

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022524Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	July 2, 2010
<b>From</b>	Sue-Chih Lee, Clinical Pharmacology Team Leader CDER/OTS/OCP/DCP3
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/ BLA #</b>	NDA 22-524
<b>Applicant</b>	Par Pharmaceuticals, Inc.
<b>Date of Submission &amp; Receipt</b>	May 4, 2010
<b>PDUFA Goal Date</b>	July 4, 2010
<b>Proprietary Name / Established (USAN) names</b>	Zuplenz® /Ondansetron
<b>Dosage forms / Strength</b>	▪ Oral Soluble Films, 4 mg & 8 mg
<b>Proposed Indication</b>	<p><u>Adults:</u></p> <ul style="list-style-type: none"> <li>• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin <math>\geq 50</math> mg/m<sup>2</sup> (CINV-HEC)</li> <li>• Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC)</li> <li>• 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)</li> <li>• Prevention of postoperative nausea and/or vomiting (PONV): As with other antiemetics, routine prophylaxis is 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.</li> </ul> <p><u>Pediatrics:</u></p> <ul style="list-style-type: none"> <li>• Prevention of CINV-MEC for patients <math>\geq 4</math> years of age</li> <li>• Safety and effectiveness of Zuplenz for other indications have not been established in any age group of pediatric patients</li> </ul>
<b>Recommended Action:</b>	Approval

## Table of Contents

1. Introduction.....	2
2. Background.....	3
3. CMC.....	5
4. Nonclinical Pharmacology/Toxicology .....	5
5. Clinical Pharmacology/Biopharmaceutics.....	6
6. Clinical Microbiology.....	6
7. Clinical – Efficacy and Safety .....	6
8. Advisory Committee Meeting.....	7
9. Pediatrics.....	7
10. Other Relevant Regulatory Issues.....	8
11. Labeling .....	8
12. Recommendations/Risk Benefit Assessment.....	10

### 1. Introduction

This is a re-submission of NDA 22-524, which was received on May 4, 2010. The original NDA, submitted on April 7, 2009, was issued a Complete Response letter on February 5, 2010, because DSI inspection of the pivotal bioequivalence study could not be conducted in time and the label needed revision.

This NDA is 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 as the reference product. There are no safety and efficacy trials to support the NDA. The sponsor conducted a bioequivalence study (Protocol OND/CR/020/08-09; Study 01905/08-09) comparing the PK parameter of the proposed product to the reference product. Both Cmax and AUC for the proposed product were found to meet the bioequivalence criteria. A request was made on June 4, 2009 for DSI inspection of both the clinical site ( (b) (4) ) and analytical site ( (b) (4) ) of this pivotal BE study. However, due to Agency-wide restrictions on foreign travel, the inspection could not be conducted before the action date.

When DSI inspections took place, the clinical site ( (b) (4) ) had ceased operation. Therefore, inspections of both the clinical and analytical portions were conducted at (b) (4) . The inspections were completed on April 22, 2010, which found deficiencies with both the clinical and analytical portions of the study. Upon evaluation of the responses from (b) (4) to address those deficiencies, DSI concluded that the data from the bioequivalence study are acceptable for review.

In the current submission, the sponsor provided the DSI inspection report, and the revised labeling.

Note that 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<sub>3</sub> receptor antagonist. Serotonin 5-HT<sub>3</sub> 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#102262) 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.

The original NDA was submitted and received on April 7, 2009. It was a standard 505(b)(2) application with a PDUFA deadline of February 7, 2010. The sponsor performed bioequivalence studies using Zofran ODT as the reference product and no safety and efficacy trials were conducted. The NDA received a Complete Response action on February 5, 2010, because a DSI inspection could not be conducted in time and the label needed revision.

### **2.2 Current Submission**

The current submission contains the DSI report on the inspection of the pivotal bioequivalence study (Protocol OND/CR/020/08-09) and the sponsor's revised labeling.

### **2.3 NDA Review documents**

In the previous review cycle, all the relevant review disciplines had 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

In this review cycle, the following review disciplines have written review documents:

- Clinical Pharmacology Review by Dilara Jappar, dated June 30, 2010

- Clinical Reviews by Tamara Johnson, dated June 24, 2010
- CMC Review by Bogdan Kurtyka dated June 24, 2010
- DSI report by John A. Kadavil dated May 17, 2010
- OSE/DRISK Review (patient labeling) by John C. Hubbard dated June 21, 2010

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

### **3. CMC**

The reader is referred to the Drug Product and Drug Substance Review by Dr. Bogdan Kurtyka dated June 24, 2010, for complete information.

In the first review cycle, the NDA was concluded to have sufficient information to assure the identity, strength, purity, and quality of Zuplenz over the proposed expiration dating period (24 months) when stored as labeled. The remaining issues are related to labeling.

In this review cycle, the sponsor has corrected the deficiencies in labeling (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, etc.).

#### **3.1 Final Recommendation**

This NDA is recommended for “Approval” from a CMC perspective at this time.

### **4. Nonclinical Pharmacology/Toxicology**

In the previous review cycle, the Nonclinical Pharmacology/ Toxicology discipline recommended approval of the NDA from their perspective. No new nonclinical Pharmacology/ toxicology information is provided by the sponsor in the current submission.

## **4.1 Final Recommendation**

An “Approval” action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline.

## **5. Clinical Pharmacology/Biopharmaceutics**

In the previous review cycle, it was concluded 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. Although Zofran ODT was approved by demonstrating bioequivalence to Zofran Tablets without additional safety and efficacy trials, it was concluded that biocreep is not an issue based on an evaluation of the overall data. However, DSI inspection of the pivotal BE study was pending. In addition, the sponsor’s proposed labeling was not acceptable.

### **5.1 Review Summary**

DSI inspection of the clinical site and analytical site for the pivotal bioequivalence study was completed on April 22, 2010. Although there were deficiencies cited following the inspection of the analytical site, the DSI recommended that the bioequivalence data be accepted for review following evaluation of the firm’s response. As such, it is concluded that Zuplenz is bioequivalent to Zofran ODT of the same strength under fed or fasting conditions.

There were many labeling issues identified in the previous review cycle (see Dr. Insook Kim’s review dated February 1, 2010). In addition to those, the main issues identified in the current review cycle are related to drug-drug interactions, including the following:

- The language for drug interaction with tramadol was vague and was revised to increase clarity based on the articles referenced in the label.
- Drug interaction with apomorphine was added to the label, which was already in the Zofran IV label.

### **5.2 Final Recommendation**

This NDA is recommended for “Approval” from a clinical pharmacology perspective.

## **6. Clinical Microbiology**

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

## **7. Clinical – Efficacy and Safety**

## 7.1 Overview

This is a 505(b)(2) submission. No clinical trials were conducted to demonstrate the safety or efficacy of the proposed product. Rather, clinical efficacy is inferred through establishing bioequivalence of the proposed product to the reference product, Zofran ODT. In the previous review cycle, 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. No new safety or efficacy information is provided in the current submission. However, additional labeling recommendations were made by Dr. Johnson.

## 7.2 Review Summary

These additional labeling recommendations include the following:

- Patient Counseling Information: Language added to inform patients of most common adverse reactions and to clarify instructions regarding how to take Zuplenz.
- 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 made to prevent misleading representation of dose, (iii) Language added to inform patients of most common adverse reactions, and (iv) Language added to alert specific patient populations of their increased risks with Zuplenz use (i.e., (b) (4)).
- Recommended not to include, in the Patient Instructions for Use, the dosage for each population and indication to avoid confusion or patient self-dosing.
- Recommended not to change (b) (4) to “adverse reactions” since the Sponsor must stay consistent with the Zofran ODT labeling as they do not have rights to the data that determined the causal relationship between ondansetron and the adverse event.

## 7.3 Final Recommendation

An “Approval” Action is recommended by the Clinical Review Team.

## 8. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

## 9. 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’s pediatric plan under PREA dated July 21, 2009 was unacceptable as it mainly addressed the indication of PONV for patients aged 4-11 years. The recommended

pediatric plan was forwarded to the sponsor and the sponsor has committed to conduct the required studies as postmarketing requirements (see Section 13.4).

## 10. Other Relevant Regulatory Issues

### 10.1 Division of Scientific Investigations (DSI) audits

A DSI inspection request was made on June 4, 2009, for the inspection of the clinical site ( [REDACTED] (b) (4) ) and analytical site ( [REDACTED] (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.” Due to foreign travel restrictions, the inspection could not be conducted before the PDUFA due date. Subsequently, the inspection was conducted in April 2010. At the time, the clinical site was no longer in operation and both the clinical and analytical portions were inspected at [REDACTED] (b) (4) . The inspections were completed on April 22, 2010, which found deficiencies for both the clinical and analytical portions. Upon review of the firm’s response to address deficiencies, DSI recommended that the study data be accepted for review. As such, the clinical pharmacology review concluded that Zuplenz Oral Soluble Film is bioequivalent to Zofran ODT.

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

### 10.2 QT Prolongation Potential

The QT prolongation potential has not been formally studied for any ondansetron products. Recently, thorough QT (TQT) studies have been conducted for three products of 5-HT<sub>3</sub> receptor antagonists, namely, Aloxi (palonosetron) IV, Sancuso (granisetron) Transdermal Patch, and Anzemet (dolasetron) IV. Out of the three studies, dolasetron IV was found to have positive QT prolongation effect while the other two had negative findings. There were discussions about the mechanism of requiring a TQT study for ondansetron products. It was decided that this issue will be further discussed and a postmarketing requirement for a TQT study will not be required of the Zuplenz sponsor when the approval action is taken.

## 11. Labeling

### 11.1 Proprietary name

During the previous review cycle, 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.

## **11.2 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 had additional recommendations on labels as described in the section below.

## **11.3 Physician Labeling / Medication Guide / Carton and Container Labeling**

SEALD, DDMAC and DMEPA all provided labeling comments during the previous review cycle while DRISK provided comments on patient package insert during this review cycle. The most notable revisions from these consults are summarized below.

### **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. [REDACTED] (b) (4) should be stated as “10 pouches each containing 1 soluble film.”

**Patient Package Insert (PPI):**

- Simplify wording to be consistent with other labeling, e.g., use the statement “What is Zuplenz?” rather than [REDACTED] (b) (4)
- Ensure that the PPI is consistent with the PI. There are several revisions under this category. For example, the following statements were added to the PPI: “It is not known if ZUPLENZ is safe and works in children to prevent nausea and vomiting with radiation therapy, or nausea and vomiting that may happen after surgery in children”, and “Who should not take ZUPLENZ?”
- The text and the associated illustrations for the instructions on use of the product should go next to each other so patients can follow easily.

## **12. Recommendations/Risk Benefit Assessment**

### **12.1 Recommended Regulatory Action**

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

- Clinical Pharmacology: Approval
- Clinical: Approval
- Pharm/Tox: Approval
- ONDQA: Approval

CDTL Recommendation for Regulatory Action: Approval

## 12.2 Risk Benefit Assessment

The proposed product (Zuplenz) is bioequivalent to the reference product (Zofran ODT) in terms of C<sub>max</sub> and AUC. 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. Zuplenz does not present any additional safety concern based on Dr. Tamara Johnson's review of safety data from all Phase 1 studies. According to Dr. Bogdan Kurtyka, the application has sufficient information to assure the identity, strength, purity, and quality of Zuplenz over the proposed expiration dating period (24 months) when stored as labeled. In addition, all CMC facilities for the drug substance and drug product are in compliance with cGMP. Therefore, the overall benefit of ZUPLENZ appears to outweigh any risk associated with use.

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

No REMS is recommended with this application.

## 12.4 Recommendation for Postmarketing Required Pediatric Studies

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 Zuplenz was held on January 6, 2010, which recommended waiver for the following:

- Waiver for CINV-HEC and CINV-MEC in patients <4 years: This is because these patients have an IV line and 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.
- Full pediatric waiver for RINV because there are too few children with disease/condition to study.

The sponsor is required to conduct the following studies as postmarketing requirements.

### *Study 1: CINV-HEC*

Deferred pediatric study under PREA for the prevention of nausea and vomiting in pediatric cancer patients ages 4 to <17 years receiving highly emetogenic chemotherapy (HEC). A PK and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric patients ages 4 to <17 years receiving HEC.

Final Protocol Submission Date: June 30, 2011

Study Completion Date: June 30, 2012  
Final Study Report Submission Date: December 31, 2012

*Study 2: CINV-HEC*

Deferred pediatric study under PREA for the prevention of nausea and vomiting in pediatric cancer patients ages 4 to <17 years receiving HEC. 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 in pediatric patients ages 4 to <17 years receiving HEC.

Final Protocol Submission Date: December 31, 2013  
Study Completion Date: June 30, 2015  
Final Study Report Submission Date: December 31, 2015

*Study 3: PONV*

Deferred pediatric study under PREA for the prevention of postoperative nausea and vomiting (PONV) in pediatric surgical patients ages 0 to <17 years. A PK and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric surgical patients ages 0 to <17 years. An age-appropriate formulation must be developed for younger pediatric patients.

Final Protocol Submission Date: June 30, 2011  
Study Completion Date: June 30, 2012  
Final Study Report Submission Date: December 31, 2012

*Study 4: PONV*

Deferred pediatric study under PREA for the prevention of PONV in pediatric surgical patients ages 0 to <17 years. 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 in pediatric surgical patients ages 0 to <17 years. An age-appropriate formulation must be developed for younger pediatric patients.

Final Protocol Submission Date: December 31, 2016  
Study Completion Date: December 31, 2017  
Final Study Report Submission Date: June 30, 2018

**12.5 Recommendation for other Postmarketing Study Requirements (PMRs)**

None

**12.6 Recommendation for Postmarketing Study Commitments (PMCs)**

None

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SUE CHIH H LEE

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