSE EVENTS, and "DOSAGE AND ADMINISTRATION" sections, however, they proposed \_\_\_\_\_

\_\_\_\_\_ Finally, it was emphasized to Baxter that an additional prospectively conducted clinical trial would be necessary for approval and that the literature that was submitted in this application would be considered supportive if the results of the new study were robust.

\_\_\_\_\_ After internal discussions, Baxter submitted their final labeling proposal on 1/31/06 which retained the 8 mg/50mL product in the label. This response has resulted in my recommendation for an approvable action for the entire application. Thus, approvable action letter will be sent to Baxter for both the 32 mg/50mL and 8 mg/50mL for this current review cycle.

**Deficiency:**

1. The deficiency identified in this review was the lack of a sufficient data to support efficacy and the need for a new clinical trial for the 8 mg/50mL dose.
2. Acceptable Final Labeling proposal.

**Other Discipline reviews:**

No outstanding issues at this time.

A BioWaiver was granted by the Office of Clinical Pharmacology and Biopharmaceutics, hence, no additional pharmacokinetic study data were submitted by the sponsor.

**Oncology Consult:**

Since this is a product that is utilized in the oncology community and the sponsor submitted treatment guidelines from the American Society of Clinical Oncologists as further justification of the 8 mg single dose, a consult was sought from the oncology division. The response stated that these guidelines are Level II recommendations (evidence obtained from at least one well-designed experimental study. Randomized trials included may have a high false-positive and/or - negative errors, such as low power or a sub optimal control). Indeed, this is the finding of our medical review (for a thorough review of clinical literature submitted see Medical Officer Review). In addition, the

oncology consult stated that the 32 mg IV single dose is standard practice for oncologists. A lower dose may be used but only in selected cases where side effects are seen that preclude the higher dose or in patients with impaired hepatic function.

**Pediatric Waiver Request:**

The medial team recommends that the Pediatric Waiver Request be granted for the 32 mg/50mL concentration, but not for the 8 mg/50mL dosing. In the next review cycle PREA will need to be addressed for this formulation if the 32 mg/50mL is recommended for approval.

**Patent History**

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):     4,695,578 expiry 1-25-2005  
                              4,753,789 expiry 12-24-2006 (Peds Exclusivity)  
                              5,578,628 expiry 2-16-2005

The 505(b)(2) status and Appendix B have been reviewed and cleared by the IO, ORP and OCC. Since the division is not approving this application at this time, disclaimer language and pediatric use will be addressed in the future when the label is finalized in the next cycle. It should be noted that the Zofran® 32mg/50mL formulation is not approved for pediatrics, however, the other the Zofran® single-use glass vial formulation is approved for pediatrics and is the basis of the exclusivity. If the approval action occurs after 12-24-2006 then this issue becomes moot. In any case, it will be addressed in the next review cycle.

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/s/

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Joyce Korvick  
2/1/2006 03:52:17 PM  
MEDICAL OFFICER