

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-915

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21,915

SERIAL NUMBER: 000

DATE RECEIVED BY CENTER: March 30, 2005

DRUG NAME: Zofran / Ondansetron, injection

INTENDED CLINICAL POPULATION: For the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

SPONSOR: Baxter Healthcare Corporation
McGaw Park, IL

DOCUMENTS REVIEWED: Vol. 1-6

REVIEW DIVISION: Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

PHARM/TOX REVIEWER: Ke Zhang, Ph.D.

PHARM/TOX SUPERVISOR: Jasti Choudary, B.V.Sc., Ph.D.

DIVISION DIRECTOR: Brain Harvey, M.D., Ph.D.

PROJECT MANAGER: Dr. Betsy Scroggs,

Date of review submission to Division File System (DFS):
November 9, 2005

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EXECUTIVE SUMMARY**1. Recommendations****1.1 Recommendation on approvability**

From a preclinical standpoint, approval of pre-mixed intravenous product of Zofran is recommended for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

1.2 Recommendation for nonclinical studies: None

Recommendations on labeling: The labeling should be revised as recommended.

2. Summary of nonclinical findings**2.1 Pharmacologic Activity:**

The results of the *in vitro* studies indicated that ondansetron inhibited the cloned human hERG K⁺ channels with IC₅₀ of 0.81 μ M in HEK-293 cells and the delayed rectifier potassium current with KD of 1.7 μ M and prolonged action potential duration by ~30% at 1 μ M in feline ventricular myocytes. In the *in vivo* study, the effects of i.v. administration of ondansetron on ECGs were examined in anesthetized dogs. The results indicated that ondansetron prolonged QTc interval in a dose dependent manner in the dose range of 0.66 to 5.25 mg/kg. At the highest dose tested (5.25 mg/kg), ondansetron produced approximately 28% prolongation of QTc interval.

3. Administrative:

Ke Zhang, Ph.D. Date
Pharmacologist, HFD-180

Comments:

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

CC:

NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Choudary

HFD-180/Dr. Zhang

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW**2.6.1 INTRODUCTION AND DRUG HISTORY**

NDA number: 21,915

Review number: 01

Sequence number/date/type of submission: March 30, 2005

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Baxter Healthcare Corporation
McGaw Park, IL

Manufacturer for drug substance:

Reviewer name: Ke Zhang

Division name: Division of Gastrointestinal and Coagulation
Drug Products

HFD #: 180

Review completion date: November 9, 2005

Drug:

Trade name: Zofran, i.v. for injection

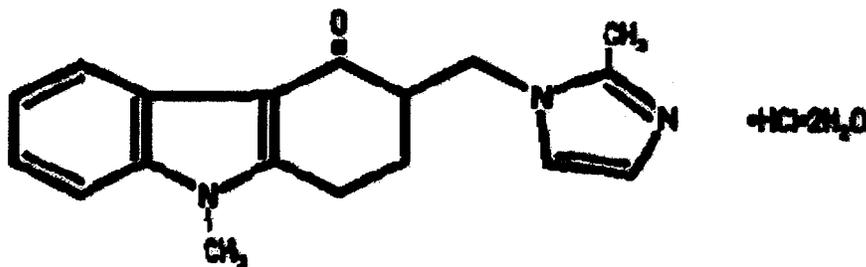
Generic name: Ondansetron

Chemical name: (\pm) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate.

CAS registry number: 103639-04-9

Molecular formula/molecular weight: $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$ and 365.9

Structure:



Relevant INDs/NDAs/DMFs: IND 68,217 / NDA 20,007

Drug class: 5-HT3 receptor antagonist

Indication: For the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

Clinical formulation: The pre-mixed drug product contains 8 mg and 32 mg ondansetron as ondansetron hydrochloride in 50 ml of 0.9% sodium chloride and citrate buffered diluent.

Route of administration: I.v. Injection.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Any information or data necessary for approval of NDA 21,915 that Baxter Healthcare Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Baxter Healthcare Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21,915.

Studies reviewed within this submission:

The cardiovascular pharmacology studies from literature.

Studies not reviewed within this submission: None.

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3.2 PHARMACOLOGY

3.2.4 Safety pharmacology

Cardiovascular pharmacology:

Effects on the cloned human cardiac Na⁺ and hERG K⁺ channels

Effects of ondansetron on the cloned human cardiac Na⁺ channel and hERG potassium channels were evaluated in HEK-293 cells using patch clamp techniques (J. Pharm. Exper. Ther., 295 (2):614-695, 2000). The results indicated that ondansetron inhibited the cloned human cardiac Na⁺ and hERG K⁺ channels with IC₅₀ of 88.5 μ M and 0.81 μ M, respectively, suggesting that ondansetron is more potent for the hERG K⁺ channel than for the Na⁺ channel. The effects of other 5-HT₃ receptor antagonists (granisetron, dolasetron, and active metabolite of dolasetron, MDL74,156) on the cloned human cardiac Na⁺ and hERG K⁺ channels were also examined in this report. The results indicated that granisetron, dolasetron, and MDL74,156 inhibited the cardiac Na⁺ channel with IC₅₀ of 2.6, 38, and 8.5 μ M, respectively. Granisetron, dolasetron, and MDL74,156 inhibited the cardiac hERG K⁺ channel with IC₅₀ of 3.71, 5.95, and 12.1 μ M, respectively. It appears that ondansetron is the most potent inhibitor for the cloned human cardiac hERG K⁺ channel among these 5-HT₃ receptor antagonists. The results were presented in Fig.5 in this report. This figure is attached below.

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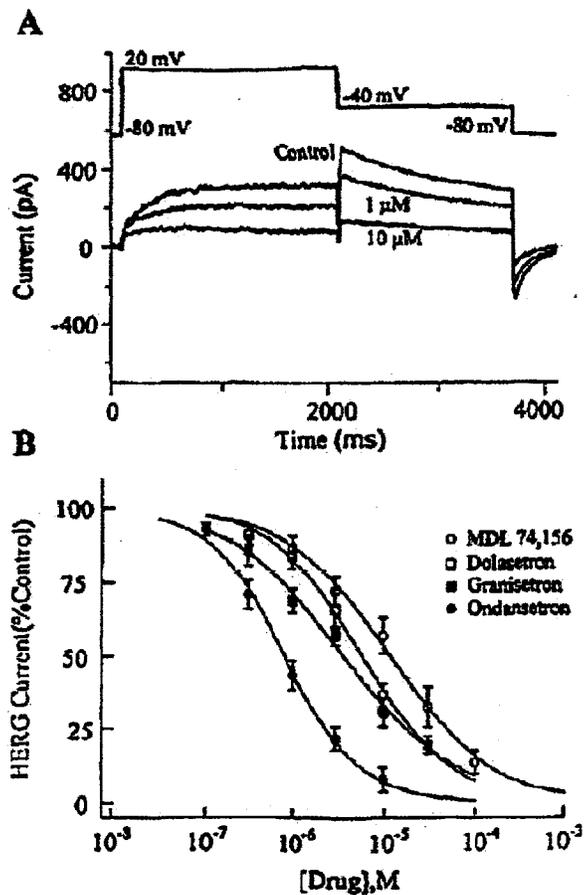


Fig. 6. Effects of antiemetic agents on HERG. A, whole-cell HERG currents were elicited by a 2-s depolarizing pulse to +20 mV from a holding potential of -80 mV. The cell was then returned to -40 mV to generate large outward tail currents. The effect of 1 and 10 μ M dolasetron on these currents is shown. B, dose-response relationships for ondansetron (●), granisetron (■), dolasetron (□), and MDL 74,156 (○) are shown. Inhibition of peak outward tail currents at -40 mV was used to generate the dose-response relationships. Error bars indicate S.E.M. ($n = 4-7$).

Effects on cardiac K⁺ currents and action potential duration in the feline ventricular myocytes

The effects of ondansetron on the cardiac K⁺ current (the delayed rectifier potassium current) and action potential duration were examined in feline ventricular myocytes (Br. J. Pharmacol., 113:527-535, 1994). The results indicated that ondansetron inhibited the delayed rectifier potassium current with KD of 1.7 μ M and prolonged action potential duration

(APD90) by over 30% at 1 μM . In contrast, granisetron, another 5-HT₃ receptor antagonist, inhibited the delayed rectifier potassium current with KD of 4.3 μM and prolonged the action potential duration (APD90) by over 30% at 3 μM . The results suggested that ondansetron is more potent than granisetron in the inhibition of the potassium current and prolongation of action potential duration.

Effects on ECG in anesthetized dogs

The effects of ondansetron on ECG were examined in anesthetized dogs (Drug Development Research, 24:277-284, 1991). The results of this study indicated that intravenous administration of ondansetron over 15 minutes prolonged QTc interval in a dose dependent manner in the dose range of 0.66 to 5.25 mg/kg. At the highest dose tested (5.25 mg/kg), ondansetron produced approximately 28% prolongation of QTc interval. In contrast, intravenous administration of zatosetron, another 5-HT₃ antagonist, also produced a dose dependent prolongation of QTc interval in the dose range of 0.22 to 3.5 mg/kg. At the dose 1.75 mg/kg, zatosetron inhibited the QTc interval by ~26%. The results were presented in Table 1 in this report. This table is attached below.

TABLE 1. Effects of Zatosetron and Ondansetron on Q-T_c Interval at Pharmacologically Equivalent Doses†

Group ^a	Compound	Dose	% change in Q-T _c interval ^b
Dose 0	Saline	1.0 ml/kg	3 ± 1
Dose 1	Zatosetron	0.22 mg/kg	10 ± 3
	Ondansetron	0.66 mg/kg	9 ± 0
Dose 2	Zatosetron	0.44 mg/kg	17 ± 3
	Ondansetron	1.31 mg/kg	12 ± 3
Dose 3	Zatosetron	0.88 mg/kg	20 ± 1*
	Ondansetron	2.63 mg/kg	19 ± 2*
Dose 4	Zatosetron	1.75 mg/kg	26 ± 2 ^b
	Ondansetron	5.25 mg/kg	28 ± 5*

†Based upon an approximately three-fold difference in pharmacological (5HT₃) potency (zatosetron > ondansetron) [Cohen et al., 1990].

^aGroups of 3-4 beagle dogs were administered saline, zatosetron, ondansetron by intravenous infusion (15 min).

^bPercent changes are shown as mean values ± S.E. observed at the completion of dose administration (15 min).

*P < 0.5, two-tailed Dunnett T on raw data relative to control values.

Both ondansetron and zatosetron had little effects on other parameters including heart rate, cardiac output, stroke volume, mean arterial blood pressure, pulmonary pressure, and peripheral vascular resistance.

LABELING:

The preclinical portion of the proposed labeling is consistent with the current labeling for Zofran. However, it should be revised in accordance to the current labeling format.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Current labeling

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg per day did not affect fertility or general reproductive performance of male and female rats.

Suggested labeling

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In a 2-year oral carcinogenicity study in mice, ondansetron was not carcinogenic at doses up to 30 mg/kg/day (about 3.75 times the recommended human dose of 32 mg based on body surface area).

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

Ondansetron was not genotoxic in the Ames tests, the gene conversion assay in *Saccharomyces cerevisiae*, the WHO nitrosation assay in *Salmonella typhimurium*, the forward mutation assay in Chinese hamster ovary cells, the human lymphocyte cytogenic assay, or the mouse micronucleus test.

Ondansetron at oral doses up to 15 mg/kg/day (about 3.75 times the recommended human dose based on body surface area) was found

to have no effect on fertility and reproductive performance of male or female rats.

Pregnancy: Teratogenic Effects:

Current labeling:

Pregnancy: Teratogenic Effects: Pregnancy Category B.

Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Suggested labeling:

Pregnancy: Teratogenic Effects: Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits at intravenous doses up to 4 mg/kg/day (about 1-2 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies may not always be predictive of human response, this drug should be used during pregnancy only if clearly needed.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Ondansetron, a 5-HT₃ receptor antagonist, is currently marketed in the U.S. by GlaxoSmithKine for the prevention of nausea and vomiting associated with the use of emetogenic cancer chemotherapy. The sponsor (Baxter Healthcare Corporation) submitted a 505(b)(2) NDA application for Ondansetron Hydrochloride Injection in IntraVia Container.

In the pre-NDA meeting, sponsor agreed to submit published reports of cardiovascular pharmacology studies including the effects of ondansetron and granisetron on the action potential duration (APD) and the delayed rectifier current (I_k) of feline isolated ventricular myocytes (Br J Pharmacol 1994; 113: 527-

535), the effects of granisetron, ondansetron, dolasetron on cloned human cardiac Na channel and hERG K⁺ channel (J Pharmacol Exp Ther 2000; 295: 614-620), and an in vivo study of the effects of intravenous ondansetron on the ECG parameters in anesthetized dogs (Drug Dev Res 1991; 24: 277-284). These study reports were provided in the NDA submission.

The results of the in vitro studies indicated that ondansetron inhibited the cloned human hERG K⁺ channels with IC₅₀ of 0.81 μM in HEK-293 cells, the delayed rectifier potassium current with KD of 1.7 μM and prolonged action potential duration by ~30% at 1 μM in feline ventricular myocytes. In the in vivo study, the effects of i.v. administration of ondansetron on ECGs were examined in anesthetized dogs. The results indicated that that ondansetron prolonged QTc interval in a dose dependent manner in the dose range of 0.66 to 5.25 mg/kg. At the highest dose tested (5.25 mg/kg), ondansetron produced approximately 28% prolongation of QTc interval. Based on the published report submitted (J. Cardiovas. Pharmacol., 1996, 28(1):53-59), ondansetron slightly but significantly prolonged QT interval following a single i.v. dose of 32 mg as compared to the control in healthy volunteers. However, the QTc was not significantly affected in this study.

In the present NDA, sponsor is seeking for approval to market 8 mg and 32 mg pre-mixed ondansetron hydrochloride injection in intraVia plastic container. Ondansetron hydrochloride is currently marketed by GlaxoSmithKline (GSK) as Zofran injection pre-mixed for the prevention of nausea and vomiting induced by emetogenic chemotherapy. The recommended i.v. dosage of zofran for adults 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 proposed i.v. dosage of ondansetron injection

The preclinical portion of the proposed labeling is consistent with the current labeling for Zofran. However, it should be revised in accordance to the current labeling format as recommended. From a preclinical standpoint, this NDA is approvable.

Recommendations:

1. From a preclinical standpoint, approval of pre-mixed intravenous product of Zofran is recommended for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.
2. The labeling should be revised as recommended.

Ke Zhang, Ph.D. Date
Pharmacologist, HFD-180

Comments:

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

CC:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Zhang

R/D Init.: J. Choudary 10/28/05

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/s/

Ke Zhang
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Jasti Choudary
11/9/2005 02:48:25 PM
PHARMACOLOGIST

Addendum to November 9, 2005 pharmacology review of NDA
21,915

The recommendation for labeling needs a few changes.

The following is the previous version:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a 2-year oral carcinogenicity study in mice, ondansetron was not carcinogenic at doses up to 30 mg/kg/day (about 3.75 times the recommended human dose of 32 mg based on body surface area).

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

Ondansetron was not genotoxic in the Ames tests, the gene conversion assay in *Saccharomyces cerevisiae*, the WHO nitrosation assay in *Salmonella typhimurium*, the forward mutation assay in Chinese hamster ovary cells, the human lymphocyte cytogenic assay, or the mouse micronucleus test.

Ondansetron at oral doses up to 15 mg/kg/day (about 3.75 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

Pregnancy: Teratogenic Effects:

Pregnancy: Teratogenic Effects: Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits at intravenous doses up to 4 mg/kg/day (about 1-2 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies may

not always be predictive of human response, this drug should be used during pregnancy only if clearly needed.

Since the recommended human dose of ondansetron is intravenous dose, the word intravenous should be added between human and dose throughout the label to emphasize the recommended human dose is intravenous dose as compared to the oral studies in animals.

The mutagenesis portion of the label provides detailed listing of the studies from the innovator's NDA. For a 505b(2) application, such detail is not needed. Therefore, it should be changed back to the current approved label.

The following recommended labeling is the final labeling.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

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

Ondansetron was not mutagenic in standard tests for mutagenicity.

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

Pregnancy: *Teratogenic Effects:*

Pregnancy: Teratogenic Effects: Pregnancy Category B:

Reproduction studies have been performed in rats at intravenous doses up to 4 mg/kg/day (about 1 time the recommended human intravenous dose based on body surface area) and in rabbits at intravenous doses up to 4 mg/kg/day (about 2 times the recommended human intravenous dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies may not always be predictive of human response, this drug should be used during pregnancy only if clearly needed.

Ke Zhang, Ph.D. Date
Pharmacologist, HFD-180

Comments:

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

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Ke Zhang
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Jasti Choudary
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PHARMACOLOGIST

PHARMACOLOGIST'S REVIEW OF NDA 21,915
(Amendment Dated October 26, 2006)

Sponsor & Address: Baxter Healthcare Corporation
McGaw Park, IL

Reviewer: Ke Zhang, Ph.D.
Pharmacologist

Date of Submission: October 26, 2006

Date of HFD-180 Receipt: October 26, 2006

Date of Review: December 19, 2006

DRUG: Ondansetron, injection

CATEGORY: 5-HT3 receptor antagonist

Submission Contents: Revised labeling for Ondansetron
Injection.

The non-clinical portion of the presently submitted labeling is identical to the recommended labeling with the approvable letter dated May 26, 2006.

SUMMARY AND EVALUATION:

The non-clinical portion of the presently submitted labeling is identical to the recommended labeling with the approvable letter dated May 26, 2006. No additional action is needed.

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Page 2

RECOMMENDATION: None.

Ke Zhang, Ph.D. Date

Comments:

Jasti B. Choudary, B.V.Sc., Ph.D. Date

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NDA
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HFD-180/Dr. Choudary
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