CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022524Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22524
Complete Response	**Class I Resubmission**
Submit Date(s)	4 May 2010
Received Date(s)	4 May 2010
PDUFA Goal Date	4 July 2010
Division / Office	DGP/ODE III/OND
Reviewer Name(s)	Tamara Johnson, MD, MS
Review Completion Date	21 June 2010
Established Name	Ondansetron
(Proposed) Trade Name	Zuplenz
Therapeutic Class	5HT3 receptor antagonist
Applicant	Par Pharmaceutical, Inc.
Formulation(s)	Oral Soluble Film
Dosing Regimen	4mg, 8mg
Indication(s)	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 (CINV-HEC); • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC); • Prevention of postoperative nausea and/or vomiting (PONV); • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV).
Intended Population(s)	• Adults (all indications) • Age 4 years to 17 years (MEC only)

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1 Recommendations/Risk Benefit Assessment

The Sponsor, Par Pharmaceutical, Inc. resubmits this 505(b)(2) application in response to the Complete Response letter dated February 7, 2010. In this submission, the Sponsor addresses the outstanding issue of site inspections and seeks to resume labeling negotiations. Their product, Zuplenz (ondansetron oral soluble film), relies upon Zofran Orally Disintegrating Tablets as the reference labeled drug for the indications of:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin≥50 mg/m2 (CINV-HEC),
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC),
- prevention of postoperative nausea and/or vomiting (PONV), and
- prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV).

1.1 Recommendation on Regulatory Action

For this second cycle review, this reviewer recommends approval of Zuplenz 8mg and 4mg oral soluble film for the same indications and target populations as Zofran® ODT. This recommendation is based upon pharmacological studies demonstrating that Zuplenz ondansetron oral soluble film is bioequivalent to Zofran® ODT, the lack of significant safety signals for this new formulation of ondansetron, and successful completion of study site inspections. As an approval action was contingent upon successful site inspections and labeling negotiations, the NDA clinical review template was not used for this resubmission review. Please see this reviewer's first cycle Clinical Review, dated December 22, 2009, for the safety evaluation of Zuplenz.

1.2 Second Cycle Review Issues

In addition to successful study site inspections, a few additional issues remain to be addressed during the second cycle of review. Firstly, final negotiations on the labeling must be completed, specifically Section 17 and the patient information section of the labeling. Secondly, the Sponsor will need to submit a revised pediatric plan for Zuplenz reflecting the Agency's advice. The Sponsor's original pediatric plan was found to be inadequate for fulfilling the Pediatric Research

Equity Act (PREA) (21 USC 355c) requirements. On January 6, 2010, the Pediatric Review Committee (PeRC) PREA Subcommittee reviewed and made new recommendations for the Zuplenz pediatric plan.

2 Introduction and Regulatory Background

2.1 Product Information

Zuplenz oral soluble film is a new formulation of ondansetron, a selective 5-HT_3 receptor antagonist which blocks stimulation on both peripherally located vagal nerve terminals and centrally located receptors in the chemoreceptor trigger zone of the area postrema. Prepared in both the 4mg and 8mg strengths, this product seeks the same indications and patient population as those for Zofran® ODT.

Ondansetron has been marketed in the US since 1991 and is provided under the tradename Zofran® and numerous generics. The availability of Zuplenz ondansetron oral soluble film would provide an additional method of administration for patients suffering from nausea and vomiting who may have difficulty swallowing a whole tablet or any moderate amount of liquid. This new formulation provides the equivalent amount of the active ingredient as Zofran® ODT, but may find better acceptance in settings where patients are less tolerant of holding a tablet in the mouth (e.g. pediatric patients).

2.2 Summary of Presubmission Regulatory Activity Related to Submission

For this 505(b)(2) NDA application by Par Pharmaceutical, Inc., reference is made to Zofran® ODT for nonclinical, clinical efficacy and safety data, for which this Sponsor does not have right of reference. In the first review cycle, the Sponsor's pharmacologic studies were reviewed and demonstrated the bioequivalence of Zuplenz oral soluble film to Zofran ODT (see Clinical Review dated December 22, 2009). Prior to the original NDA submission, the Sponsor met with the Agency on two previous occasions to reach agreement on its clinical program. On July 2, 2008, a pre-IND meeting was held where the Agency agreed to the Sponsor's clinical program and the 505(b)(2) type of NDA submission. On February 25, 2009, a pre-NDA teleconference meeting was held at which the Agency agreed to include the 4mg dosage for the pediatric CINV-MEC indication.

3 Inspection

Two sites were selected for inspection by the Division of Scientific Investigations (DSI); the bioequivalence study site and bioanalytical site, both in (b) (4) Inspections of the key study sites were delayed due to a travel advisory for the region where the sites are located. Site inspection was conducted at (b) (4) on April 19 – 22, 2010. Form FDA 483 was issued citing procedural and protocol deviations. (b) (4) responded to the Form FDA 483 observations in a letter dated May 3, 2010. Upon evaluation of the inspectional findings and the firm's response, the DSI recommends that the inspected clinical and analytical portions be accepted for review. The inspection findings should not adversely impact the study results. For further details, please see the full review by DSI reviewer, Dr. J.A. Kadavil.

4 Pediatric Plan

The Sponsor's original pediatric plan was found to be inadequate for fulfilling the Pediatric Research Equity Act (PREA) requirements. On January 6, 2010, the Pediatric Review Committee (PeRC) PREA Subcommittee reviewed the Sponsor's original pediatric plan. The Division is in agreement with the PeRC recommendations. The recommended pediatric plan, as listed below by indication, has been forwarded to the Sponsor.

1. ***Prevention of nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy***

a. A partial waiver for pediatric patients aged 0<4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).
b. Deferred pediatric study in pediatric cancer patients ages 4 to <17 years receiving highly emetogenic chemotherapy (HEC).
    i. A PK and safety study to characterize the pharmacokinetic parameters of Zuplenz (ondansetron) oral soluble film compared to standard therapy.
    ii. An adequately powered, well-controlled, and randomized dose-response study to evaluate the safety and efficacy of Zuplenz (ondansetron) oral soluble film compared to standard therapy.

2***. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy***

a. Partial waiver for pediatric patients aged 0<4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).
b. The product is appropriately labeled for use in patients 4 years to 17 years of age based on Zofran ODT labeling.

3. Prevention of nausea and vomiting associated with radiotherapy

A. Full waiver of studies in pediatric patients because studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

4. Prevention of postoperative nausea and vomiting

a. Deferred pediatric study in pediatric surgical patients ages 0 to <17 years.
   i. A PK and safety study to evaluate the pharmacokinetics of Zuplenz (ondansetron) oral soluble film compared to standard therapy.
   ii. An adequately powered, well-controlled, and randomized dose-response study to evaluate the safety and efficacy of Zuplenz (ondansetron) oral soluble film compared to standard therapy.
   iii. An age-appropriate formulation must be developed for younger pediatric patients.

5 Safety of Related Drugs

Although no new safety information has been submitted by the Sponsor for Zuplenz, there have been changes to labeling of other drugs in the class.

5.1 Important Safety Issues With Consideration to Related Drugs

Ondansetron, the first drug approved in the $5HT_3$ receptor antagonists class, has widespread distribution and a generally good safety profile. However, there exists the serious risk of cardiac arrhythmia with the class of $5HT_3$ receptor antagonists. These events are rare and mostly documented with intravenous use. All drugs in the class are noted to cause cardiac ion channel blockade, however, individual drug effect on QT prolongation varies. The effect of QT prolongation is more pronounced in dolasetron than ondansetron.[1,2] Whereas

1 Katzung, editor. Basic and Clinical Pharmacology. 11th edition, 2009.

no significant QT prolongation was found for palonosetron or the granisetron patch. Table 1 lists updated product labeling language regarding cardiovascular adverse events known to the class of $5HT_3$ receptor antagonists.

2 Keefe DL. The cardiotoxic potential of the 5-HT3 receptor antagonist antiemetics: is there cause for concern? Oncologist 2002;7:65 - 72.

Table 1: Cardiovascular Safety Labeling in Drug Class

Safety Labeling in the $5HT_3$ Receptor Antagonists Class
Zofran ondansetron (2007 label): Precautions: Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Adverse Reactions (Cardiovascular): Rare cases of angina (chest pain), hypotension, and tachycardia have been reported. Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT interval prolongation and ST segment depression), palpitations, and syncope.
KYTRIL granisetron (2009 label): Precautions: An adequate QT assessment has not been conducted, but QT prolongation has been reported with granisetron. Therefore, granisetron should be used with caution in patients with pre-existing arrhythmias or cardiac conduction disorders, as this might lead to clinical consequences. Patients with cardiac disease, on cardio-toxic chemotherapy, with concomitant electrolyte abnormalities and/or on concomitant medications that prolong the QT interval are particularly at risk. Adverse Reactions: (Cardiovascular): Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including non-sustained tachycardia, and ECG abnormalities have been observed rarely.
ANZEMET dolasetron (2009 label): Warnings: Dolasetron can cause ECG interval changes (PR, QTc, JT prolongation and QRS widening). These changes are related in magnitude and frequency to blood levels of the active metabolite. These changes are self-limiting with declining blood levels. Some patients have interval prolongations for 24 hours or longer. Interval prolongation could lead to cardiovascular consequences, including heart block or cardiac arrhythmias. These have rarely been reported. Precautions: Dolasetron should be administered with caution in patient who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. Adverse reactions: Hypotension; rarely-edema, peripheral edema, The following events also occurred rarely and with a similar frequency as placebo and/or active comparator: Mobitz I AV block, chest pain, orthostatic hypotension, myocardial ischemia, syncope, severe bradycardia, and palpitations.
ALOXI palonosetron (2008): Adverse reactions: **CINV** (Cardiovascular): 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, Supraventricular extrasystoles and QT prolongation; <1%: hypertension, transient arrhythmia, first degree atrioventricular block, second degree atrioventricular block, QTc prolongation. **PONV** common adverse events (incidence ≥ 2%) are QT prolongation, bradycardia, headache, and constipation.

*Table adapted from Corken-Mackey (OSE) review dated June 26, 2006, and updated February 15, 2010.

6 Labeling Recommendations

In addition to those labeling recommendations made in the first cycle clinical review, this reviewer further recommends revisions that improve compliance to the Physician's Labeling Rule format and improve communication with the patient. These additional labeling recommendations include the following:

A. Use in Specific Populations (*§*8)
    i. Correct subheading titles

B. Patient Counseling Information (*§17*)
    i. Language added to inform patients of most common adverse reactions and to clarify instructions regarding how to take Zuplenz.
    ii. Deleted section numbers.

C. Patient Instructions for Use
    i. Language added to clarify the population ages for each approved indication
    ii. Modification to the illustrated step-by-step instructions are needed to prevent misleading representation of dose
    iii. Language added to inform patients of most common adverse reactions
    iv. Language added to alert specific patient populations of their increased risks with Zuplenz use (i.e., those with impaired liver function patients or women of reproductive age)

The following consultant division also provided reviews of the labeling.

A. OSE/Division of Risk Management (DRISK): Please see the full review by J. C. Hubbard.
B. Division of Drug Marketing, Advertising and Communication (DDMAC): Please see the full review by K. Klemm.
C. Study Endpoints and Label Development (SEALD): Please see the full reviews by L. Cantin and D. Beitzell.

Reviewer Comments
This reviewer agrees with most recommendations from the consultant divisions, except for those discussed below.

- *This reviewer disagrees with the recommendation by DDMAC to include, in the Patient Instructions for Use, the dosage for each population and indication. Such language equates to a large amount of text and will prove more confusing than helpful to the layperson. Additionally, it may lead to the patient self-dosing.*

- *This reviewer disagrees with the recommendation by SEALD to change* (b) (4) *to "adverse reactions". Adverse reactions (21 CFR 201.57(c)(7)) is defined as adverse events observed during use of a drug which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. The current application is a 505(b)(2). The Sponsor must stay consistent with the Zofran ODT labeling because they do not have rights to the data that determined the causal relationship between ondansetron and the adverse event. Therefore, they cannot support a change to the term "adverse reaction".*

For final labeling agreements, the reader is directed to the approved labeling for Zuplenz oral soluble film.

7 Conclusions

This reviewer recommends approval of Zuplenz 8mg and 4mg oral soluble film for the proposed indications for adults and pediatric patients aged 4 years and older. This recommendation is based upon the demonstration that Zuplenz ondansetron oral soluble film is bioequivalent to Zofran® ODT, the lack of significant safety signals, acceptable study site inspections, successful labeling negotiations, and a revised pediatric plan that adequately addresses PREA.

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/

TAMARA N JOHNSON
06/23/2010

NANCY C SNOW
06/24/2010
The medical team leader agrees with conclusions and recommendations of the medical reviewer.

Summary Review for Regulatory Action

Date	February 5, 2010
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	022524
Applicant Name	Par Pharmaceutical, Inc.
Date of Submission	Received: April 7, 2009
PDUFA Goal Date	February 7, 2010
Proprietary Name / Established (USAN) Name	Zuplenz Ondansetron
Dosage Forms / Strength	Oral soluble film/ 4 mg and 8 mg
Proposed Indication(s)	Adults 1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 (CINV-HEC) 2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, (CINV-MEC) 3. Prevention of postoperative nausea and/or vomiting (PONV) 4. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV) Pediatrics: 1. Prevention of CINV-MEC in children ages 4 years and older.
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tamara Johnson, MD, MS/Nancy Snow, DO
Pharmacology Toxicology Review	Charles Wu, Ph.D./ Sushanta Chakder, Ph.D.
CMC Review	Bogdan Kurtyka, Ph.D./Moo Jhong Rhee, Ph.D.
Biopharmaceutics Review ONDQA	Houda Mahayni, Ph.D./Patrick Marroum, Ph.D.
Clinical Pharmacology Review	Insook Kim, Ph.D./Sue-Chih Lee, Ph.D.
DDMAC	Kathleen Klemm/Sheetal Patel
DSI	pending
CDTL Review	Sue-Chih Lee, Ph.D.
OSE/DMEPA	Lori Cantin, R.Ph./Kristina Arnwine, PharmD/Denise P. Toyer, PharmD

SEALD	Debbie Beitzell, BSN
Pediatric and Maternal Health Staff	Amy M. Taylor, MD, MHS/Lisa Mathis, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
ONDQA = Office of New Drug Quality Assessment
SEALD = Study Endpoints and Label Development

APPEARS THIS WAY ON ORIGINAL

Division Director Summary Review

1. Introduction

In this 505(b)(2) application, Par Pharmaceutical, Inc. proposes a new ondansetron oral dosage form – oral soluble film, in 4 mg and 8 mg doses. The applicant references the Agency's previous findings of safety and efficacy in the ondansetron NDAs Zofran Tablet (NDA 20103) and Zofran ODT (orally disintegrating tablet NDA 20781). The applicant has submitted studies in this NDA to demonstrate bioequivalence of Zuplenz to Zofran ODT. Zofran ODT was itself approved based on demonstration of bioequivalence of Zofran ODT to Zofran tablets. The proposed indications for Zuplenz are:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 (CINV-HEC) in adults
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, (CINV-MEC) – in adults and children ages 4 years and older.
3. Prevention of postoperative nausea and/or vomiting (PONV) in adults
4. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV) in adults

The Zofran Tablet and Zofran ODT product labels carry a pediatric indication with instructions for pediatric dosing for moderately emetogenic cancer chemotherapy only. The approved indications and ondansetron doses found in the Zofran Tablets and Zofran ODT product labels are:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin **≥** 50 mg/m^2.

    - The recommended **adult** oral dosage of ZOFRAN is 24 mg given as three 8-mg tablets.
    - The label states that there is **no experience** with the use of a 24 mg dosage in **pediatric** patients.

2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

    - The recommended **adult** oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet given twice a day.
    - For pediatric patients **12 years of age and older**, the dosage is the same as for adults.

- For pediatric patients **4 through 11 years of age**, the dosage is one 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet given 3 times a day.

3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.

    - The recommended oral dosage **for adults** is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet given 3 times a day.

      For total body irradiation, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

      For single high-dose fraction radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

      For daily fractionated radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

    - There is no experience with the use of ZOFRAN Tablets or ZOFRAN ODT Tablets in the prevention of radiation-induced nausea and vomiting **in pediatric patients.**

4. Prevention of postoperative nausea and/or vomiting.

    - The recommended dosage for **adults** is 16 mg given as two 8-mg ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets 1 hour before induction of anesthesia.
    - There is no experience with the use of ZOFRAN Tablets or ZOFRAN ODT Tablets in the prevention of postoperative nausea and vomiting **in pediatric patients**.

2. Background

Ondansetron is a 5-HT3 receptor antagonist. There are multiple ondansetron products currently marketed, including generics and oral dissolving tablets. Consideration was given to whether this application should most appropriately be reviewed by Office of Generic Drugs as a 505(j) application; however, the Agency reviewed information provided by the applicant regarding the product and manufacturing process and determined that a 505(b)(2) application for a oral soluble film would be appropriate.

The applicant met with the Agency at a pre-IND meeting and a pre-NDA meeting. In the latter meeting the Agency agreed to review the 4 mg dosage for the pediatric CINV-MEC indication (which is the Zofran labeled dosage for children ages 4 years to <12 years).

3. CMC

I concur with the conclusions reached by the Chemistry Reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing sites were acceptable. Stability testing supports an expiry of 24 months when stored at controlled room conditions. I concur with the reviewer's recommendations that the NDA cannot be approved in the present form due to the outstanding site inspection of the sites that conducted one of the bioequivalence studies and analytical site. In addition, labeling negotiations have not been finalized. The label in its current state cannot be approved.

The drug product is two distinct films, a 4 mg dose film and an 8 mg dose film, which are dose proportional and manufactured in the same process. The different dosages are derived from different surface areas of the film (high dose surface area is twice the surface area of the lower dose). The film is placed on the tongue, where it remains in place and dissolves. The drug is carried into the gastrointestinal tract in the saliva.

Each of the product's excipients has precedent for use in pharmaceutical products approved by FDA, with the exception of erythritol. Erythritol is widely used in food as a sweetener. The CMC reviewer noted that the FDA has not made a determination regarding the GRAS status of erythritol, but that it is being considered by CFSAN, assuming a use of 13 grams/person/day. The CMC reviewers concluded at the low dose in Zuplenz, (b) (4) in the ondansetron 8 mg film strip, the erythritol component is acceptable without requiring additional pre-clinical data.

The applicant proposed a reduced testing plan for microbial limits – once per year on a regular production batch. The chemistry reviewers found this plan acceptable after they reviewed the applicant's response to an information request letter dated October 5, 2009, in which the applicant provided data to demonstrate that (b) (4)

The chemistry reviewers' recommendations for labeling included updating the dosage form to "Oral Soluble Film". They noted that Section 3 of the label should include shape, color, and imprinting. Section 11 of the label was found to include a number of inaccuracies, including wrong structural formula, incomplete excipient list (missing sucralose), and inaccurate expression of butylated hydroxytoluene, hydroxypropyl methylcellulose, (b) (4) and silicon dioxide. In addition, they noted that Section 16 of the label described storage conditions that were not consistent with the USP definition of controlled room temperature. Storage conditions should be revised to "Store at 20-25°C (68-77°F)" per the USP controlled room temperature definition".

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. No nonclinical study report was submitted in this NDA. The NDA relies on studies not conducted by or for the applicant. This NDA is supported by reference to the Agency's previous findings of safety and efficacy for the following products: Zofran Tablet (NDA 20103) and Zofran ODT (orally disintegrating tablet, NDA 20781). The applicant submitted published nonclinical studies to further support the product's safety.

5. Clinical Pharmacology/Biopharmaceutics

The applicant submitted two bioequivalence trials that compared Zuplenz to Zofran ODT in support of this 505(b)(2) application. Protocol OND/CR/020/08-09 studied fasting conditions and Protocol OND/CR/021/08-09 studied fed conditions, and both were conducted in healthy male and female volunteers. In addition, a single bioavailability study was conducted to demonstrate that the bioavailability of Zuplenz is similar when it is taken with or without water. Two pilot studies submitted for review were conducted to inform sample size calculations for the "pivotal" bioequivalence studies.

The applicant proposes two dosage strengths for marketing, 4 mg and 8 mg, but only conducted bioequivalence studies (comparing Zuplenz to Zofran ODT) for the 8 mg strength. The Biopharmaceutics reviewers from ONDQA noted in their review that a waiver of bioequivalence studies for the lower 4 mg strength of Zuplenz was justified based on the fact that the applicant had demonstrated that the dissolution characteristics of the product are not dependent on product strength. Both strengths are cut from bulk film product rolls of the same composition and method of manufacture. The products are dose proportional. Dissolution profiles of the 4 mg and 8 mg strengths of Zuplenz and Zofran ODT were demonstrated to be comparable.

The Clinical Pharmacology reviewers found that the two bioequivalence trials demonstrated that Zuplenz 8 mg is bioequivalent to Zofran ODT 8 mg under fasting and fed conditions. They examined results of the bioequivalence study that supported approval of the reference product Zofran ODT, which compared Zofran ODT vs. Zofran Tablets, and determined that there is no evidence to support that there are issues of "biocreep" in the current application.

The PK parameters for the fasting conditions bioequivalence trial, Protocol OND/CR/020/08-09, are summarized in the table below, which is reproduced from the CDTL review (Table 1 of the CDTL review). The CDTL states in her review, the "Mean Cmax and AUC for Zuplenz were about 8-9% lower than those for Zofran ODT. However, the 90% confidence intervals associated with the least square geometric mean ratios of Cmax and AUC fell within the bioequivalence criteria 80-125% (90%CI: 85.5-97.1% for Cmax and 87.7-95.9% for $AUC_{0-\infty}$)."

Table 1 Mean (S) PK parameters of Ondansetron after administration of Zuplenz 8mg (test) and Zofran 8 mg (reference) under fasting conditions (n=46)

PK Parameter (Units)	Ondansetron	
	Treatment A (Test)	Treatment B (Reference)
C_{max} (ng/mL)	37.282 (14.9177)	41.108 (17.2442)
AUC_{0-t} (ng.hr/mL)	216.269 (83.2883)	239.463 (100.0745)
$AUC_{0-\infty}$ (ng.hr/mL)	225.032 (88.2551)	250.673 (107.9654)
T_{max} (Hour)	1.33 (1.00, 4.00)	1.17 (0.67, 3.00)
$t_{1/2}$ (Hour)	4.673 (0.8491)	4.786 (1.1740)
Kel (1/hr)	0.154 (0.0356)	0.156 (0.0550)

*For T_{max} Median (Min, Max) are presented.

In the bioequivalence trial conducted under fed conditions, Protocol OND/CR/021/08-09, the 90% confidence interval associated with the least square geometric mean ratios of Cmax and AUC also fell within the bioequivalence criteria 80-125% (90% CI: 94.7-106.0% for Cmax and 89.2-98.6% for $AUC_{0-\infty}$).

The median time required for Zuplenz to dissolve on the tongue was measured in the bioequivalence studies and was 10.6 sec (range: 4.8-20.7 sec) and 10.3 sec (range: 4.2-17.5 sec) for the fasting and fed studies, respectively. These times were 3-4 seconds longer than the median oral disintegration time of Zofran ODT .

Protocol OND/CR/051/08-09, which evaluated the pharmacokinetics of the product administered with and without water demonstrated that similar bioavailability can be expected with either mode of administration. This is summarized in the table below, which is a reproduction of Table 3 from the CDTL review.

Table 2. Ratio of Least Squares Geometric Means of Treatment associated 90% CI of ratio

Treatment Comparison	Cmax (n=17)	AUC (n=17)	AUCinf (n=17)
A vs. C	103.38 (93.57, 114.21)	102.33 96.50, 108.51)	102.38 (96.31, 108.82)
B vs. C	106.28 (96.20, 117.43)	102.43 (96.60, 108.62)	101.93 (95.90, 108.35)
A vs. B	97.26 (88.03, 107.46)	99.90 (94.21, 105.93)	100.44 (94.49, 106.76)

A: Zuplenz administered without water
B: Zuplenz administered with water
C: Reference Product (Zofran ODT) administered without water

I concur with the Clinical Pharmacology reviewers that the data appear to support approval of Zuplenz for the proposed indications. However, inspection of the "pivotal" bioequivalence trial Protocol OND/CR/020/08-09 (site in (b) (4)) and the analytical site (in (b) (4)) could not be conducted due to a Travel Advisory issued by the Department of State for these regions in (b) (4) The CDTL states in her review the Division of Clinical Pharmacology 3 considered it acceptable to defer the inspection until it is safe to do so, approving the product in the interim. If the trial results were called into question at the site inspection, the CDTL notes that the FDA actions would include obtaining "a commitment to repeat the pivotal trial on an accelerated manner (i.e. protocol to be initiated within 6 months of notification by the FDA); up to and

including removal from the market if safety issues are identified that were previously not revealed to the Agency". I disagree with that proposed plan. If there is concern that the data upon inspection might be found unacceptable to support the NDA, the product should not be approved. Establishment of the safety and efficacy of the proposed product in this NDA hinges on the bioequivalence study that the Division of Clinical Pharmacology has determined needs to be inspected.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The clinical reviewer evaluated the clinical pharmacology studies submitted in this NDA and concluded that there were no clinical safety concerns that preclude approval and that the data appeared to demonstrate that Zuplenz ondansetron oral soluble film is bioequivalent to Zofran ODT. I concur that the overall benefit of Zuplenz appears to outweigh any risk associated with its use; however, the clinical pharmacology bioequivalence study is the foundation for this 505(b)(2), and the clinical pharmacology reviewers determined that it is critical to inspect the study site from one of the bioequivalence studies and the bioanalytical site. The sites are in (b) (4), and DSI was unable to inspect the sites before the action date for this NDA due to a Travel Advisory issued by the Department of State. Although Dr. Johnson initially recommended approval of Zuplenz 8 mg and 4 mg soluble film for the same indications and target populations as Zofran ODT, the product cannot be approved until 1) the clinical site inspections are conducted and found acceptable, and 2) product labeling has been finalized. She filed a memorandum on February 4, 2010, after her initial review, to document her revised recommendation for regulatory action, i.e. complete response. In that memorandum she also states that the pediatric plan proposed by the applicant in this NDA is not acceptable.

8. Safety

Dr. Johnson reviewed the safety data from the 5 open label pharmacokinetic studies submitted in this NDA, in addition to post-marketing safety data for ondansetron from the AERS database and the medical literature. Of the 134 healthy adult volunteers exposed to Zuplenz in these trials, 117 received a single 8 mg dose and 17 (13%) received two 8 mg doses separated by a 3 day washout period. The trials were designed as cross-over studies, so 133/134 subjects also were administered one 8 mg dose of Zofran ODT (the two products were separated by a 3-7 day washout). The majority of subjects were male (83%). In these134 subjects, 3 reported 4 adverse events: abdominal pain (2), vomiting (1), and an upper respiratory infection (1). There were no deaths, SAEs or discontinuations due to adverse events. There were elevations of transaminases, total bilirubin and eosinophils in the laboratory data. Dr. Johnson noted that hypersensitivity and hepatic abnormalities are found in the current ondansetron labels.

The population of healthy subjects studied in the trials that support this application were Asian (Indian) males with a mean BMI less than the average for the current US population (22.2 +/- 2.2 kg/m2). Dr. Johnson concluded that because of the lower BMIs the safety results from the pharmacokinetic studies "cannot be considered generalizable to the US population". The lower BMI's would be anticipated to result in higher exposures and increased risk for adverse events in these bioequivalence studies. Exploration of the pharmacokinetic parameters observed in the bioequivalence studies that supported the approval of Zofran ODT reveal that the AUC and Cmax observed in those studies were numerically lower than observed with Zofran ODT in the bioequivalence trials submitted in this application. Cross-study comparisons, however, are of limited validity and exploratory in nature. The bioequivalence of Zuplenz to the approved Zofran ODT product indicates that Zuplenz will have a comparable safety profile to the approved and marketed Zofran ODT.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application. The product is not an NME.

10. Pediatrics

In this 505 (b)(2) application the applicant references the FDA's previous findings of safety and efficacy for the Zofran Tablet (NDA 20103) and Zofran ODT (orally disintegrating tablet, NDA 20781). The bioequivalence study submitted in this application compared Zuplenz to Zofran ODT. The proposed doses of Zuplenz, 4 mg and 8 mg, are the same doses marketed for the referenced Zofran products, and the proposed Zuplenz indications are the same labeled indications as those products. The Zofran ODT product label includes instructions for pediatric dosing for the moderately emetogenic cancer chemotherapy indication (CINV-MEC) only. For that indication the dosing instructions for children ages 12 years and older are the same as for adults. Additional dosing instructions extend down to children age 4 years for CINV-MEC. (b) (4)

The proposed product is a new dosage form. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The applicant proposes to label Zuplenz for the same populations as the reference product, Zofran ODT, which includes a single pediatric indication CINV-MEC for children ages 4 years and older. In this NDA the applicant proposed:

- a partial waiver of the requirements to submit pediatric data in children less than 4 years; (The reasons given by the applicant for this proposal were: a) the applicant believes there are safety concerns with use of an orally dissolving film in children

this age since ondansetron is dosed mg/kg , which they say can't be accomplished with a film; b) Zuplenz does not represent a meaningful therapeutic benefit over existing therapies in this young patient population since an intravenous formulation of ondansetron exists; c) administration of Zuplenz to young children could entail risk related to adults placing their fingers in children's mouths to put the film on the tongue; d) a child may remove the film before it dissolves or drool it out, negatively impacting efficacy, and e) the applicant stated that the incidence of PONV and CINV is low in children less than 4 years of age.)

- (b) (4)
- a deferral (b) (4) in children between the ages of (b) (4) years; (The background information provided by the applicant suggests that the deferral refers to the PONV indication.) and
- (b) (4)

The documents submitted by the applicant to address their pediatric development plan request waivers, partial waivers and deferrals by age group and not by specific indication (see above). The submitted supporting information does specifically address indications for each age group, with the exception of radiotherapy, on which the applicant is silent.

The Division consulted the Pediatric and Maternal Health Staff during this review. The application was discussed at a PeRC meeting on January 6, 2010. The reviewers noted that the oral soluble film formulation might be useful in the pediatric population, since it does not require swallowing a capsule/tablet or holding a tablet in the mouth. The summary recommendations from the PeRC meeting follow:

1. Prevention of nausea and vomiting associated with initial and repeat courses of Highly Emetogenic Chemotherapy (HEC)

The PeRC agreed with the Division to grant a partial waiver for 0 to <4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s). The PeRC also agreed to the deferral of studies for pediatric patients 4 -17 years of age until a PK and adequately controlled efficacy and safety studies are conducted (the Division may consider an adequately powered dose-response study to support efficacy).

2. Prevention of nausea and vomiting associated with initial and repeat courses of Moderately Emetogenic Chemotherapy (MEC)

The PeRC agreed with the Division to grant a partial waiver for 0 to <4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for

pediatric patients in this/these subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s). The PeRC also agreed with the Division that the product is appropriately labeled for use in patients 4 years to 17 years of age based on Zofran Orally Disintegrating Tablets labeling.

3. Prevention of nausea and vomiting associated with Radiotherapy

The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

4. Prevention of postoperative nausea and vomiting (PONV)

The PeRC agreed with the Division to the deferral of studies for pediatric patients birth to 17 years until adequately controlled efficacy and safety studies are conducted (the Division may consider an adequately powered dose-response study to support efficacy). Please note that an age-appropriate formulation would be needed for the younger age group.

The indication for CINV-MEC can be given to Zuplenz for age groups 4-11 years and 12-17 years since Zofran ODT is indicated for these age groups in CINV-MEC. .

11. Other Relevant Regulatory Issues

The Clinical Pharmacology reviewers selected two sites for inspection by Division of Scientific Investigations (DSI) – the bioequivalence study site in India and the bioanalytical site in India. Unfortunately, due to a Department of State Travel Advisory for India, those site inspections could not be scheduled by DSI during this review cycle. Satisfactory results of the inspections are necessary for final approval of this NDA.

Dr. Johnson noted in her review that the applicant certified there were no financial arrangements with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. No investigators disclosed a proprietary interest in Zuplenz or a significant equity interest in the applicant.

12. Labeling

The DMEPA reviewers found the proposed proprietary name, Zuplenz, acceptable in the initial review, dated July 20, 2009, and again after a re-evaluation December 30, 2009 .

DDMAC also found the name acceptable from a promotional perspective in reviews dated March 5, 2009 and November 4, 2009. DDMAC provided a labeling review of the proposed carton and container labels and recommended that labels be revised to present the dosage strength in direct conjunction and in equal prominence with the display of the dosage form.. In addition, DDMAC raised concern about the text, (b) (4) because of vagueness and overstatement of efficacy. They also recommended that the Patient

Counseling Information in the package insert be revised from [redacted] to "…then swallow with saliva".

Labeling negotiations had not been completed at the time of the regulatory action for this NDA.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Complete Response

- Risk Benefit Assessment – I concur with the CDTL that the risk and benefit characteristics of Zuplenz appear similar to those of the approved and currently marketed reference ondansetron product, Zofran ODT. The clinical pharmacology reviewers have determined that the site of one of the key bioequivalence studies and the bioanalytical site need to be inspected. Those sites could not be inspected during this review cycle because they are located in [redacted] and the State Department issued a Travel Advisory for the region. Satisfactory results of the site inspections are necessary for final product approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None

- Recommendation for other Postmarketing Requirements and Commitments
  The product will not be approved this cycle. When the inspections can be scheduled (in light of the current Department of State Travel Advisory for [redacted]) and conducted, and it has been determined that the product can be approved, pediatric studies will be required as described in the PeRC recommendations in Section 10 of this review.

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

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

/s/

DONNA J GRIEBEL
02/05/2010

Cross-Discipline Team Leader Review

Date	February 4, 2010
From	Sue-Chih Lee, Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP3
Subject	Cross-Discipline Team Leader Review
NDA/ BLA #	NDA 22-524
Applicant	Par Pharmaceuticals, Inc.
Date of Submission & Receipt	April 7, 2009
PDUFA Goal Date	February 7, 2010
Proprietary Name / Established (USAN) names	Zuplenz® Ondansetron
Dosage forms / Strength	▪ Oral Soluble Films, 4 mg & 8 mg
Proposed Indication	Adults: • Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 (CINV-HEC) • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC) • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV) • Prevention of postoperative nausea and/or vomiting (PONV): As with other antiemetics, routine prophylaxis in not recommended for patients in whom there is little expectation that nausea and/or vomiting must be avoided postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, Zuplenz is recommended even where the incidence of postoperative nausea and/or vomiting is low. Pediatrics: • Prevention of CINV-MEC for patients ≥ 4 years of age • Safety and effectiveness of Zuplenz for other indications have not been established in any age group of pediatric patients
Recommended Action:	Complete Response (CR) under 21 CFR 314 Remaining issues: inspection for the pivotal BE study, package insert and pediatric plan

Table of Contents

1. Introduction

This NDA, received April 7, 2009, is an original application for a new oral dosage form of ondansetron, namely an oral soluble film to be placed on the tongue and allowed to be dissolved there in a short time period (< 30 seconds). It is a 505(b)(2) submission using GSK's Zofran ODT (and Zofran Tablets) as the reference products. As with Zofran ODT, the proposed product also has two strengths, 4 mg and 8mg. The applicant is seeking all the indications that have been approved for Zofran ODT, which include prevention of CINV-HEC, CINV-MEC, RINV, and PONV in adults, and CINV-MEC only for pediatric patients 4 years and older.

The proposed dosing regimens for the above indications are similar to the approved regimens for Zofran ODT as shown below.

Proposed Adult Indications:

- CINV-HEC: 24 mg given successively as three 8 mg oral soluble film administered 30 minutes before the start of single-day highly emetogenic chemotherapy
- MEC CINV: one 8-mg oral soluble film given twice a day
- Radiotherapy: one 8-mg oral soluble film given 3 times a day
- PONV: 16 mg given successively as two 8 mg oral soluble film 1 hour before induction of anesthesia

Proposed Pediatric Indications:

CINV-MEC (this indication only):

- ≥12 years of age: One 8-mg oral soluble film given twice a day
- 4 to < 12 years of age: One 4-mg film given 3 times a day prior to 30 minutes before the start of chemo, with subsequent doses 4 and 8 hours after the first dose. One 4-mg film should be administered 3 times a day for 1 to 2 days after completion of chemotherapy.

2. Background

Ondansetron is a 5-HT_3 receptor antagonist. Serotonin 5-HT_3 receptors are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not clear whether the antiemetic action of ondansetron is mediated centrally, peripherally, or both.

2.1 Regulatory History

2.1.1 Ondansetron Drug Products

Ondansetron for antiemetic use was first approved in 1991 as Zofran injection. Currently, there are various dosage forms available in the U.S. as listed below. For all these dosage forms, generic products are also available in the market.

Innovator's ondansetron products:

(1) Zofran injection (NDA 20-007; approved in 1991): 2 mg base/mL
(2) Zofran tablets (NDA 20-103; approved in 1992): 4 mg, 8mg & 24mg
(3) Zofran and Dextrose in plastic container (NDA 20-403; approved in 1995): 0.64 mg base/mL
(4) Zofran oral Solution (NDA 20-605; approved 1997): 4 mg base/5 mL
(5) Zofran ODT (NDA 20-781; approved in 1999): 4 mg & 8mg

The applicant's proposed product is a new dosage form (oral soluble film).

2.1.2 Regulatory History of Zuplenz

Two meetings were held between the sponsor and the Agency during the development of the product. In the Pre-IND (PIND# (b) (4)) meeting held on July 2, 2008, there was agreement that no additional nonclinical studies were necessary. However, there were concerns whether the NDA could come in as a 505(b)(2) application because it might be similar to an ODT and 505(j) might be the path forward. As requested by the Agency, the applicant submitted CMC information on the product and manufacturing process. Subsequently, the applicant was informed in a correspondence dated September 23, 2008, that a 505(b)(2) application would be appropriate. In a pre-NDA meeting held on March 26, 2009, the applicant was advised of contacting the Office of Compliance for issues related to process validation plans for the manufacture of the product. In addition, the sponsor was advised of providing safety data for each pharmacokinetics/bioavailability study.

2.2 Current Submission

The NDA submission was dated and received on April 7, 2009. It was classified as a standard submission with a PDUFA deadline of February 7, 2010. This is a 505(b)(2) NDA.

There are no safety and efficacy trials conducted for the approval of the proposed product. The bridging studies conducted are Protocol OND/CR/020/08-09 and Protocol OND/CR/021/08-09, using Zofran ODT as the reference product in both studies. Therefore,

the applicant is relying on the safety and efficacy findings of Zofran ODT which in turn relies on the clinical trial safety and efficacy findings of Zofran tablets. As such, both Zofran ODT (NDA 20-781) and Zofran tablets (NDA 20-103) are considered the reference products for this application.

In addition to the bioequivalence studies mentioned above, the sponsor also conducted a study to demonstrate similar bioavailability when Zuplenz was taken with or without water to allow clinical use in either condition. Although there are no new nonclinical studies, the applicant provided relevant literature information in the application. For CMC, the applicant references DMF (b) (4) for information related to the drug substance (ondansetron base) and provided detailed information on the drug product.

The three pivotal pharmacokinetics/bioavailability studies are listed below. The applicant provided two additional pilot studies, which were conducted mainly to inform pharmacokinetic variability for sample size calculations.

(1) Protocol OND/CR/020/08-09: "An open-label randomized, single oral dose, two way crossover bioequivalence study to compare Ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) in 48 healthy, adult, human study participants under fasting conditions"

- This is a bridging study to link the proposed product to Zofran ODT (the reference product) for the 8 mg strength by establishing bioequivalence under fasting conditions. As bioequivalence studies under fasting conditions are generally more discriminating in formulation differences, this study is considered the primary bridging study for the application.

(2) Protocol OND/CR/021/08-09: "An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg (Manufactured by MonoSol Rx, USA) with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] (Manufactured by Cardinal Health Blagrove, Swindon, Wiltshire, UK, SN58RU for Glaxo SmithKline, Research Triangle Park, NC 27709, Made in England) in 48 healthy, adult, human study participants under fed conditions"

- The above study establishes the bioequivalence of the proposed product to the reference product for the 8 mg strength under fed conditions.

(3) Protocol OND/CR/051/08-09: "An open-label randomized, single oral dose, three way crossover comparative water effect bioavailability study to compare ondansetron Orally Dissolving Filmstrip (ODFS) 8mg (MonoSol Rx, USA) with and without water with Zofran Orally Dissolving Tablets (ODT®) (Containing Ondansetron 8 mg) (Glaxo SmithKline, USA) without water in 18 adult, healthy human study participants under fasting conditions"

- This study showed that bioavailability of ondansetron was similar whether the film was taken with or without water.

There are no in vivo bridging studies for the 4 mg strength. The ONDQA Biopharm Team found this acceptable as biowaiver can be granted for the lower strength.

No Advisory Committee meeting was convened to discuss this application.

2.3 NDA Review documents

The relevant review disciplines have all written review documents as listed below:

- Clinical Pharmacology Review by Insook Kim, dated February 1, 2010
- Clinical Reviews by Tamara Johnson, dated December 22, 2009, and February 4, 2010
- PMHS review by Amy Taylor dated July 21 and December 23, 2009
- Pharm/Tox review by Charles Wu dated December 11, 2009
- ONDQA Biopharm review by Houda Mahayni dated September 10, 2009
- CMC Review by Bogdan Kurtyka dated December 15, 2009
- DMEPA Reviews by Lori Cantin:
  - Proprietary Name Review, dated July 20 and December 30, 2009 (proposed name acceptable)
  - Labeling Review, dated December 30, 2009 (different color for strengths on carton)
- DDMAC Labeling Review by Kathleen Klemm, dated January 20, 2010
- SEALD Labeling Review by Debbie Beitzell, dated January 20, 2010

These reviews should be consulted for more specific details of the application.

This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

3. CMC

The reader is referred to the Drug Product and Drug Substance Review by Dr. Bogdan Kurtyka dated December 15, 2009, for complete information.

3.1 Review Summary

Overview of Drug Substance (DS):
Zuplenz oral soluble film contains ondansetron base as the drug substance. Ondansetron is controlled by the USP monograph. The applicant references DMF (b) (4) for details on the description, characterization, manufacture, packaging, quality control testing, and stability of ondansetron. The Letter of Authorization is provided in the application. DMF (b) (4) was last reviewed on 23-OCT-2006 (review #5) and found adequate to support ANDA 78-139 (orally disintegrating tablets with the same amount of drug substance as in the drug product under review). Since the last review, the DMF has not been updated.

Overview of Drug Product (DP):
The drug product has been classified as "oral soluble film." The applicant originally proposed a name for the dosage form as "orally dissolving film strip," which was rejected by ONDQA.

The application describes manufacturing and controls of two distinct strengths – 4 mg and 8 mg. The two strengths are manufactured by the same process. (b) (4) [redacted]
Different strengths come from different surface areas of the film with the higher strength (8mg) having the surface area twice as large as the lower strength (4mg). The specification of the drug product includes appearance, identification, assay, and content uniformity of active ingredients, dissolution, impurities, moisture, and microbial limits.

The application includes results of 12 months long-term stability data. The applicant has proposed a 24 month expiration dating period when stored at controlled room conditions. The submitted data support the proposed expiration dating period.

Packaging:
Each dose of the drug product is individually packaged (b) (4) [redacted] The product does not move within the primary pouch minimizing the possibility of shipping damage to the product. The container/closure system is adequate to protect the drug product.

3.2 Final Recommendation

The CMC section of the application is acceptable provided that a mutual agreement on the label language can be reached.

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of Zuplenz over the proposed expiration dating period (24 months) when stored as labeled. Facilities are in compliance with cGMP. However, there are many labeling issues (e.g., incorrect structural formula of the drug substance, incomplete list of ingredients, shape and color of dosage form unidentified, and storage conditions not conforming to USP definition) which need to be resolved before approval action can be taken.

4. Nonclinical Pharmacology/Toxicology

No new studies were conducted by the applicant. Instead, the applicant conducted a literature search and submitted relevant articles and their summaries. The information provided appears to be consistent with what is already included in the approved Zofran product label. The discipline is not recommending any revision to the proposed label. The reader is referred to the Pharm/Tox Review by Dr. Charles Wu dated December 11, 2009, for complete information.

4.1 Review Summary

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-HT_3 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. Ondansetron is metabolized by multiple P450 enzymes, including CPY3A4, CYP2D6 and CYP1A2. Oral repeat dose toxicological studies 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 the highest proposed human dosage of 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.

4.2 Final Recommendation

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology and Biopharmaceutics Review by Dr. Insook Kim dated February 1, 2010, for complete information. The review concludes that, based on the data provided in the NDA, Zuplenz is bioequivalent to Zofran ODT of the same strength under fed or fasting conditions and can be given with or without water. However, DSI inspection of the pivotal BE study is still pending.

5.1 Review Summary

The studies reviewed by Dr. Insook Kim and her conclusions are summarized below:

The pivotal bioequivalence study (Protocol OND/CR/020/08-09; Study 01905/08-09) is titled "*An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] in 48 healthy, adult, human study participants under fasting conditions*."

A DSI inspection request (see Attachment 1 on Page 18) was sent on June 4, 2009, by Ms. Frances Fahnbulleh (RPM of DGP) through Dr. E. Dennis Bashaw (Division Director of Clinical Pharmacology 3) to Associate Director of Bioequivalence, Division of Scientific Investigations to inspect the clinical site (b) (4) and analytical site (b) (4) of the above study.

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
01905/08-09	(b) (4)	

The review of the study report determines that Zuplenz 8 mg (Test) is bioequivalent to Zofran ODT 8 mg (Reference) administered under fasting conditions. However, the DSI inspection is pending due to travel advisory against visit to the above regions in (b) (4).

The PK parameters of this bioequivalence study are given in Table 1. Mean Cmax and AUC for Zuplenz was about 8-9% lower than those for Zofran ODT. However, the 90% confidence intervals associated with the least square geometric mean ratios of Cmax and AUC fell within the bioequivalence criteria 80-125% (90%CI: 85.5-97.1% for Cmax and 87.7-95.9% for $AUC_{0-\infty}$).

Biocreep is determined not to be an issue after examining the bioequivalence study results for Zofran ODT vs. Zofran Tablets (Table 2) as documented in the Clinical Pharmacology and Biopharmaceutics review of NDA 20-781 by Dr. Alfredo R. Sancho dated July 29, 1998.

Table 1. Mean (SD) PK parameters of Ondansetron after administration of Zuplenz 8mg (test) and Zofran 8 mg (reference) under fasting conditions (n=46)

PK Parameter (Units)	Ondansetron	
	Treatment A (Test)	Treatment B (Reference)
C_{max} (ng/mL)	37.282 (14.9177)	41.108 (17.2442)
AUC_{0-t} (ng.hr/mL)	216.269 (83.2883)	239.463 (100.0745)
$AUC_{0-\infty}$ (ng.hr/mL)	225.032 (88.2551)	250.673 (107.9654)
T_{max} (Hour)	1.33 (1.00, 4.00)	1.17 (0.67, 3.00)
$t_{1/2}$ (Hour)	4.673 (0.8491)	4.786 (1.1740)
Kel (1/hr)	0.154 (0.0356)	0.156 (0.0550)

*For T_{max} Median (Min, Max) are presented.

Table 2. Geometric Mean Ratios (and the 90% CI) of Cmax and AUC of Zofran ODT 8 mg to Zofran tablet 8 mg

Ratio (90% CI)	Test 8 mg w/o	Test 8mg w/ water
Cmax	1.03 (0.98-1.09)	0.96 (0.91-1.01)
$AUC_{0-\infty}$	1.03 (0.99-1.08)	1.01 (0.97-1.06)

*Adapted from Clinical Pharmacology and Biopharmaceutics Review of NDA 20-781 dated July 29, 1998 by Dr. Alfredo R. Sancho.

The sponsor also conducted a study (Protocol OND/CR/021/08-09) to demonstrate that Zuplenz 8 mg is bioequivalent to Zofran ODT 8 mg administered under fed conditions. The 90% confidence interval associated with the least square geometric mean ratios of Cmax and AUC fell within the bioequivalence criteria 80-125% (90% CI: 94.7-106.0% for Cmax and 89.2-98.6% for $AUC_{0-\infty}$).

In addition, Zuplenz can be administered with or without water as either mode of administration resulted in similar bioavailabilty (Table 3; Protocol OND/CR/051/08-09).

Table 3. Ratio of Least Squares Geometric Means of Treatment associated 90% CI of ratio

Treatment Comparison	Cmax (n=17)	AUCt (n=17)	AUCinf (n=17)
A vs. C	103.38 (93.57, 114.21)	102.33 96.50, 108.51)	102.38 (96.31, 108.82)
B vs. C	106.28 (96.20, 117.43)	102.43 (96.60, 108.62)	101.93 (95.90, 108.35)
A vs. B	97.26 (88.03, 107.46)	99.90 (94.21, 105.93)	100.44 (94.49, 106.76)

A: Zuplenz administered without water
B: Zuplenz administered with water
C: Reference Product (Zofran ODT) administered without water

It is noted that, as observed previously with Zofran products, the systemic exposure (AUC) to ondansetron was more than 50% higher in female subjects than in male subjects following administration of Zuplenz.
The time for Zuplenz and Zofran ODT to dissolve on the tongue was measured in the two bioequivalence studies. The median times it took to dissolve Zuplenz on the tongue were 10.6 sec (range: 4.8-20.7 sec) and 10.3 sec (range: 4.2-17.5 sec) for the fasting and fed studies, respectively, which were 3-4 seconds longer than the median oral disintegration time of Zofran ODT .

No bioequivalence study was conducted for Zuplenz 4 mg. This is acceptable as a biowaiver for this lower strength was granted by the ONDQA based on the reasons described below. (See Biopharmaceutics Review by Dr. Houda Mahayni dated September 10, 2009 for details).

(1) The formulation for the 4mg strength is the same as that for the 8mg strength. The only difference is the film size. Thus, the two strengths are considered proportionally similar.

(2) The comparative dissolution profiles for the 4 mg and 8 mg strengths met the criteria for similarity.

Conclusion: Based on the data provided in the NDA, Zuplenz is bioequivalent to Zofran ODT of the same strength under fed or fasting conditions and can be given with or without water.

5.2 Final Recommendation

From a clinical pharmacology perspective, the application may be granted an approval with specific conditions.

Due to the travel advisory, DSI inspections of the clinical and analytical sites for the pivotal bioequivalence study (Protocol OND/CR/020/08-09; Study 01905/08-09) has not been conducted. As this is a unique situation and the sites had good records, the Division of Clinical Pharmacology 3 considers it acceptable to defer the inspection until it is safe to do so. In the interim, the application may be approved. However, as the inspection is only deferred and not waived the sponsor should be aware that should the subsequent inspections reveal problems with the study sufficient to call the results into question then the sponsor agrees and commits to work with the Agency to expeditiously resolve this matter. This could involve revision of the label to remove data and/or restrict use of the product; a commitment to repeat the pivotal trial on an accelerated manner (i.e. protocol to be initiated within 6 months of notification by the FDA); up to and including removal from the market if safety issues are identified that were previously not revealed to the Agency or any combination of these options at the FDA's discretion.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because the proposed product is not an antimicrobial agent.

7. Clinical - Efficacy

7.1 Overview

This is a 505(b)(2) submission. No clinical trials were conducted to demonstrate the efficacy of the proposed product. Rather, clinical efficacy is inferred through establishing bioequivalence of the proposed product to the reference product, Zofran ODT (see Section 5 Clinical Pharmacology/Biopharmaceutics of this document and the Clinical Reviews by Dr. Tamara Johnson dated December 22, 2009 and February 4, 2010).

7.2 Final Recommendation

Dr. Johnson indicated in her review of February 4, 2010, that approval of this application is contingent on the following conditions:

(1) inspection of the clinical and analytical sites for the pivotal bioequivalence study is satisfactory,
(2) a mutual agreement on label language can be reached, and
(3) a revised pediatric plan is submitted which conforms to the PeRC recommendations.

8. Clinical - Safety

The reader is referred to the Clinical Review by Dr. Tamara Johnson dated December 22, 2009 for complete information.

8.1 Review Summary

This is a 505(b)(2) submission. No clinical trials were conducted to demonstrate the safety of the proposed product. The safety of ZUPLENZ was examined from results of five open-label pharmacokinetic studies conducted to evaluate bioequivalence, the medical literature, and the AERS database system. Of the 134 healthy adult volunteers exposed to the ZUPLENZ 8mg film, three subjects (2%) reported 4 adverse events (AE); abdominal pain (2), vomiting (1), and an upper respiratory infection (1). All AEs were mild and resolved without sequelae. There were no deaths, serious AEs, or discontinuations due to AE. Although, there were no sustained changes in serum or hematology laboratory values in any healthy subject administered ZUPLENZ, elevations in liver transaminases, total bilirubin, and eosinophils were demonstrated. While hepatic abnormalities may be expected with ondansetron products, this reviewer notes the elevated eosinophil levels seen in 6 (4.3%) healthy volunteers without associated clinical manifestations of immune reaction. Due to study design issues, this effect could not be attributed specifically to ZUPLENZ or ZOFRAN® ODT. The risk of hypersensitivity is, however, already included in the labeling for all ondansetron products. ZUPLENZ is not approved in foreign markets; therefore, no postmarketing experience is available.

8.2 Final Recommendation

An Approval Action is contingent on the satisfactory results of the inspection for the pivotal BE study.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

By demonstrating bioequivalence of Zuplenz to Zofran ODT, the Applicant will receive the same pediatric indication as Zofran ODT (i.e., CINV-MEC for patients aged 4 years and older).

The Applicant submitted a pediatric plan dated July 21, 2009. In that proposed plan, the Applicant apparently mainly addressed the indication of PONV and requested waiver for patients aged < 4 years or ≥ 12 years and a deferral for patients aged 4-11 years. (b) (4)

Dr. Taylor concluded that the Applicant's assertion that PONV is rare is not supported by evidence. In addition, the Applicant's contention that oral soluble film can't be tailored to weight based (mg/kg) dosing does not preclude them from PREA requirements since development of an age appropriate formulation is part of the requirements. In general, CINV should be studied down to 1 month and PONV down to newborn. For RINV, Dr. Taylor agrees that a full waiver appears reasonable as the need for anti-emetics due to RINV in pediatric patients is low.

The application was presented to the Pediatric Research Committee (PeRC) on January 6, 2010. The committee's recommendation is included in Section 13.4 of this document.

11. Other Relevant Regulatory Issues

11.1 Division of Scientific Investigations (DSI) audits

A DSI inspection request was sent on June 4, 2009, by Ms. Frances Fahnbulleh (RPM of DGP) through Dr. E. Dennis Bashaw (Division Direcotr of Clinical Pharmacology 3) to Associate Director of Bioequivalence, Division of Scientific Investigations. This request is for the inspection of the clinical site (b) (4) and analytical site (b) (4) of the pivotal bioequivalence study (Protocol OND/CR/020/08-09; Study 01905/08-09) titled "An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] in 48 healthy, adult, human study participants under fasting conditions." (See Attachment 1).

Due to the travel advisory against visit to the above regions in (b) (4), the DSI inspection is still pending. DSI will re-evaluate the situation on February 1, 2010.

According to Dr. Bogdan Kurtyka, reviewing Chemist of ONDQA, all CMC facilities for the drug substance and drug product are in compliance with cGMP.

12. Labeling

12.1 Proprietary name

In two separate reviews, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proprietary name of "Zuplenz" was acceptable as it was not vulnerable to name confusion that could lead to medication errors. Please see DMEPA Proprietary Name Reviews dated July 20, 2009 and December 20, 2009 by Lori Cantin, RPh, for complete information.

12.2 Division of Drug Marketing, Advertising, and Communications (DDMAC) Comments

- The Division of Drug Marketing, Advertising and Communications (DDMAC) had no objection to the proposed trade name of Zuplenz from a promotional perspective as documented in the review by Kathleen Klemm dated January 20, 2010. Dr. Klemm has additional recommendations on labels as described below.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The Applicant was informed that their proposed labeling as submitted on January 11, 2010, is in a different format than the one submitted in the original application dated April 7, 2009. Currently, all disciplines have revised the label using the April 7, 2009, version. The most notable revisions so far from SEALD, DDMAC and DMEPA are summarized below. It should be noted that internal labeling discussions are still ongoing.

Physician Labeling:

SEALD comments:
- Contraindications (Section 4 of Label): If the drug is contraindicated in patients with hypersensitivities, the known hypersensitivities must be stated.
- Pediatric Use (Section 8.3 of Label): Indications NOT approved for pediatric population need to be listed.
- PATIENT COUNSELING INFORMATION (Section 17 of Label): This section must reference FDA-approved patient labeling.

DDMAC comments:
- Differentiate the product from the active ingredient as appropriate. (This comment applies throughout the label.)
- Important Administration Instruction (Section 2.6 of Label): To state that the product will dissolve in seconds is vague and may be used promotionally to overstate the efficacy of the product. Additional context such as time range for the film to dissolve should be considered.

- PATIENT COUNSELING INFORMATION (Section 17 of Label): This section should also include information on most important safety issues.

Carton and Container Labeling:

DMEPA Comments:

- The colors for presenting the 4 mg and 8mg strengths as proposed by the Applicant are the same colors as the trade dress (blue and green). Using the same color for the trade dress as well as for displaying the strength minimizes the effect of color to differentiate the two strengths. DMEPA recommends that the label be revised to ensure the two strengths are well differentiated by the use of unique colors that are not present in the trade dress.

- The prominence of the established name is not commensurate with the proprietary name. The established name should be at least ½ as large as the proprietary name. Other factors such as typography, layout, and contrast should be taken into account to ensure the appropriate prominence of the established name.

- The carton label should reflect the correct dosage form of the product. (b) (4) should be stated as "10 pouches each containing 1 soluble film."

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The recommendations from individual review disciplines *based on the respective information reviewed* are as follows:

- Clinical Pharmacology: The acceptability of the pivotal bioequivalence study is contingent on the DSI inspection results for the clinical and analytical sites of the study. Approval with specific conditions (see Section 5.2) is deemed acceptable due to the unique circumstances (travel advisory) causing the delay in DSI inspections and the good records of the sites, if there are no other pending issues.

- Clinical: Complete Response

- Pharm/Tox: Approval

- ONDQA: Approval only after labeling issues are resolved

CDTL Recommendation for Regulatory Action:
As CDTL for this application, I agree with the Division of Gastroenterology Product's decision for a Complete Response (CR) action. DSI inspection of the clinical and analytical sites for the pivotal bioequivalence study is necessary to confirm the validity of the study. Since the inspection cannot be waived and a re-evaluation of the travel advisory status by the

Agency is imminent, it is most appropriate to take a CR action. As such, labeling negotiation process has not been initiated.

13.2 Risk Benefit Assessment

The risk and benefit characteristics appear in general similar to those of already marketed Zofran ODT products for the treatment of CINV, PONV and RINV. The product has a favorable risk/benefit profile.

The reader is referred to the Clinical Review by Dr. Tamara Johnson dated December 22, 2009 for complete information.

The availability of ZUPLENZ ondansetron oral soluble film would provide an additional method of administration for patients suffering from nausea and vomiting who may have difficulty swallowing a whole tablet or any moderate amount of liquid. This new formulation provides the equivalent amount of the active ingredient as ZOFRAN® ODT, but may find better acceptance in settings where patients are less tolerant of holding a tablet in the mouth (e.g. pediatric patients). To this consideration, further study of this formulation in pediatrics patients is warranted, and required by the Pediatric Research Equity Act (PREA) (21 USC 355c).

A review for safety issues specific to ZUPLENZ did not uncover significant concerns over those already documented within the numerous ondansetron product labels. There were few adverse events and none were determined to be related to ondansetron. Theoretical concern remains regarding elevated eosinophil levels seen in 6 (4.3%) of healthy volunteers, however, no clinical manifestations of immune reaction were reported. Due to study design issues, the effect could not be attributed specifically to ZUPLENZ or to ZOFRAN® ODT. As the risk of hypersensitivity is already included in the labeling for all ondansetron products, only postmarketing monitoring appears to be needed at this time. Therefore, based on materials presented in this application, the overall benefit of ZUPLENZ appears to outweigh any risk associated with use.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No REMS is recommended with this application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

This application will receive a Complete Response action during this review cycle. However, postmarketing required pediatric studies have been discussed within the review team and in a PeRC meeting.

The proposed product is a new dosage form. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain

an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

A PeRC meeting for Suplenz was held on January 6, 2010. Waiver and required pediatric studies with development of age appropriate formulations under PREA are recommended as follows:

(1) CINV-HEC:

Prior to the PeRC meeting, DGP recommended a partial waiver for pediatric patients 0 to <1 month because there are too few children with disease/condition to study and a deferral for patients <1 month to 17 years because additional adult safety or efficacy data is needed.

PeRC recommendations:

- ≤ 4 years of age: waiver (These patients have an IV line. In this pediatric subpopulation, the proposed product does not represent a meaningful therapeutic benefit over existing therapies AND is not likely to be used in a substantial number of patients.)
- > 4 years of age: Required are PK and adequately controlled efficacy and safety studies, which may be designed as adequately powered dose response studies. (No oral ondansetron products are available at this time). Deferral of these studies is granted.

(2) CINV-MEC:

Prior to the PeRC meeting, DGP recommended a partial waiver for pediatric patients 0 to <1 month because there are too few children with disease/condition to study and a deferral for patients >1 month to <4 years because additional safety and efficacy data is needed and that the product will have an indication for patients from 4 years to 17 years when the NDA is approved.

PeRC recommendations:

- ≤ 4 years of age: waiver (These patients have an IV line. In this pediatric subpopulation, the proposed product does not represent a meaningful therapeutic benefit over existing therapies AND is not likely to be used in a substantial number of patients.)
- > 4 years of age: The indication will be granted when the NDA is approved since Zofran ODT already has this indication

(3) RINV:

Prior to the PeRC meeting, DGP recommended full pediatric waiver because there are too few children with disease/condition to study.

PeRC recommendations:

- Full pediatric waiver because studies would be impossible or highly impracticable as there are too few children with disease/condition to study.

(4) PONV:

Prior to the PeRC meeting, DGP recommended a deferral of studies for patients ages birth to 17 years because additional safety or efficacy data are needed.

PeRC recommendations:

- The PeRC agreed with DGP. Deferral of PK and adequately controlled efficacy and safety studies is granted. An age-appropriate oral formulation would be needed for the younger age group. (IV ondansetron product is available for pediatric patients aged 1 month and older.)

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

No PMR studies other than the pediatric studies required under PREA are considered necessary at this time.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

No PMC studies are considered necessary at this time.

13.7 Recommended Comments to Applicant

The following comments should be communicated to the Applicant:

A Complete Response action is taken. Due to travel advisory, the Agency has postponed the inspection of the clinical site (b) (4) and analytical site (b) (4) for the pivotal bioequivalence study (Protocol OND/CR/020/08-09; Study 01905/08-09) titled "*An open-label randomized, single oral dose, two way crossover bioequivalence study to compare ondansetron Orally Dissolving FilmStrip (ODFS) 8mg with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] in 48 healthy, adult, human study participants under fasting conditions*." This is a pending issue since satisfactory inspection of these sites is necessary for final approval of the product. The sponsor should also be notified of two other pending issues, i.e., both label and pediatric plan need to be revised.

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DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: May 19, 2009

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3, OCP/OTS

FROM: Frances Fahnbulleh, Regulatory Health Project Manager, HFD-180

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-524
ZUPLENZ (Ondansetron) Orally Dissolving Film Strip, 4mg & 8mg

International Inspections:

We have requested an international inspection because:

_____ There is a lack of domestic data that solely supports approval;

__X__ Other (please explain): All BE studies were conducted in (b) (4)

The following studies/sites pivotal to approval have been identified for inspection:

Study Title: An Open-Label Randomized, Single Oral Dose, Two Way Crossover Bioequivalence Study To Compare Ondansetron Orally Dissolving Film Strip (ODFS) 8mg with Zofran Orally Disintegrating Tablets [ODT® (Containing Ondansetron 8 mg)] in 48 Healthy, Adult, Human Study Participants Under Fasting Conditions.

NDA 22-524
Page 2NDA xxx
Request for Biopharmaceutical Inspection
Page 3

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
01905/08-09	(b) (4)	

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by October 12, 2009.

Should you require any additional information, please contact Frances Fahnbulleh at 301-796-0942.

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/s/

Dennis Bashaw
6/4/2009 05:52:08 PM

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/

SUE CHIH H LEE
02/04/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products

MEMORANDUM

DATE	February 4, 2010
TO	Donna Griebel, MD, Division Director, Division of Gastroenterology Products
THROUGH	Nancy Snow, MD, MPA, Acting Medical Team Leader, Division of Gastroenterology Products
FROM	Tamara Johnson, MD, MS, Medical Officer, Division of Gastroenterology Products
SUBJECT:	Recommendation for Complete Response
Application Type	NDA
Application Number(s)	22-524
Received Date(s)	April 7, 2009
PDUFA Goal Date	February 7, 2010
Established Name	Ondansetron
(Proposed) Trade Name	ZUPLENZ
Therapeutic Class	5HT3 receptor antagonists
Applicant	Par Pharmaceutical, Inc.
Formulation(s)	Oral Soluble Film
Dosing Regimen	4mg, 8mg
Indication(s)	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 (CINV-HEC); • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC); • Prevention of postoperative nausea and/or vomiting (PONV); • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV).

PURPOSE

This memorandum is provided to explain a change in the recommended regulatory action from approval to that of complete response (CR) for ZUPLENZ 8mg and 4mg oral soluble film for the same indications and target populations as ZOFRAN® ODT. This document will also discuss outstanding issues that remain to be considered during the second cycle review of ZUPLENZ.

BACKGROUND

The sponsor, Par Pharmaceutical, Inc. submitted a 505(b)(2) application to support their product ZUPLENZ (ondansetron oral soluble film) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin≥50 mg/m2 (CINV-HEC), prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC), prevention of postoperative nausea and/or vomiting (PONV), and prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV). ZOFRAN ODT® is the reference label drug.

ZUPLENZ appeared appropriate for approval based upon pharmacological data that demonstrated ZUPLENZ oral soluble film is bioequivalent to ZOFRAN® ODT and safety data showing a lack of significant safety risks with this new formulation of ondansetron (see Clinical Review dated December 22, 2009). Two sites were selected for inspection by the Division of Scientific Investigations (DSI); the bioequivalence study site and bioanalytical site, both in (b) (4). Inspections of the key study sites, however, have been delayed due to a travel advisory and civil unrest in the region where the sites are located. The situation is such that inspections will not be completed before the PDUFA goal date (February 7, 2010).

RATIONALE

A complete response action is recommended because the selected sites for inspection are the locations where two out of the three submitted pharmacological studies were performed. An unsuccessful inspection would jeopardize the evidence supporting this NDA application. Therefore, approval is conditional upon successful study site inspections.

OUTSTANDING ISSUES TO BE ADDRESSED

In addition to successful study site inspections, a few additional issues remain to be addressed during the second cycle of review. First, final negotiations on the labeling must be completed. Second, the sponsor will need to submit a revised pediatric plan for ZUPLENZ. The sponsor's original pediatric plan was found to be inadequate for fulfilling the Pediatric Research Equity Act (PREA) requirements. On January 6, 2010, the Pediatric Review Committee (PeRC) PREA Subcommittee reviewed the sponsor's original pediatric plan and the Division's proposed revisions to the plan. The PeRC made new recommendations for the ZUPLENZ pediatric plan. The Division is in agreement. The PeRC recommendations are listed below by indication:

1. ***Prevention of nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy***

a. The Division recommended a partial waiver for pediatric patients 0<1 month because there are too few children with disease/condition to study and a deferral for patients 1 month to 17 years because adult studies are completed and ready for approval. The PeRC agreed with the Division to grant a partial waiver 0<4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).
b. The PeRC also agreed to the deferral of studies for pediatric patients 4-17 years of age until a PK and adequately controlled efficacy and safety studies are conducted. An adequately powered dose-response study to support efficacy may be considered.

2***. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy***

a. The Division recommended a partial waiver for pediatric patients 0<1 month because there are too few children with disease/condition to study and a deferral for patients 1 month to <4 years because adult studies are completed and ready for approval, and the product is appropriately labeled from 4 years to 17 years. The PeRC agreed with the Division to grant a partial waiver 0<4 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).
b. The PeRC also agreed with the Division that the product is appropriately labeled for use in patients 4 years to 17 years of age based on Zofran Orally Disintegrating Tablets labeling.

3. Prevention of nausea and vomiting associated with radiotherapy

a. The Division recommended a full waiver of studies in pediatric patients because there are too few 2 children with disease/condition to study. The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

4. Prevention of postoperative nausea and vomiting

a. The Division recommended a deferral of studies for patients ages birth to 17 years because adult studies are completed and ready for approval. The PeRC agreed with the Division to the deferral of studies for pediatric patients birth to 17 years of age until adequately controlled efficacy and safety studies are conducted. An adequately powered dose-response study to support efficacy may be considered. Please note that an age-appropriate formulation would be needed for the younger age group.

Lastly, the Division, with the Pediatric and Maternal Health Staff, should further discuss the appropriateness of a written request for nausea and vomiting associated with severe gastroenteritis.

CONCLUSION

The regulatory action for ZUPLENZ 8mg and 4mg oral soluble film has been changed from approval to complete response (CR) due to a delay in study site inspections. Approval should be reconsidered upon successful study site inspections, successful labeling negotiations, and an acceptable pediatric plan.

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/

TAMARA N JOHNSON
02/04/2010

NANCY C SNOW
02/04/2010
I agree with recommendations from Medical Reviewer

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22524
Priority or Standard	Standard
Submit Date(s)	7 Apr 2009
Received Date(s)	7 Apr 2009
PDUFA Goal Date	10 Feb 2010
Division / Office	DGP/ODE III/OND
Reviewer Name(s)	Tamara Johnson, MD, MS
Review Completion Date	December 9, 2009
Established Name	Ondansetron
(Proposed) Trade Name	ZUPLENZ
Therapeutic Class	5HT3 receptor antagonists
Applicant	Par Pharmaceutical, Inc.
Formulation(s)	Oral Soluble Film
Dosing Regimen	4mg, 8mg
Indication(s)	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 (CINV-HEC); • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC); • Prevention of postoperative nausea and/or vomiting (PONV); • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV).
Intended Population(s)	(b) (4)

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1 Recommendations/Risk Benefit Assessment

The sponsor, Par Pharmaceutical, Inc. presents this 505(b)(2) application to support their product ZUPLENZ (ondansetron oral soluble film) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin≥50 mg/m2 (CINV-HEC), prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC), prevention of postoperative nausea and/or vomiting (PONV), and prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV). ZOFRAN ODT® is the reference label drug.

1.1 Recommendation on Regulatory Action

Based upon review of the pharmacological studies demonstrating that ZUPLENZ ondansetron oral soluble film is bioequivalent to ZOFRAN® ODT and the lack of significant safety signals for this new formulation of ondansetron, this reviewer recommends approval of ZUPLENZ 8mg and 4mg oral soluble film for the same indications and target populations as ZOFRAN® ODT.

1.2 Risk Benefit Assessment

Ondansetron has been marketed in the US since 1991 and is provided under the tradename ZOFRAN® and numerous generics. The availability of ZUPLENZ ondansetron oral soluble film would provide an additional method of administration for patients suffering from nausea and vomiting who may have difficulty swallowing a whole tablet or any moderate amount of liquid. This new formulation provides the equivalent amount of the active ingredient as ZOFRAN® ODT, but may find better acceptance in settings where patients are less tolerant of holding a tablet in the mouth (e.g. pediatric patients). To this consideration, further study of this formulation in pediatrics patients is warranted, and required by the Pediatric Research Equity Act (PREA) (21 USC 355c). A review for safety issues specific to ZUPLENZ did not uncover significant concerns over those already documented within the numerous ondansetron product labels. There were few adverse events and none were determined to be related to ondansetron. Theoretical concern remains regarding elevated eosinophil levels seen in 6 (4.3%) of healthy volunteers, however, no clinical manifestations of immune reaction were reported. Due to study design issues, the effect could not be attributed specifically to ZUPLENZ or to ZOFRAN® ODT. As the risk of hypersensitivity is already included in the labeling for all ondansetron products, only postmarketing monitoring appears to be needed at this time. Therefore, based on materials presented in this application, the overall benefit of ZUPLENZ appears to outweigh any risk associated with use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a Risk Evaluation and Mitigation Strategy (REMS) plan.

1.4 Recommendations for Postmarket Requirements and Commitments

In accordance with PREA, the sponsor is required to evaluate the use of ZUPLENZ in the pediatric population for the same indications as adults. In consultation with OND's Pediatric and Maternal Health Staff, the following pediatric plan is recommended. (See 7.6.3 Pediatrics and Assessment of Effects on Growth for further details.)

Par Pharmaceutical should conduct studies for:

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin≥50 mg/m^2 (CINV-HEC): to include pharmacokinetic (PK) studies and well-controlled trials for safety and efficacy for ages 1 month to 17 years, using an age-appropriate formulation. A timeline is yet to be determined.
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC): to include a PK study and a well-controlled trial for safety and efficacy for ages 1 month to <4 years, using an age-appropriate formulation. A timeline is yet to be determined.
- Prevention of postoperative nausea and/or vomiting (PONV): to include PK studies and well-controlled trials for safety and efficacy for ages 0 to 17 years, using an age-appropriate formulation. A timeline is yet to be determined

The following indication is to be waived for all pediatric age groups:

- Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV).

2 Introduction and Regulatory Background

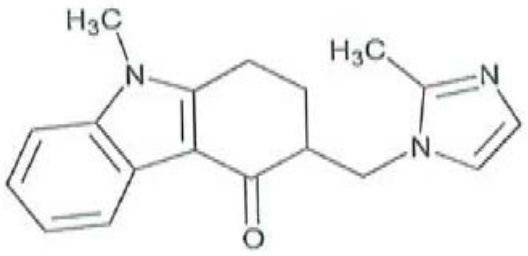
2.1 Product Information

ZUPLENZ oral soluble film is a new formulation of ondansetron, a selective 5-HT_3 receptor antagonist which blocks stimulation on both peripherally located vagal nerve terminals and centrally located receptors in the chemoreceptor trigger zone of the area

postrema. Prepared in both the 4mg and 8mg strengths, this product seeks the same indications and patient population as those for ZOFRAN® ODT.

ZUPLENZ, as an oral soluble film, consists of a thin polymeric film impregnated with ondansetron base. When placed on the tongue, the film dissolves in 20-30 seconds without the aid of water for dissolution. Chemically, it is (±) 1, 2, 3, 9- tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. The structural formula is shown in Figure 1.

Figure 1: Chemical Structure of Ondansetron



C18H19N3O; molecular weight of 293.4
Each oral soluble film also contains the inactive ingredients of butylated hydroxyl toluene, calcium carbonate, erythritol, hypromellose, monoammonium glycyrrhizinate, peppermint flavor, polyethylene oxide, silicone dioxide, sodium bicarbonate, titanium dioxide and xanthan gum.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Prescription Products for the Proposed Indications

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
5-HT3 Receptor Antagonists		
ZOFRAN® (ondansetron) Oral tablets Orally disintegrating tablets Oral solution Intravenous injection (GlaxoSmithKline)	1991	**Adults** **CINV –**32mg IV x 1 or 0.15mg/kg IV q4 hrs. x 3 **CINV-HEC** -- 24mg oral x 1 day **CINV-MEC –** 8mg oral BID x 2-3 days **PONV—** 4mg IV; 16mg oral 1 hr prior to induction **RINV –** 8mg oral TID x 1-3 days **Pediatrics** **CINV –** for ≥6 mo., 0.15-mg/kg IV q4 hrs. x 3 **CINV-MEC –** for 6mo. to 18yrs, 0.15mg/kg IV q4 hrs x 3; for ≥12 y.o., same oral as adult; 4-11y.o., 4mg oral TID x 2-3 days **PONV—**IV only, 1 month to 12 y.o. – a single 0.1-mg/kg dose for patients weighing ≤ 40 kg, or a single 4-mg dose for patients weighing > 40 kg **RINV** – N/A

DRUG NAME Formulations (Sponsor)	**Approval Date**	**Indications and Dosages***
ANZEMET (dolasetron mesylate) Oral tablet Oral solution Intravenous injection (Aventis Pharmaceuticals)	1997	**Adults** **CINV--**1.8 mg/kg IV x1 or 100mg mg IV x1; 100mg oral x 1 **PONV –** 12.5mg IV x 1; 100mg oral x 1 **RINV–** N/A **Pediatrics** **CINV** – for 2y.o. and older, 1.8mg/kg IV x 1; for 2 y.o. and older, 1.8mg/kg oral x 1 **PONV–** for 2 y.o. and older, 0.35mg/kg IV x 1; 1.2mg/kg oral x1 **RINV –** N/A
KYTRIL (granisetron) Oral tablet Oral solution Intravenous injection (Roche Pharmaceuticals)	1993	**Adults** **CINV-** 10mcg/kg IV on the days chemotherapy is given; 2mg oral on the days chemotherapy is given **PONV –** 1mg IV x 1 **RINV–** 2mg oral x 1 **Pediatrics** **CINV –** IV same as adults for 2 y.o. and older **PONV–** N/A **RINV–** N/A
ALOXI (palonosetron HCl) Oral capsule Intravenous injection (MGI Pharma)	2003	**Adults** **CINV-HEC** – 0.25mg IV x 1 **CINV-MEC –** 0.25mg IV x 1; 0.5mg oral x 1 capsule **PONV** – 0.075mg IV x 1 ***No Approved Pediatric Indications***

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
H1 Receptor Antagonists		
Hydroxyzine hydrochloride oral capsule oral suspension intramuscular injection (Generic) *Note: oral syrups and tablets are available but approved for indications other than antiemesis.*	1957	**Adults** **NV --** 25–100 mg IM **Pre- and Postoperative adjunctive medication --** 25–100 mg IM **RINV –** N/A **Pediatrics** **NV--** 0.5 mg/lb body weight IM **Pre- and Postoperative adjunctive medication --** 0.5 mg/lb body weight IM **RINV –** N/A
NK1 Receptor Antagonists		
EMEND (aprepitant/fosaprepitant dimeglimine) Oral capsule Intravenous injection (Merck)	2003	**Adults** **CINV-HEC** – 125mg PO or 115mg IV on Day 1; 80mg PO on Days 2 & 3 **CINV-MEC –** 125mg PO or 115mg IV on Day 1; 80mg PO on Days 2 & 3 **PONV** – 40mg IV x 1 ***No Approved Pediatric Indications***

***** **CINV-HEC** = Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy; **CINV-MEC** = Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy; **PONV** = Prevention of postoperative nausea and/or vomiting; **RINV** = Prevention of nausea and vomiting associated with radiotherapy

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, ondansetron, was first approved in 1991 in ZOFRAN® Injection. Ondansetron is currently marketed in the US as the ZOFRAN® brand, as well as numerous generic products. Ondansetron hydrochloride is available in injectable form for intravenous or intramuscular administration, and in oral solution and oral tablet formulations. In addition, ondansetron base is available in the form of an orally dissolving tablet (ODT), first approved as ZOFRAN ODT® in 1999. ZOFRAN® ODT 4 and 8 mg ODT dosages were found bioequivalent to ZOFRAN® Tablets and ZOFRAN® Oral Solution. In this NDA application, Par Pharmaceutical, Inc. submits ZUPLENZ ondansetron oral soluble film as an alternative dosage form for patients who may have difficulty swallowing and/or holding down tablets.

2.4 Important Safety Issues With Consideration to Related Drugs

Ondansetron is a drug with widespread distribution and a generally good safety profile. However, there exists the serious risk of cardiac arrhythmia with the class of $5HT_3$ receptor antagonists. These events are rare and mostly documented with intravenous use. All drugs in the class are noted to cause cardiac ion channel blockade and QT prolongation. The effect of QT prolongation is more pronounced in dolasetron where a faster onset of ECG changes has been demonstrated[1,2] The EMEA has contraindicated use of dolasetron in pediatric patients because of cases of cardiovascular events. A previous review by CDER's Office of Surveillance and Epidemiology (2006) for cardiac events in $5HT_3$ receptor antagonists found 65 reported cases in a distribution of (b) (4) ondansetron prescriptions; making the risk to this patient population less than 0.005%. Cardiovascular adverse events known to the class of $5HT_3$ receptor antagonists (ondansetron, granisetron, dolasetron, and palonosetron) and included in product labeling are listed in Table 2.

Table 2: Safety Issues Related to Drug Class

Safety Labeling in the $5HT_3$ Receptor Antagonists Class*
Ondansetron: Adverse Reactions (Cardiovascular): Rare cases of angina (chest pain), hypotension, and tachycardia have been reported. Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block and

1 Katzung, editor. Basic and Clinical Pharmacology. 11th edition, 2009.
2 Keefe DL. The cardiotoxic potential of the 5-HT3 receptor antagonist antiemetics: is there cause for concern? Oncologist 2002;7:65 - 72.

ST segment depression), palpitations, and syncope.
Granisetron: Adverse Reactions: (Cardiovascular): Hypertension (2%); hypotension, arrhythmias such as sinus bradycardia, atrial fibrillation, varying degrees of A-V block, ventricular ectopy including nonsustained tachycardia, and ECG abnormalities have been observed rarely.
Dolasetron: Warnings: Dolasetron can cause ECG interval changes (PR, QTc, JT prolongation and QRS widening). Precautions: Dolasetron should be administered with caution in patient who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. Adverse reactions: Hypotension; rarely-edema, peripheral edema, The following events also occurred rarely and with a similar frequency as placebo and/or active comparator: Mobitz I AV block, chest pain, orthostatic hypotension, myocardial ischemia, syncope, severe bradycardia, and palpitation.
Palonosetron: Precautions: Palonosetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy. Adverse reactions: (Cardiovascular): 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, Supraventricular extrasystoles and QT prolongation.

*Table borrowed from Corken-Mackey (OSE) review dated June 26, 2006.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

For this 505(b)(2) NDA application by Par Pharmaceutical, Inc., reference was made to ZOFRAN® ODT for nonclinical, clinical efficacy and safety data, for which this sponsor does not have right of reference. The sponsor only submits studies demonstrating bioequivalence of ZUPLENZ oral soluble film to ZOFRAN ODT. The sponsor has met with the Agency on two previous occasions to reach agreement on its clinical program. On July 2, 2008, a pre-IND meeting was held where the Agency agreed to the sponsor's clinical program and the 505(b)(2) type of NDA submission. On February 25, 2009, a pre-NDA teleconference meeting was held at which the Agency agreed to include the 4mg dosage for the pediatric CINV-MEC indication.

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the overall submission was good. It was well-organized, with appropriately placed links to allow easy navigation throughout the application.

3.2 Compliance with Good Clinical Practices

Studies were carried out in accordance with the provisions of the current version of the ICH-Good Clinical Practice and the principles enunciated in the Declaration of Helsinki (WMA General Assembly, Tokyo 2004) and requirements of CDSCO Schedule Y (Amended Version -2005), ICMR Ethical Guidelines for Biomedical Research on Human Study participants. All potential volunteers were explained in non-technical terms about the study objective, the risks involved and the procedures to be conducted. This was conducted in a language familiar to the volunteer i.e., either in Tamil or English. Sufficient time was given to the volunteers to read, understand and clarify any doubts on the contents of the informed consent form before signing.

For this application, Clinical Pharmacology selected two sites for inspection by the Division of Scientific Investigations (DSI); the bioequivalence study site and bioanalytical site, both in (b) (4). The final report from the inspection was still pending at the time this clinical review was completed. Please see the DSI review for full details.

3.3 Financial Disclosures

The sponsor certified that there were no financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. Each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in ZUPLENZ or a significant equity in the sponsor; no investigators disclosed any such interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The dosage strengths for ZUPLENZ oral soluble film 4mg and 8mg have a quantitatively identical formulation, with exactly the same proportions of active pharmaceutical ingredient and inactive excipients. Both strengths are cut from bulk film product rolls of the same composition and method of manufacture. Therefore, the high strength 8mg and low strength 4 mg products are considered dose proportional. The dissolution profiles of the ZUPLENZ 4mg and 8mg and ZOFRAN® ODT were found to have comparable dissolution. Therefore, a waiver of bioequivalence studies for the lower strength 4 mg ondansetron oral soluble film was found justifiable by CDER's ONDQA. The original formulation term, *orally dissolving film strip (ODSF)*, was found unacceptable in CMC review and was changed to oral soluble film. For further details on the CMC evaluation of ZUPLENZ oral soluble film, please see the full review by Dr. Bogdan Kurtyka.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

As a 505(b)(2) application, the nonclinical data for this application comes primarily from previously approved NDAs for ZOFRAN® (ondansetron HCl) for Injection [NDA 20-007], (ondansetron HCl) Tablets [NDA 20-103]) and Oral Solution [NDA 20-605], and ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets [NDA 20-781], supplemented by available published literature. Nonclinical studies on the pharmacology of ondansetron were initially performed with isolated tissue preparations and more recently in purified systems. The pharmacokinetics and safety of ondansetron have been studied in numerous animal studies and extensively in man. The observed margin between efficacy and any systemic effect was about 10-fold, and the margin between efficacy and behavioral effect was about 25-fold (Smith et al. 1989). The only significant toxicity observed was central nervous activity at near lethal doses. The drug was not genotoxic and had no reproductive or oncogenic potential. For further details on the nonclinical evidence in support of this application, please see the full review by Dr. Charles Wu.

4.4 Clinical Pharmacology

The bioavailablity study and the two pivotal bioequivalence studies (conducted in healthy male and female volunteers) demonstrated that administration of ZUPLENZ resulted in similar blood concentrations of the ondansetron as ZOFRAN® ODT. The two pivotal studies showed that C_{max} and AUC met the 80.00% to 125.00% confidence interval criteria whether the products were dosed in the fasting or fed states. The bioavailability study established the bioequivalence of the test product (when dosed with or without water) compared to the reference product when dosed with and without water. For further details on the clinical pharmacology of ZUPLENZ oral soluble films, please see the full review by Dr. Insook Kim.

5 Sources of Clinical Data

The clinical studies for this product were limited to an assessment of the bioequivalence of ZUPLENZ oral soluble film and ZOFRAN ODT®. Five bioavailability studies were conducted: two pilot studies, two pivotal bioequivalence studies, and one bioavailability study to assess the pharmacokinetics of ZUPLENZ when taken with versus without water and compared to ZOFRAN ODT® taken without water.

5.1 Tables of Studies/Clinical Trials

Table 3: Clinical Studies

Study Number Investigator	Completion Status (Start Date) Country	Study Design Route of Administration	Treatment Doses Conditions *	Subjects Number Completed/ Number Enrolled	Age Range (Mean)	Gender (M/F) Race	Total Duration of Drug Treatment
Pivotal Bioequivalence Studies in Healthy Volunteers							
01905/08-09 Principal Investigator: Dr. Sudershan Vishwanath. Medical Investigator: Dr. B. Satish Kumar.	Complete (26 Sep, 2008) (b) (4)	Open-label randomized, single dose, two way crossover bioequivalence study Oral	1 x 8 mg OSF 1 x 8 mg ODT Fasting with water	46/48	M: 18 – 40 (25.0) F: 27 – 38 (33.4)	M: 41 F: 7 Southeast Asian	2 Single Doses
01906/08-09 Principal Investigator: Dr. Sudershan Vishwanath. Medical Investigator: Dr. B. Kamalesh Kumar, MD	Complete (6 Oct, 2008) (b) (4)	Open-label randomized, single dose, two way crossover bioequivalence study Oral	1 x 8 mg OSF 1 x 8 mg ODT Fed with water	45/48	M: 18-41 (25.5) F: 20-39 (30.3)	M: 36 F: 12 Southeast Asian	2 Single Doses

Study Number Investigator	Completion Status (Start Date) Country	Study Design Route of Administration	Treatment Doses Conditions *	Subjects Number Completed/ Number Enrolled	Age Range (Mean)	Gender (M/F) Race	Total Duration of Drug Treatment
Bioequivalence Study with and without water in Healthy Volunteers							
04795/08-09 Principal Investigator: Dr. Salil Budhiraja, MD Medical Investigator: Dr. B. Kamalesh Kumar, MD	Complete (30 Aug) 2008 (b) (4)	Open-label randomized, single dose, three way crossover comparative water-effect bioavailability study Oral	1 x 8 mg OSF with water 1 x 8 mg OSF without water 1 x 8 mg ODT without water All Fasting	17/18	M: 19 – 39 (25.9) F: 33 – 39 (35.0)	M: 14 F: 4 Southeast Asian	3 Single Doses
Pilot Bioequivalence Studies in Healthy Volunteers							
10221/06-07 Principal Investigator: Dr. Vishwanath Sudershan. Medical Investigator: Dr. B. Satish Kumar.	Complete 03 Sep 2007 (b) (4)	Open-label randomized, single dose, two way crossover comparative bioavailability study Oral	1 x 8 mg OSF 1 x 8 mg ODT Fasting with water	12/12	M: 20 – 41 (25.3)	All Males Southeast Asian	2 Single Doses

Study Number Investigator	Completion Status (Start Date) Country	Study Design Route of Administration	Treatment Doses Conditions *	Subjects Number Completed/ Number Enrolled	Age Range (Mean)	Gender (M/F) Race	Total Duration of Drug Treatment
10222/06-07 Principal Investigator: Dr. Vishwanath Sudershan. Medical Investigator: Dr. B. Kamalesh Kumar, MD	Complete 03 Sep 2007 (b) (4)	Open-label randomized, single dose, two way crossover comparative bioavailability study Oral	1 x 8 mg OSF 1 x 8 mg ODT Fed with water	12/12	M: 18 – 36 (25.5)	All Males Southeast Asian	2 Single Doses

From NDA 22524, Module 2.7.6.
*OSF= ZUPLENZ oral soluble film

5.2 Review Strategy

As a 505(b)(2) application, the clinical review of efficacy relies on evidence previously submitted and reviewed for the FDA approvals of ZOFRAN® (ondansetron HCl) for Injection [NDA 20-007], (ondansetron HCl) Tablets [NDA 20-103]) and Oral Solution [NDA 20-605], and ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets [NDA 20-781]. The sponsor seeks the same indications for ZUPLENZ:

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin≥50 mg/m2 (CINV-HEC)
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC)
- Prevention of postoperative nausea and/or vomiting (PONV)
- Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen (RINV).

No further review of efficacy will be conducted in this document.

The clinical review of safety will examine safety results from the 5 pharmacokinetic studies in healthy volunteers, and additional information relevant to oral soluble films available in the medical literature or AERS database.

5.3 Discussion of Individual Studies/Clinical Trials

Please see the review by Dr. Kim regarding a discussion in these pharmacokinetic studies.

6 Review of Efficacy

Efficacy Summary

See sections 4.4 Clinical Pharmacology and 5.2 Review Strategy.

6.1 Indication

N/A

7 Review of Safety

Safety Summary

The safety of ZUPLENZ (ondansetron oral soluble film) was examined from results of five open-label pharmacokinetic studies conducted to evaluate bioequivalence, the medical literature, and the AERS database system. Of the 134 healthy adult volunteers exposed to the ZUPLENZ 8mg film, three subjects (2%) reported 4 adverse events (AE); abdominal pain (2), vomiting (1), and an upper respiratory infection (1). All AEs were mild and resolved without sequelae. There were no deaths, serious AEs, or discontinuations due to AE. Although, there were no sustained changes in serum or hematology laboratory values in any healthy subject administered ZUPLENZ, elevations in liver transaminases, total bilirubin, and eosinophils were demonstrated. While hepatic abnormalities may be expected with ondansetron products, this reviewer notes the elevated eosinophil levels seen in 6 (4.3%) healthy volunteers without associated clinical manifestations of immune reaction. Due to study design issues, this effect could not be attributed specifically to ZUPLENZ or ZOFRAN® ODT. The risk of hypersensitivity is, however, already included in the labeling for all ondansetron products. ZUPLENZ is not approved in foreign markets; therefore, no postmarketing experience is available.

7.1 Methods

In addition to the safety data from previous FDA approvals of ZOFRAN® (ondansetron HCl) for Injection [NDA 20-007], (ondansetron HCl) Tablets [NDA 20-103]) and Oral Solution [NDA 20-605], and ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets [NDA 20-781], the sponsor submits additional safety data collected from the five pharmacokinetic studies performed to evaluate bioequivalence and information from medical literature. The published literature was reviewed to identify additional pertinent data. Literature searching on Medline was conducted through March 2009 using the key words “ondansetron,” “human studies,” “clinical trials,” “meta-analysis,” “reviews,” and “pharmacokinetics.”

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The five pharmacokinetic studies (#’s 01905/08-09, 01906/08-09, 04795/08-09, 10221/06-07, and 10222/06-07) were used to evaluate the safety of ZUPLENZ ondansetron oral soluble film. See section 5.1 Tables of Studies/Clinical Trials for a listing of the conducted studies.

7.1.2 Categorization of Adverse Events

All adverse events were coded verbatim from investigator’s reports.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooling of study data was appropriate due to the small size of the five individual studies. However, the small number of pooled adverse events (n=4) and the 2.2% AE incidence may not adequately represent the expected AE incidence for ZUPLENZ.

7.2 Adequacy of Safety Assessments

Clinical safety assessments included monitoring of adverse events, such as adverse drug reactions, periodic physical examinations, and vital signs. Assessments were monitored at regular predetermined intervals and whenever deemed appropriate by an investigator. A clinical assessment, which included medical history and a general and systemic examination, was done at both the pre-study screening and at the end of the final treatment period. At the pre-study screening visit, 12-lead electrocardiogram (ECG), chest X-ray, urinalysis, and serology tests were conducted to determine individual health status. Hematology and serum chemistry assessments were performed pre-enrollment and repeated after study completion. At pre-study, urine pregnancy screening was performed for female volunteers (and repeated at final visit), and urine drug screening (UDS) was performed to identify and exclude study participants with recent substance abuse.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Worldwide patient exposure to the active ingredient, ondansetron, has been significant since the initial approval in 1991, however, ZUPLENZ ondansetron oral soluble film has been administered to only 134 healthy volunteers. Of these 134 subjects, 117 (87%) received a single ZUPLENZ 8mg dose and 17 subjects (13%) received two 8 mg ZUPLENZ doses, separated by a washout period of 3 days. Due to the crossover design of the studies, most of the 8 mg treated-subjects (133/134) also received one 8 mg dose of ZOFRAN ODT®; the two formulations separated by a 3-7 day washout period.

The demographics of the healthy volunteer population reflect a South Asian population, specifically Indian ethnicity. The majority were male (83%) and aged from 18 to 41 years, with a mean age of 26.5 ± 5.8 (SD) years. Five (3.6%) were current smokers. The mean height was 164.6 ± 9.1 cm (range, 124 – 182 cm); mean weight was 60.4 ± 7.2 kg (range, 50 – 84 kg); and the mean BMI was 22.2 ± 2.2 kg/m2 (range, 18 – 25 kg/m^2). Additional limitations deal with the fact that this is a population of healthy volunteers.

Medical Reviewer's Comment
Overall, exposure to the high strength 8mg ZUPLENZ appears appropriate to evaluate safety for short-term use because the active ingredient is generally tolerated by patients and the inactive ingredients are generally recognized as safe. Further assessment of risks associated with longer term repeated use of the oral soluble film should be monitored in the postmarketing period.

The study population is ethnically homogeneous composed of young South Asian males with a mean BMI less than that for the current US population. The safety results from the ZUPLENZ pharmacokinetic studies cannot be considered generalizable to the US population, nor to the majority of cancer patients. However, considering that ZUPLENZ does not contain a new active ingredient and there is substantial clinical safety information from current US-marketed ondansetron formulations in the target populations, monitoring in the postmarketing period should be sufficient to identify any concerns.

7.2.2 Explorations for Dose Response

No explorations of dose response were performed because only the 8mg dose of ZUPLENZ was administered in clinical studies.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* studies were conducted for this application.

7.2.4 Routine Clinical Testing

The clinical testing performed was appropriate for these 1-2 dose exposures to the ZUPLENZ film; however, the frequency of testing, pre-study and final visit, was insufficient to capture changes in the laboratory values before the treatment regimen was switched. Due to the crossover design of the studies, each subject received at least one dose of each treatment, ZUPLENZ and ZOFRAN® ODT.

Medical Reviewer's Comment
An additional laboratory testing period should have been performed during the washout period, before exposure to the second treatment. In this way, changes seen in lab test results could be appropriately attributed to one treatment or the other.

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Key to this safety review is an evaluation for the cardiovascular and hepatic adverse events. The sponsor has attempted to address these concerns in a medical literature review. See 7.3.4 Significant Adverse Events.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the clinical program for ZUPLENZ.

7.3.2 Nonfatal Serious Adverse Events

No serious AEs occurred during the clinical program for ZUPLENZ.

7.3.3 Dropouts and/or Discontinuations

No discontinuations due to AE occurred during the clinical program for ZUPLENZ. Six subjects did discontinue from the program: 3 voluntarily, 2 with positive urine drug screen results prior to the second period of the study, and 1 due to noncompliance with the fasting requirement.

7.3.4 Significant Adverse Events

The safety profile of ondansetron is primarily taken from the Prescribing Information for oral formulations of ZOFRAN® (February, 2006). Published literature was also reviewed to identify potential risks related to seizures, hepatobiliary system, cardiovascular events, and pediatric use.

Nervous System
The sponsor presents information on seizures (including tonic-clonic seizures) reported rarely in patients receiving ondansetron. Ten patients developed 'seizures' during initial clinical studies, but it was considered that all these patients had predisposing factors such as brain metastases, severe metabolic and electrolyte abnormalities, and antineoplastic therapy (Sargent 1993). This evidence points to several etiologies for the occurrence of seizures and cannot be isolated to ondansetron use. Nonetheless, the ZOFRAN® ODT label has documented the risk of grand mal seizures under other reported adverse reactions.

Hepatobiliary System

Ondansetron is known to cause liver enzyme abnormalities. A systematic review of clinical trial data on prophylaxis of PONV revealed that approximately 3% of patients receiving ondansetron will have elevated levels of liver enzymes (e.g.: AST, ALT), which is a marker for hepatic impairment (Tramer et al. 1997). The ZOFRAN® ODT label reports this risk where 1-2% of CINV patients were observed with transaminases levels > 2x ULN.

Cardiovascular Events

The sponsor conducted a review of the literature regarding cardiac effects with the use of ondansetron. Their review summarizes that while ondansetron has the propensity to induce clinically significant QTc prolongation, presumably by blocking human cardiac sodium channels (Kuryshev et al. 2000), it is likely to do so under conditions of pre-existing cardiac risk factors or when administered at high doses (i.e., 32 mg) (Boike et al. 1997; Benedict et al. 1996). The class of 5-HT_3 receptor antagonists are generally associated with electrocardiography (ECG) changes that can exacerbate pre-existing cardiovascular maladies such as cardiomyopathy and prolongation of the QTc interval. For example, in a nonrandomized study of patients with post operative nausea and vomiting (PONV), an increase in the QTc interval was observed with a mean maximal QTc lengthening of 20 ± 13 ms after administration of 4 mg ondansetron as an IV. bolus (Charbit et al. 2005). Approximately 20% of these subjects already had a prolonged QTc interval prior to PONV treatment with ondansetron. In some of these patients, this interval was lengthened to greater than 500 ms after ondansetron administration, -- an increased risk for drug-induced torsade de pointes (Haddad and Anderson 2002). Similar QTc lengthening was observed by Chan et al in patients undergoing laparoscopic surgery after an equivalent I.V. dose of ondansetron (Chan et al 2006). This prolongation (9.9 ± 34.7 ms), however, was not considered clinically significant. In contrast to these studies, significant QTc lengthening after 4 mg ondansetron was not observed in a subset of adult patients undergoing various surgical procedures (Lee et al. 2007). Similar results confirming cardiac tolerability and lack of serious dysrhythmias with ondansetron was also obtained in another subset of elective surgical patients (Rosow et al. 2008).

In consideration of the pediatric population, no significant changes in ECG measurements, including heart rate, QT and QTc dispersions, and PR or QRS durations were observed in a cohort of children in response to 0.1 mg/kg ondansetron I.V. before receiving chemotherapy for acute leukemia (Buyukavci et al. 2005). In a separate study, the effects of this dose of ondansetron on ECG were evaluated in children (aged 2-12 years old) receiving chemotherapy for acute leukemia (n=11; ondansetron group). No significant changes in a variety of ECG parameters were found after ondansetron treatment suggesting the lack of cardiotoxicity in this patient group (Chan et al. 2006).

The sponsor concludes that these data indicate caution must be exercised in evaluating patient demographic and predisposition to any cardiovascular anomalies before ondansetron therapy.

Pediatric Use

Pediatric patients administered ondansetron have shown similar incidence of common adverse reactions as placebo groups. In a double blind PONV study (n=335; ondansetron group) with 1 to 24-month old pediatric patients receiving 0.1 mg/kg ondansetron intravenously, no significant difference in the number of adverse events between the placebo and treatment group was found. However, less than 2% had agitation, nonspecific swelling, swelling of face and eye, and aggressive behavior, and were considered to be possibly related to the study drug (Khalil et al. 2005). Meanwhile, a PONV study (n= 31) on the efficacy and safety of 4 mg ondansetron oral disintegrating tablets in children (aged 5-11 years old) found no drug related adverse events (Cohen et al. 2005). The presented risk for adverse reactions varies by ondansetron formulation, but suggests tolerated use of ondansetron in certain pediatric age groups.

Other Safety Issues Identified by this Medical Reviewer

While the oral film is a new formulation for approved prescription drugs, various unapproved over-the-counter drug products have been marketed as oral films for several years (Dixit et al. 2009). These products include cold medicines, oral hygiene products, and dietary supplements. Aside from the active ingredient, excipients used in these OTC formulations should be listed as Generally Regarded As Safe (GRAS) in the FDA Inactive Ingredient Guide. Review of the medical literature was conducted to find safety data related to these products. A report of two cases documented palatal erythema due to contact hypersensivity to Listerine® Cool Mint PocketPaks® Oral Care Strips (Pham et al. 2005). The patients had regularly used the product and irritation resolved when use was discontinued. A review of the FDA AERS database was conducted to seek spontaneous reports related to this and similar products. No AERS adverse event reports could be found specific to the film formulations of Triaminic Thin Strips®, Listerine® PocketPaks®, or Theraflu® Thin Strips®. (b) (4)

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 4 adverse events (AEs) were experienced by 3 subjects (2%) in the ZUPLENZ clinical development program. These data represent pooled AEs from all five studies and all treatment conditions (fasted, fed, with water, without water, and consecutive doses); however, AEs were only observed in Study 01905/08-09. Of the four AEs reported, two incidents of abdominal pain and one of vomiting were reported during period I while one upper respiratory tract infection (URI) was reported during the post-clinical period. The one case of vomiting occurred 8 hours post dosing and was considered neither temporally nor pharmacologically related to drug treatment. The two cases of abdominal pain (subjects #44 and #47) were resolved with one 150mg dose of ranitidine and neither was considered related to treatment. Similarly, the URI case was considered unlikely related to treatment. All cases were mild and resolved without sequelae, except for the one subject with URI who was lost on follow-up. AEs are listed in the table below.

Table 4: Adverse Events in ZUPLENZ Clinical Program

Study Number	Adverse Event	Subject Number	Treatment Sequence	Period of Occurrence	Intensity Causality	Intensity Causality
01905	Abdominal Pain	44	OSF/ODT	I	Mild	Unlikely related
01905	Abdominal Pain	47	OSF/ODT	I	Mild	Unlikely related
01905	URI	47	OSF/ODT	Post-clinical	Mild	Unlikely related
01905	Vomiting	46	OSF/ODT	I	Mild	Unrelated

Adapted from NDA 22524, Module 2.7.4.

Medical Reviewer's Comment:
Although considered unrelated, ZUPLENZ alone may contribute to abdominal pain. Both cases presented approximately 12-13 hours after dosing. However, the number of cases is too small to rule out a chance occurrence.

Aside from the AEs noted above, none of the expected common adverse events for ondansetron occurred in these studies. In the ZOFRAN® ODT labeling, the most common adverse drug reactions (≥5%) reported in clinical trials of CINV were: headache, malaise/fatigue, constipation, diarrhea and dizziness. The adverse events reported in clinical trials for RINV were similar to those for CINV. The most common adverse event reported in clinical trials of PONV occurring at a rate significantly different from placebo was headache.

7.4.2 Laboratory Findings

A total of 23 subjects (17%) experienced 25 changes in laboratory parameters. There were no sustained, clinically-relevant changes in laboratory values in any subject in any of the trials. However, due to the crossover design and the 1 post-clinical assessment, there is no way to distinguish if any of the changes were possibly related to ZUPLENZ or ZOFRAN® ODT. Overall, laboratory changes were generally nonspecific and resolved without sequelae. The sponsor reports that both treatments appear to be generally tolerated by the healthy volunteer population.

As demonstrated below in Table 5 , laboratory findings of increased AST, ALT, and total bilirubin were considered possibly related.

- Study 01905 Participant 13 had an increased AST level (i.e.87 U/L, Reference Range: 15-37 U/L), during the post-clinical assessment. The repeated laboratory value was within reference range (i.e. 25 U/L). The change in laboratory value was graded as mild and considered possibly related by the investigator.

- Study 01905 Participant 15 had total bilirubin increased (i.e.1.44 mg/dL, Reference Range: 0.30-1.20 mg/dL), during the post-clinical assessment. The repeated laboratory value was further increased beyond the upper limit of reference range (i.e. 1.92 mg/dL). A second repeated laboratory value was still not within reference range (i.e. 1.29 mg/dL), but considered as clinically not significant by the medical investigator. The change in laboratory value was graded as mild and was considered as possibly related to study drug by the investigator.

- Nine study participants had ALT increases considered possibly related to treatment. ALT levels varied from 4 to 33 units above the upper limit of normal (65 U/L); maximum 1.5 x ULN. Levels resolved to normal ranges within 1-2 months post dosing.

In addition, increased eosinophil levels were reported in 6 (4.3%) of participants. Mild to moderate eosinophil increases varied up to 22% (normal range: 1-6%). The sponsor reports these are unlikely related to treatment.

Table 5: Laboratory Finding from Pharmacokinetic Studies

Laboratory Finding	Number of Subjects (%)	Intensity	Causality
Eosinophil increase	6 (4.3)	4 Mild 2 Moderate	Unlikely related
AST increase	2 (1.4)	Mild	1 Possibly related 1 Unlikely related
Bilirubin increase	1 (0.7)	Mild	Possibly related
ALT increase	9 (6.5)	Mild	Possibly related
Platelet decrease	1 (0.7)	Mild	Unlikely related
Lymphocyte increase	3 (2.2)	Mild	2 Unlikely related 1 Unrelated
WBC increase	3 (2.2)	Mild	2 Unlikely related 1 Unrelated

Medical Reviewer's Comment:
Although we are unable to determine if any of the changes were possibly related to ZUPLENZ or ZOFRAN® ODT, the occurrence of elevated liver transaminases is consistent with adverse reactions on the hepatobiliary system noted in the ZOFRAN® ODT prescribing information. The case of elevated total bilirubin is likely related to either drug. The 4.3% incidence of eosinophilia raises concern for either therapy, but no clinical symptoms of an immune reaction were associated with these laboratory findings.

7.4.3 Vital Signs

All study participants were found to be normal in vital signs and on physical examination during the study and at the time of study exit.

7.4.4 Electrocardiograms (ECGs)

All study participants were evaluated by ECG during the screening period to rule out subjects with at risk for cardiovascular events.

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

There have been no studies conducted in the pediatric population with the product currently being reviewed. The sponsor relies on pediatric safety and efficacy data collected from ZOFRAN ODT, to which ZUPLENZ is bioequivalent. Par Pharmaceutical has submitted a pediatric plan proposing:

- A partial waiver of the requirements to submit pediatric data in children less than 4 years of age;
- (b) (4)
- A deferra (b) (4) in children between the ages of (b) (4) years old; and
- (b) (4)

The Division, in consultation with the Pediatric and Maternal Health Staff (PMHS), has reviewed the submitted pediatric plan and has recommendations as, outlined below, to ensure that studies appropriately address the PREA requirements. The revised plan is to be reviewed by PeRC on January 6, 2010. Please see Dr. Amy Taylor's (PMHS) review for addition discussion of the sponsor's original pediatric plan.

The sponsor shall conduct studies for the following indications:

- CINV-HEC: The sponsor shall revise their pediatric plan to include PK studies, and well-controlled trials for safety and efficacy for the CINV-HEC indication in ages 1 month to 17 years, using an age-appropriate formulation (i.e. oral soluble film or oral solution). An age-appropriate formulation must be considered, such as a smaller oral soluble film or an oral solution, because the current oral soluble film may pose a choking hazard for younger children (i.e. <3 years of age).
- CINV-MEC: The sponsor shall revise their pediatric plan to include a PK study, and a well-controlled trial for safety and efficacy for the CINV-MEC indication in children 1 month to <4 years of age, using an age-appropriate formulation (i.e. oral soluble film or oral solution).
- PONV: The sponsor shall revise their pediatric plan to include PK studies, and well-controlled trials for safety and efficacy for the PONV indication in ages 0 to 17 years, using an age-appropriate formulation (i.e. oral soluble film or oral solution). The following are the proposed age groupings for the PONV studies:
    - *PK Studies:* 0-1 month, 1 month to <6 months, 6 months to < 2 years, 2 to <6 years, 6-11 years, and 12-17 years.
    - *Safety and Efficacy Studies*: 0-1 month, 1 month to < 2 years, 2 to <6 years, 6-11 years, and 12-17 years.

The following indications or age groups are to be waived:

- CINV-MEC: ZUPLENZ orally soluble film has demonstrated bioequivalence to ZOFRAN ODT and may be indicated for children as young as 4 years-old for this indication. Studies in age groups 4-11 years-old and 12-17 years-old have been waived and the PREA requirement considered met for these age groups.
- RINV: Studies in all pediatric age groups will be waived due to the low usage of radiotherapy in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

There is no postmarketing experience.

9 Appendices

9.1 Literature Review/References

1. Benedict, C., Arbogast, R., Martin, L., Patton, L., Morrill, B. and Hahne, W. (1996). Single blind study of the effects of intravenous dolasetron mesylate versus ondansetron on electrocardiographic parameters in normal volunteers. *J Cardiovasc Pharmacol* 28, 53-59.
2. Boike, S.C., Ilson, B., Zariffa, N., and Jorkasky, D.K. (1997). Cardiovascular effects of IV granisetron at two administration rates and of ondansetron in healthy adults. *Am J Health Syst Pharm* 54(10), 1172-1176.
3. Chan, M.T.V., Choi, K.C., Gin, T., Chui, P.T., Short, T.G., Yuen, P.M., et al. (2006). The additive interactions between ondansetron and droperidol for preventing postoperative nausea and vomiting. *Anesth Analg.* 103(5), 1155-62.
4. Cohen, I.T., Joffe, D., Hummer, K., and Soluri, A. (2005). Ondansetron oral disintegrating tablets: acceptability and efficacy in children undergoing adenotonsillectomy. *Anesth Analg.* 101(1), 59-63.
5. Dixit, R.P. and Puthli, S.P. Oral strip technology: Overview and future potential. J Control Release 139(2): 94-107. Epub 2009 Jun 24.
6. Haddad, P.M. and Anderson, T.M. (2002). Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 62(11), 1649-71.
7. Khalil, S.N., Roth, A.G., Cohen, I.T., Simhi, E., Ansermino, J.M., Bolos, M.E., et al. (2005). A double-blind comparison of intravenous ondansetron and placebo for preventing postoperative emesis in 1- to 24-month-old pediatric patients after surgery under general anesthesia. *Anesth Analg* 101, 356-361.
8. Kuryshev, Y.A., Brown, A.M., Wang, L., Benedict, C.R., and Rampe, D. (2000). Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J Pharmacol Exp Ther* 295(2), 614-620.
9. Lee, Y., Wang, P.K., Lai, H.Y., Yao, L.Y., Chin, C.C., and Wang, J.J. (2007). Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting. *Reports of Original Investigations* 54:5, 349-354.
10. Pham CL, Wood AJ, Lambert MB, Carpenter W. Palatal erythema in patients using Listerine Cool Mint PocketPaks Oral Care Strips: case reports. J Dent Child (Chic). 2005 May-Aug;72(2):52-5.
11. Rosow, C.E., Haspel, K.L, Smith, S.E, Grecu, L., and Bittner, E.A. (2008). Haloperidol vs ondansetron for prophylaxis of postoperative nausea and vomiting. *Anesthesia and Analgesia* 106(5), 1407-1409.
12. Smith RN. Safety of ondansetron. Eur J Cancer Clin Oncol, 1989; 25(Suppl 1): S47-S50.

13. ZOFRAN®- ZOFRAN ODT®. Prescribing Information. GlaxoSmithKline, USA, February 2006. ZOFRAN® Injection. Prescribing Information. GlaxoSmithKline, USA, August 2006.

9.2 Labeling Recommendations

Changes recommended to the ZUPLENZ label include:

- Change formulation description to oral soluble film (b) (4)
- Under section 6 *Adverse Reactions*, delete section 6.1 because it is redundant to the *Warnings and Precautions* section 5.1 immediately preceding it in the label.
- Under section 6 *Adverse Reactions*, change the term (b) (4) to adverse reactions to comply with PLR labeling practices.
- Under section *7 Drug Interactions,* combine sections 7.2 and 7.3 with section 7.1. These sections are exactly the same except for the drug name (phenytoin, carbamazepine, and rifampicin) and are combined in the RLD label. The new section 7.1 heading should reflect all potent inducers of CYP3A4.
- Under section 14 *Clinical Studies,* remove subsection numbering to comply with PLR labeling practices.
- Under section 17.2 *FDA-Approved Patient Labeling,* the term medication guide is used incorrectly and was removed, and as well the section was extensively revised to provide appropriate information for the patient. A medication guide is a regulatory element that is part of a risk evaluation and mitigation strategy (REMS) and is used to describe a serious safety issue requiring safety labeling changes under the Food and Drug Administration Amendments Act of 2007 (FDAAA). A medication guide is currently not indicated for this class of drug products and this section wound not satisfy the requirement for a medication guide.

9.3 Advisory Committee Meeting

No advisory committee was held for this application.

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

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

/s/

TAMARA N JOHNSON
12/22/2009

NANCY C SNOW
12/22/2009
The Medical Team Leader agrees with the conclusions and recommendations of the Medical Reviewer.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-524	Applicant: Par Pharmaceutical Companies, Inc.	Stamp Date: April 7, 2009
Drug Name: Ondansetron Orally Dissolving Film Strip (Zuplenz)	NDA/BLA Type: 505 (b)(2)	

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				**505(b)(2)** Zofran (ODT) Orally Disintegrating Tablets **(NDA 20-781)**
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	**5** bioequivalence studies but no phase 2 and 3 clinical studies
EFFICACY					

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Indications: ➢ Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 ➢ Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. ➢ Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen. ➢ Prevention of postoperative nausea and/or vomiting.			X	Efficacy to be established by bioequivalence studies All 5 studies are bioequivalence studies 1. **01905/08-09** (48 subjects) 2. **01906/08-09** (48 subjects) 3. **04795/08-09** (18 subjects) 4. **10221/06-07** (12 subjects) 5. **10222/06-07** (12 subjects) All are open label, randomized, single dose, crossover studies, mostly males
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	Informed by DGP that bioequivalence studies sufficient for clinical development program if the sponsor can demonstrate bioequivalence 7/2/2008 meeting. Reviewed documentation and 505(b)(2) status granted on 9/23/2008 per chemistry review.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	studies performed on healthy volunteers and not the target populations and no clinical endpoints utilized
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		All bioequivalence studies conducted in India
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		No new data submitted. Reference made to NDA 20-007, NDA 20-103, NDA 20-605, NDA 20-781 However, the agency cannot locate results or prior reviews of thorough QT studies for any of the NDAs listed above.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this			X	No marketing experience

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	product?				is available for ondansetron ODFS
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	The agency historically has not required long term safety studies for the CINV, PONV or RINV indications
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	No clinical studies conducted
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	No discussion of which dictionary was used to assess safety in bioequivalence studies
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	All are open label studies and the applicant refers to prior ondansetron NDAs for assessment of safety
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No deaths occurred in the studies. CRFs have been submitted as requested by clinical pharmacology
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requesting a waiver for 4 years and < Requesting a deferral for 4-11 yrs old (b) (4) The sponsor will need a pediatric plan for 0-4 years old since waiver is unlikely

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
					to be granted
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X		
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		All bioequivalence studies conducted in (b) (4)
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		No datasets submitted Unable to find them in electronic submission
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No clinical studies conducted
34.	Are all datasets to support the critical safety analyses available and complete?		X		No datasets submitted
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		No datasets submitted
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes, depending on CMC and clinical pharmacology's final assessment____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. (b) (4) The applicant will need to submit a more comprehensive pediatric plan that includes all age groups and all indications.
2. Thorough QTc studies may be necessary
3. Electronic datasets should be submitted unless not necessary per clinical pharmacology reviewer.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Helen Sile, MD	5-14-09
Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

Frances G Fahnbulleh
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Nancy Snow
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