CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022524Orig1s000

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:	**22-524**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**April 7, 2009**
PRODUCT:	**Ondansetron Oral Soluble Film (Zuplenz)**
INTENDED CLINICAL POPULATION:	**Cancer patients receiving highly or moderately emetogenic chemotherapies, and patients undergoing surgical procedures**
SPONSOR:	**Par Pharmaceutical Inc.**
DOCUMENTS REVIEWED:	**Electronic submission of the NDA**
REVIEW DIVISION:	**Division of Gastroenterology Product (HFD-180)**
PHARM/TOX REVIEWER:	**Charles Wu, Ph.D.**
PHARM/TOX SUPERVISOR:	**Sushanta Chakder, Ph.D.**
DIVISION DIRECTOR:	**Donna Griebel, M.D.**
PROJECT MANAGER:	**Frances Fahnbulleh, Pharm.D.**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. **Recommendation on approvability:** From a nonclinical standpoint, the NDA application is approvable.

B. **Recommendation for nonclinical studies:** None.

C. **Recommendations on labeling:** In this 505(b)(2) NDA submission, the sponsor did not submit any new nonclinical studies. The nonclinical sections of the labeling are adopted from the innovator's labeling. Therefore, no changes in the labeling are recommended.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The sponsor did not provide any nonclinical study report under NDA 22-524. Instead, the following statement was made: "This NDA is submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and relies on studies that were not conducted by or for the applicant and for which this applicant does not have right of reference. Specifically, this NDA is supported by reference to the Agency's previous findings for the products: ZOFRAN Tablet (NDA 20103) and ZOFRAN (ODT) Orally Disintegrating Tablet (NDA 20781), by GlaxoSmithKline". In this submission, the sponsor has provided published studies to support the safety of the drug from a nonclinical standpoint. Pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron are well-established.

Ondansetron is a highly selective 5-HT_3 receptor antagonist. Ondansetron was initially approved in 1991 for use in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, prevention of nausea and vomiting associated with radiotherapy, and prevention of postoperative nausea and/or vomiting. The orally-dissolving film strip formulation offers an alternative delivery route of the drug to patients who may have difficulty swallowing and holding down tablets or who may prefer a thin film to other oral forms.

The pharmacodynamics of ondansetron has been well studied both *in vivo* and *in vitro*. In ligand binding studies, ondansetron shows a high degree of specificity (100 to >1000-fold) for the 5-HT_3 ligand-gated channel over other serotonin receptors and unrelated receptors. Ondansetron shows no detectable binding to dopamine receptors. In isolated tissue preparations, ondansetron inhibited the concentration dependent, serotonin-induced depolarization of the vagus nerve as well as the superior cervical ganglion. However, the dose-response curve was non-linear. The antiemetic effect of ondansetron was established in various animal models.

The pharmacokinetics of ondansetron, as studied in rats and dogs, demonstrated rapid and extensive absorption across the gastrointestinal tract, followed by extensive first pass metabolism. Ondansetron is metabolized by multiple P450 enzymes, including CPY3A4, CYP2D6 and CYP1A2.

Toxicological studies were performed in both rodents and dogs, using dose levels from 30- to 100-fold higher than human doses for as long as 18 months. Near the lethal dose, animals exhibited subdued activity, ataxia and convulsions. In some animals there were small, transient increases in serum transaminase levels. At the end of the study, necropsies showed no changes in the liver or other organs. Toxicology studies showed no genetic, reproductive, teratogenic or oncogenic adverse effects.

This is a 505(b) (2) application and no new indications have been applied for. The applicant has not submitted any new non-clinical information, and an overview based on a literature review is therefore appropriate and acceptable.

B. Pharmacologic activity

Ondansetron hydrochloride is an anti-emetic agent acting through selective inhibition of type 3 serotonin ($5\text{-}HT_3$) receptors.

C. Nonclinical safety issues relevant to clinical use:

None

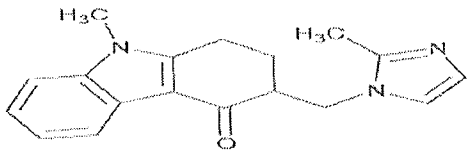
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-524
Review number: 01
Sequence number/date/type of submission: 000/original/April 7, 2009
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Par Pharmaceutical Inc.
Manufacturer for drug substance: (b) (4)
Reviewer name: Charles Wu, Ph.D.
Division name: Division of Gastroenterology Products
HFD #: 180
Review completion date: December 11, 2009

Drug:

Trade name: Zuplenz
Generic name: Ondansetron Oral Soluble Film
Code name: N/A
Chemical name: 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one
CAS registry number: N/A
Molecular formula/molecular weight: $C_{18}H_{19}N_3O$/293.26 (base)
Structure:



Relevant INDs/NDAs/DMFs: NDAs 20,103 (Tablets) and 20,781 (Orally disintegrating Tablet), GSK.

Drug class: 5-HT_3 receptor antagonist

Intended clinical population: Cancer patients receiving highly or moderately emetogenic chemotherapies, and patients undergoing surgical procedures

Clinical formulation: Ondansetron ODFS is available in the following strengths/dimensions: 1. Ondansetron (8 mg ondansetron) ODFS contains 8 mg ondansetron base; dimensions 0.875" x 1.25" (22 mm x 32 mm); 2. Ondansetron (4 mg ondansetron) ODFS contains 4 mg ondansetron base; dimensions 0.875" x 0.625" (22 mm x 16 mm). Besides the active pharmaceutical ingredient, the formulations contain the following major types of excipients: (b) (4)

(b) (4)

Route of administration: Oral

Disclaimer: N/A

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-524 are owned by Par Pharmaceutical or are data for which Par Pharmaceutical has obtained a written right of reference. Any information or data necessary for approval of NDA 22-524 that Par Pharmaceutical 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 Par Pharmaceutical 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 22-524.

Studies reviewed within this submission: The Sponsor did not provide any nonclinical study report under NDA 22-524. However, several published study reports were submitted in this submission.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief Summary

Ondansetron is a potent reversible competitive antagonist of the 5-hydroxytryptamine (5-HT_3) receptor. In ligand binding studies, ondansetron showed a high degree of specificity (100 to >1000-fold) for the 5-HT_3 ligand-gated channels over other serotonin receptors and unrelated receptors. Unlike metoclopramide, ondansetron showed no detectable binding to dopamine receptors. In isolated tissue preparations, ondansetron inhibits the concentration-dependent, serotonin-induced depolarization of the vagus nerve as well as the superior cervical ganglion. The antiemetic effect of ondansetron was established in various animal models. In preclinical efficacy studies, ondansetron completely inhibited cisplatin-, cyclophosphamide- and radiation-induced emesis in ferrets. The margin between efficacy and any systemic effect was about 10-fold and the margin between efficacy and behavioral effects were about 25-fold.

2.6.2.2 Primary pharmacodynamics

The following published pharmacology studies were submitted and reviewed:

Pharmacological properties of Ondansetron, a novel antagonist at 5-HT_3. Butler A, *et al* Br. J. Pharmacol., Vol.94: 397-412, 1988

The pharmacological properties of ondansetron have been studied in vagus nerve isolated from rat and rabbit and also in superior cervical ganglion of the rat. On the isolated vagus nerve and superior cervical ganglion of the rat, ondansetron behaved as a reversible competitive antagonist of 5-HT_3-induced depolarization with pK_B values of 8.61 ± 0.08 (n = 19) and 8.13 ± 0.07 (n = 16), respectively. The resolved R- and S-isomers of ondansetron were approximately equipotent as 5-HT_3 antagonists on the rat vagus nerve: the pK_B values were 8.95 ± 0.05 (n = 16) and 8.63 ± 0.08 (n = 17), respectively. Ondansetron was also an effective antagonist of 5-HT_3 on the rabbit isolated vagus nerve: in this case the pK_B value was 9.40 ± 0.14 (n = 4).

The potency and duration of action of R,S-ondansetron in blocking 5-HT_3 receptors *in vivo* were assessed by measuring its ability to antagonize the bradycardic response to 5-HT or 2-methyl-5-HT administered orally and intravenously (IV) in anaesthetized animals. In the rat, ondansetron showed to be a potent antagonist of both 2-methyl-5-HT and 5-HT-induced falls in heart rate with good duration of action. Following oral administration (60 min pretreatment), the ED_{50} values (with 95% confidence limits) for ondansetron against 2-methyl-5-HT and 5-HT were 7.0 (3.0-22.0) μg/kg and 8.0 (4.0-34.0) μg/kg (n = 8-10 per dose level), respectively. Following IV administration to rats, the ED_{50} for R, S-ondansetron against 2-methyl-5-HT (100 μg/kg) was 0.4 (95% confidence limits 0.18- 0.87) μg/kg (n = 10). In the anesthetized cat, 2-methyl-5-HT (3-20 μg/kg) caused transient but reproducible falls in heart rate and blood pressure. The dose-response curve for the falls in heart rate was much steeper in the cat than in the rat.

5-HT_3 receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Higgins GA, et al. Br. J. Pharmacol., 97:247-255

To identify and investigate the role of 5-hydroxytryptamine (5-HT_3) receptors in the area postrema in the control of cisplatin-induce emesis, the homogenate binding and autoradiography experiments were conducted in the ferret using the high affinity 5-HT_3 receptor ligand, [^{3}H]-GR65630 (ondansetron). Intraperitoneal injection (i.p.) of the 5-HT_3 receptor antagonists, Ondansetron, GR6S630A and MDL72222, at doses of 1, 0.1 and 1 mg/kg, respectively, inhibited emesis induced by cisplatin at 9 mg/kg i.p. Direct injection of low doses of the 5-HT_3 receptor antagonists into the area postrema region also inhibited cisplatin-induce (9 mg/kg i.p.) emesis. The doses used were: Ondansetron, 0.01-1 μg, GR6S630A, 0.001-0.1 μg; MDL72222, 0.1-10 μg. However, Cisplatin-induced emesis was not inhibited by direct injection of 30 μg ketanserin or methiothepin (5-HT_1, 5-HT_5 and 5-HT_7 antagonists), into the area postrema. These results confirmed a role of 5-HT, and in particular 5-HT_3 receptor in the area postrema, in the control of cisplatin-induced emesis and showed that ondansetron inhibited cisplatin-induced emesis in ferrets.

2.6.2.3 Secondary pharmacodynamics: No studies were submitted.

2.6.2.4 Safety pharmacology: No studies were submitted.

2.6.2.5 Pharmacodynamic drug interaction: N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Ondansetron has been extensively studied in preclinical animal studies, and its pharmacokinetic profile is well understood. The pharmacokinetics of ondansetron, as studied in rats and dogs, demonstrated rapid and extensive absorption across the gastrointestinal tract, followed by extensive first pass metabolism. Ondansetron is metabolized by multiple P450 enzymes, including CPY3A4, CYP2D6 and CYP1A2. Metabolic similarities between rats, dogs and humans support the relevance of rat and dog studies to human toxicology.

The following published pharmacokinetic studies were submitted and reviewed:

The Metabolism of Ondansetron. Saynor DA and Dixon CM, Eur. J Cancer Clin Oncol. 25(1): S75-S77, 1989

Rats and dogs received intravenous or oral ^{14}C-ondansetron at a dose level of 1 mg/kg. Ondansetron concentrations in plasma were determined by high performance thin layer chromatography (HPTLC) or high performance liquid chromatography (HPLC). Total radio-activity in plasma, urine and feces was determined by liquid scintillation counting. Metabolites were separated and isolated using a combination of solid phase extraction, liquid extraction and HPLC fractionation. They were then characterized using a combination of MS/NMR, enzyme hydrolysis and co-chromatography with authentic standards.

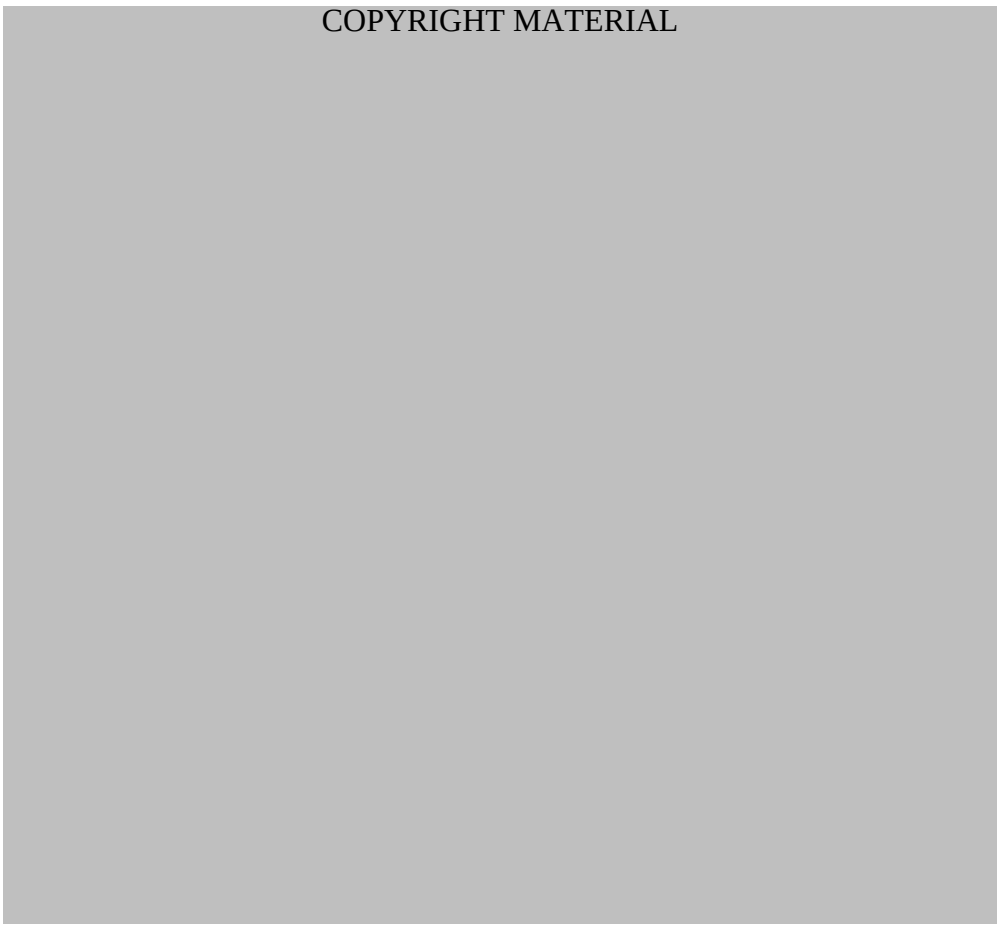
The PK parameters of ondansetron in rat and dog after oral administration are summarized in the following table.

Table 1. Summary of the pharmacokinetic parameters of ondansetron

Absorption of radio-labeled material across the gastrointestinal tract was rapid (Tmax <40 min) and extensive. However, due to high first pass metabolism, the systemic bioavailability of ondansetron in animals is low (<10%). The high systemic clearance of the drug also results in a very short half life in both rats (10 min) and dogs (30 min). The renal clearance of ondansetron is low (less than the glomerular filtration rate), also indicating that the major route of systemic clearance is by metabolism.

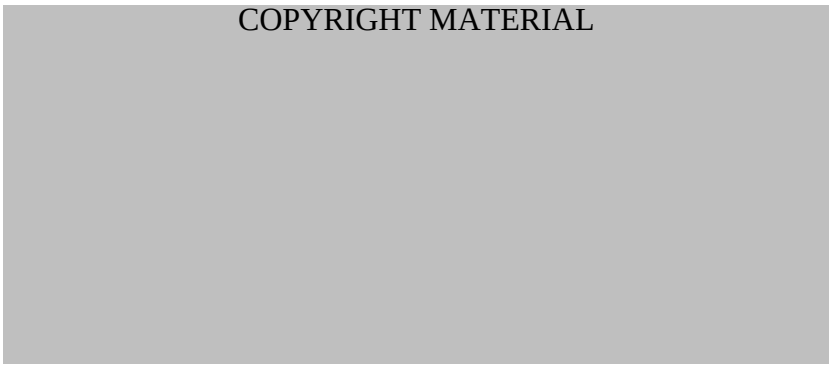
The routes of metabolism of ondansetron in animals and man are summarized in the figure below.

Metabolism of Ondansetron



Hydroxylation followed by glucuronide or sulphate conjugation is a major route of metabolism. N-demethylation is a minor route of metabolism in the rat and man, but a major route in the dog. The routes of metabolism in animals and man appear qualitatively similar, indicating that the species used in the toxicological testing of ondansetron were appropriate.

The excretion of radioactivity in urine and feces after intravenous and oral administration of ^{14}C-ondansetron is shown in the Figure below.



The recoveries of radioactivity in urine and feces were similar after oral and intravenous administration indicating that extensive absorption of the radiolabel occurs after oral administration. The routes of excretion of drug-related material differ between laboratory animals and man, with the major proportion of radio-labeled dose excreted via the bile in the rat and dog, whereas in man the predominant route of excretion is via the urine. Very little ondansetron (<5% of dose) is excreted unchanged.

The metabolism of the 5HT3 antagonists ondansetron, alosetron and GR87442 I: A comparison of *in vitro* and *in vivo* metabolism and *in vitro* enzyme kinetics in rat, dog and human hepatocytes, microsomes and recombinant human enzymes Somers GI, *et al.* 2007 Xenobiotica, 37(8): 832-854

The metabolism of the structurally related 5-HT_3 antagonists ondansetron, alosetron and GR87442 in male Wistar rat, male beagle dog and human was determined in hepatocytes, liver microsomes and human recombinant microsomes.

The profiles of phase I metabolites detected by LCMS were similar in human hepatocytes and microsomes. The metabolites of all three compounds produced in rat, dog and human microsomes and hepatocytes were similar to those seen in vivo, with the major routes of metabolism being N-dealkylation and/or hydroxylation as shown in the table below:

Table II. The major rat, dog and human *in vivo* and *in vitro* metabolites of ondansetron, alosetron and GR87442.

The inhibition of CYP-mediated metabolism by ondansetron was investigated using human recombinant enzymes expressed in *E. coli* (Bactosomes™). The IC_{50} values for the competitive inhibition of recombinant enzymes rbtCYP1A2, rbtCYP2C9, rbtCYP2C19, rbtCYP2D6 and rbtCYP3A4 by ondansetron, alosetron and GR877442 are shown in the table below. CYP1A2 was potently inhibited by all three compounds with an IC_{50} of less than 10 μM in this assay. All compounds also inhibited the other isoforms (CYP2C9, CYP2C19, CYP2D6 and CYP3A4) but at higher concentrations.

Table III. The inhibition of human recombinant enzymes by ondansetron, alosetron and GR87442.

Incubation of ondansetron, alosetron and GR87442 with the recombinant enzymes, rbtCYP1A2, rbtCYP2C9, rbtCYP2C19, rbtCYP2D6 and rbtCYP3A4, produced a range of metabolites similar to those produced by hepatocytes and microsomes. Following incubation with ondansetron, no single human recombinant enzyme investigated produced the same metabolite profile observed in native human liver microsomes. Overall, the pharmacokinetics of the three 5-HT_3 antagonists investigated were dominated by CYP3A4 (and/or 2C9) compared with CYP1A2 in man.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

N/A

2.6.6 TOXICOLOGY

The following published toxicology studies were submitted and reviewed:

Ondansetron: Pre-clinical Safety Evaluation. Tucker ML *et al.* Eur J Cancer Clin Oncol. 1989 25(1): S79- S93

Toxicology studies for pre-clinical safety evaluation of ondansetron have been undertaken which involved a series of studies - single dose toxicity studies, repeat dose toxicity studies, reproduction studies, genotoxicity studies, oncogenicity studies, local irritancy studies, and a hypersensitivity study. Toxicological studies were performed in both rodents and dogs, using dose levels from 30- to 100-fold higher than human doses for as long as 18 months.

Single dose study

Methods: The animals used were CR/H strain albino mice, and RH strain pigmented rats. Maximum non-lethal single oral and IV dose level were determined in 10 animals/sex/group. After a 3-day observation period, half of the animals were killed to assess early onset changes in major organs, including histopathology. The rest were killed after 14 days to allow detection of late onset changes and to assess reversibility.

Results: The max. non-lethal dose levels are summarized in the following table:

Table 1. *Maximum non-lethal dosages*

At these dose levels, the following effects were noted. Oral dosing: subdued behavior, prostration, ataxia, dyspnea, protruding eyes and erythema (in rats only). These effects lasted for approx. 1h in mice and 4h in rats. After IV dosing, no effects were observed in mice. However, in the rats, IV dosing produced the same outcome as oral dosing.

Repeat dose study

Methods: The studies were conducted in the RH strain pigmented rats for up to 18 months at 0, 1, 6 and 36 mg/kg/day ondansetron and in the beagle dogs at 0, 1, 4 and 12.5 mg/kg/day for 12 months by daily oral administration of ondansetron.

Results: In male rats, at 36 mg/kg/day, salivation, tenseness and/or hunched posture, decreased weight gain and food consumption were observed. The minor increase in ALT (Ca. 50%) and AST (Ca. 10%) levels found only in the early part of study were not associated with any histopathologic changes in the liver. The NOAEL was considered to be 6 mg/kg/day. In dogs, at 12.5 mg/kg/day, there was low incidence of transient mydriasis, occasional loose feces, ataxia, subdued activity were observed. No macroscopic or microscopic changes were found. No other hematologic and clinical biochemistry changes or changes in urine measurements were noted. Thus, the NOAEL was considered to be 12.5 mg/kg/day.

Reproductive toxicity studies:

Methods: For the fertility (segment I) study, male rats were treated with ondansetron for 10 weeks prior to and throughout the mating period. Females were treated for 3 weeks prior to mating, during mating and throughout pregnancy at 1, 4 and 15 mg/kg/day. A proportion of animals were then killed and their fetuses examined for morphological defects. The rest were allowed to litter and to raise their offspring to weaning. In the

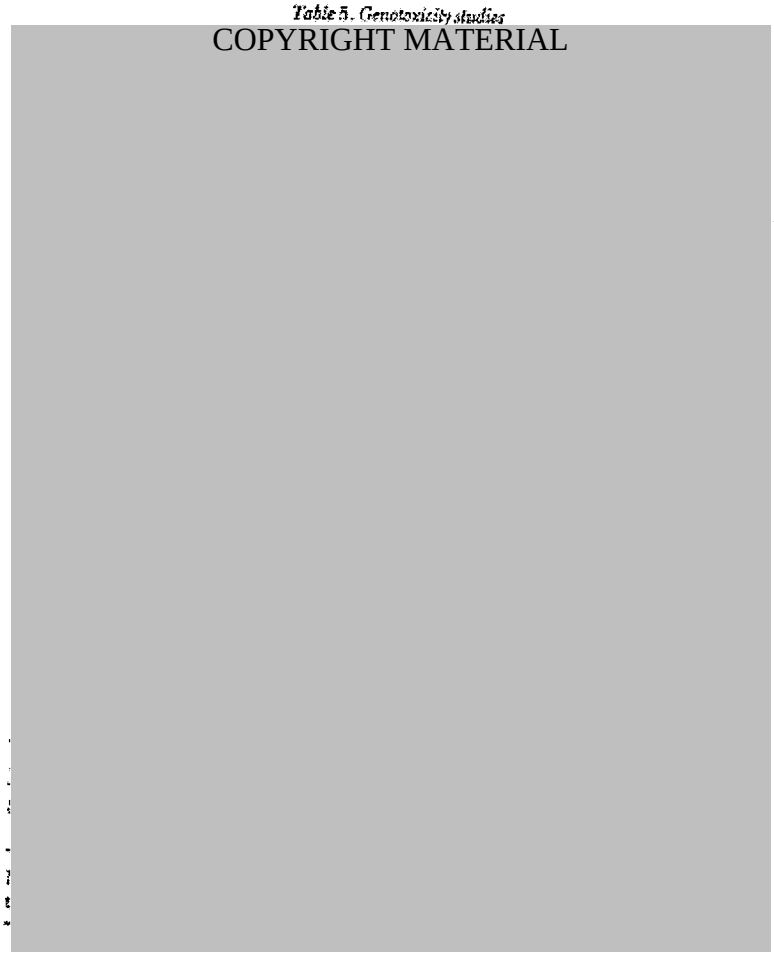
segment II study, treatment of ondansetron in female rats continued from days 7-16 of pregnancy inclusive. A proportion of the dams were killed on day 21 of pregnancy and their fetuses examined for morphological defects. The remainder were allowed to give birth. The subsequent development of the pups was assessed. Studies in rabbits involved ondansetron treatment from days 8-20 of pregnancy inclusive. The dams were killed on day 30 and their fetuses examined for morphological defects. For the segment III study in rats, ondansetron treatment continued from day 17 of pregnancy to day 22 post-partum. All female rats were allowed to litter and their offspring were monitored for both physical and functional development. Randomly selected rats were allowed to reach maturity and were then mated. The dams were killed on day 21 of pregnancy and their fetuses examined for morphological defects.

Results: In the segment I study, there was no effect of ondansetron at up to 15 mg/kg/day on rat fertility except for a small dose-related reduction in weight gain in F_0 males and females. In the segment II study, there was a transient mydriasis and dyspnea in rat dams at 15 mg/kg/day. No adverse effects were observed on pregnancy, fetal or post-natal development. In rabbits, there were no adverse effects on pregnancy or fetal development at up to 30 mg/kg/day except for a slight decrease in maternal weight gain. In the segment III studies, there were no adverse effects on rat pregnancy in F_0 and F_1 generations, or F_1 post-natal development except for slight decreases in weight gain in F_0 and F_1 animals.

Genotoxicity studies

Methods: The genotoxicity studies of ondansetron were conducted using *in vitro* Ames assay in bacteria and yeast, Cytogenetics assay with human peripheral lymphocytes and Gene mutation assay with Chinese hamster V79/Hgprt+ cells, and also *in vivo* Micronucleus test in mouse as listed in the following table.

Table 5. Genotoxicity studies



Results: Microbial tests showed negative results using a range of bacterial and yeast test strains, both in the presence and absence of an external rat liver metabolizing system (S9 mix). In Gene mutation assay in Chinese hamster (V79) cells, no significant increases in mutant Hgprt$^-$ colonies were obtained after treatment with ondansetron in the presence and absence of an external rat-liver metabolizing system (S9 mix). In human peripheral lymphocyte assay, ondansetron did not induce any significant increase in chromosome damage in cells treated with a range of concentrations of the drug in the presence and absence of an external rat-liver metabolizing system (S9-mix). In mouse micronucleus test, oral administration of ondansetron at doses of 1, 3, and 10 mg/kg had no effect on the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow.

Carcinogenicity Study

Methods: The animals used were inbred C57/B1 strain pigmented mice, and random bred Crl:CD(SD)BR strain albino rats. Ondansetron was administered orally for a duration of 2 years. In rats, ondansetron was given at 1, 5 and 25/15/10 mg/kg/day via

gavage and in mouse, ondansetron was given at 1, 5.5 and 30 mg/kg/day in drinking water.

Results: High dose level of ondansetron given to rats was reduced because of increased mortality. After reduction to 10 mg/kg/day in week 24, mortality reduced to control group level. There was no treatment-related increase in tumor incidence up to 10 mg/kg/day. In mouse, no treatment-related increase in mortality or tumor incidence was observed up to 30 mg/kg/day.

Local Irritancy Studies

Methods: Nine New Zealand White rabbits were each given an intramuscular injection and a subcutaneous injection of 1 ml buffered ondansetron (2.5 mg/ml), Contralateral sites were treated with saline as controls. Three animals were killed after 3, 8 and 15 days. Additional animals were treated with benzyl penicillin (200 mg/ml) as positive controls. As macroscopic signs of irritancy were still apparent at 15 days, some animals were retained for a further week.

Results: No changes were detected at any of the time points in any of the subcutaneously treated ondansetron sites.

Hypersensitivity Study

Methods: A group of 10 Guinea pigs of each sex received a series of dermal applications to the same site of a solution of ondansetron that had been found to be slightly irritant in a preliminary study. Freunds Complete Adjuvant was administered intradermally to separate adjacent sites on the same occasions. The animals were subsequently challenged by intradermal and dermal applications of ondansetron. The solutions used were 50 µl of 5% w/v ondansetron formulated in 95% ethanol/methyl cellosolve/Tween 80 45:45:10.

Results: None of the 20 animals showed a positive reaction to the challenge at either 24 or 48 h as opposed to 19/19 positive reactions at both time points in a control group treated with benzyl penicillin.

Summary of Toxicology Studies:

In the single dose toxicity study, the non-lethal dosages were 10 mg/kg in mouse and 80 mg/kg in rats treated orally with ondansetron. The non-lethal dosages were 1 mg/kg in mouse and 15 mg/kg in rats treated intravenously. At these dose levels, the following effects were noted. Oral dosing: subdued behavior, prostration, ataxia, dyspnea, protruding eyes and erythema (in rats only). These effects lasted for approx. 1h in mice and 4h in rats. After IV dosing, no effects were observed in mice. However, in the rats, IV dosing produced the same outcome as oral dosing.
In repeat oral dose toxicity studies in rats a minor increase ALT and AST levels were found in the early part of study only, and not associated with any histopathologic changes in the liver. In dogs, no macroscopic or microscopic changes were found. Thus, the

NOAELs were considered to be 6- and 12.5-mg/kg/day in 18-month rat and 12-month dog toxicity studies, respectively.
In reproductive toxicity studies, in the segment I study, there were no significant adverse effects in rats and/or rabbits. Ondansetron was not genotoxic in a battery of *in vitro* and *in vivo* genotoxicity assays.
In 2-year carcinogenicity studies in rats and mice, there was no treatment-related increase in tumor incidences up to 10 mg/kg/day in rats and up to 30 mg/kg/day in mice.
There was on positive changes found in the local irritancy study conducted in rabbits and hypersensitivity study conducted in Guinea pigs.

LABELLING:

Proposed Text for the labeling of Zuplenz (4 and 8 mg film):

8.1 Pregnancy

Proposed version

Teratogenic Effects:
Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, 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, Zuplenz should be used during pregnancy only if clearly needed.

Evaluation: No changes are recommended in this section.

8.3 Nursing Mothers

Proposed version

Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zuplenz is administered to a nursing woman.

Evaluation: No changes are recommended in this section.

13. NONCLINICAL TOXICOLOGY:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Proposed version

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.
Evaluation: No changes are recommended in this section.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The sponsor submitted this original NDA (22-524) under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and relies on studies that were not conducted by or for the applicant and for which this applicant does not have right of reference. The NDA is supported by reference to the Agency's previous findings for the following products: ZOFRAN Tablet (NDA 20103) and ZOFRAN (ODT) Orally Disintegrating Tablet (NDA 20781), sponsored by GlaxoSmithKline". In this submission, the sponsor did not submit any nonclinical studies. Instead, the sponsor provided published studies to support the safety of the drug from a nonclinical standpoint. Pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron are well-established.

Ondansetron is a highly selective 5-HT_3 receptor antagonist. Ondansetron was initially approved in 1991 for use in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, prevention of nausea and vomiting associated with radiotherapy, and prevention of postoperative nausea and/or vomiting. The orally-dissolving film strip formulation offers an alternative delivery route of the drug to patients who may have difficulty swallowing and holding down tablets or who may prefer a thin film to other oral forms.

The pharmacodynamics of ondansetron has been well studied both in vivo and in vitro. In ligand binding studies, ondansetron showed a high degree of specificity (100 to >1000-fold) for the 5-HT3 ligand-gated channel over other serotonin receptors and unrelated receptors. Unlike metoclopramide, ondansetron showed no detectable binding to dopamine receptors. In isolated tissue preparations, ondansetron inhibited the concentration dependent, serotonin-induced depolarization of the vagus nerve as well as the superior cervical ganglion. The pharmacokinetics of ondansetron, as studied in rats and dogs, demonstrated rapid and extensive absorption across the gastrointestinal tract, followed by extensive first pass metabolism. Ondansetron is metabolized by multiple P450 enzymes, including CPY3A4, CYP2D6 and CYP1A2. Oral repeat dose toxicological studies were performed in both rodents for 18 months and dogs for 12 months and established the NOAELs of 6 mg/kg/day in rats and 12.5 mg/kg/day in dogs, thus, providing more than 10- and 25- fold safety margin for proposed human dosage 24

mg/day (0.48 mg/kg/day for a 50-kg person). Near the lethal dose, animals exhibited subdued activity, ataxia and convulsions. In some animals there were small, transient increases in serum transaminase levels. Toxicology studies also showed no genetic, reproductive, teratogenic or oncogenic effects.

In conclusion, this is a 505(b) (2) application and no new indications have been applied for. The applicant has not submitted any new non-clinical information and an overview based on a literature review is therefore appropriate and acceptable.

Recommendations: From a nonclinical standpoint, approval of the NDA application is recommended.

Charles Wu, Ph.D. Date
Pharmacologist, HFD-180

Comments:

Sushanta Chakder, Ph. D. Date
Supervisory Pharmacologist, HDF-180

cc.:
IND
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HFD-180/CSO
HFD-180/Dr. Wu
HFD-180/Dr. Chakder

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22524	ORIG-1	PAR PHARMACEUTICAL	ZUPLENZ (ONDASETRON) ORALLY-DISSOLVING F

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/s/

CHARLES G WU
12/11/2009

SUSHANTA K CHAKDER
12/11/2009