

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022524Orig1s000**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 21, 2010

To: Donna Griebel, M.D., Director  
**Division of Gastroenterology Products (DGP)**

Through: Director or Mary Willy, PhD, Deputy Director  
**Division of Risk Management (DRISK)**

Sharon Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: John C. Hubbard, MPAS, PA-C  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): ZUPLENZ (ondansetron) Oral Soluble Film

Application Type/Number: NDA 22-524

Applicant/sponsor: Par Pharmaceuticals, Inc.

OSE RCM #: 2010-1031

## **1 INTRODUCTION**

On April 7, 2009, Par Pharmaceuticals, Inc., submitted an original 505(b)(2) New Drug Application, NDA 22-524, for ZUPLENZ (ondansetron) oral soluble film. FDA took a Complete Response (CR) action on February 5, 2010 because the DSI inspection was postponed due to travel restrictions, and product labeling was not agreed upon.

Par Pharmaceuticals, Inc., submitted their Complete Response Resubmission to the Agency's CR action letter on May 4, 2010. The Applicant's resubmission includes revised Prescribing Information, patient labeling, and carton/container labeling.

This review is written in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for ZUPLENZ (ondansetron) oral soluble film.

Please let us know if DGP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2 MATERIAL REVIEWED**

- Draft ZUPLENZ (ondansetron) oral soluble film Prescribing Information (PI) re-submitted on May 4, 2010, revised by the Review Division and provided to DRISK on June 7, 2010.
- Draft ZUPLENZ (ondansetron) oral soluble film Patient Package Insert (PPI) re-submitted on May 4, 2010 revised by the review division and provided to DRISK on June 7, 2010

## **3 RESULTS OF REVIEW**

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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JOHN C HUBBARD  
06/21/2010  
ZUPLENZ PPI IFU NDA 022524

MARY E WILLY  
06/21/2010  
I concur

MEMORANDUM

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

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DATE: May 17, 2010

TO: Donna J. Griebel, M.D.  
Director  
Division of Gastroenterology Products (DGP)

FROM: John A. Kadavil, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. \_\_\_\_\_  
Acting Team Leader (Bioequivalence)  
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIR Covering NDA 22-524, Zuplenz  
(Ondansetron) Orally Dissolving Film Strip 8 mg,  
Sponsored by Monosol Rx

At the request of DGP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 22-524:

**Study Number:** 01905/08-09

**Study Title:** "An open-label randomized, single oral dose, two way crossover bioequivalence study to compare Ondansetron Orally Dissolving Film Strip (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"

The clinical portion of Study 01905/08-09 was conducted at \_\_\_\_\_ and the analytical portion was conducted at \_\_\_\_\_

(b) (4)

(b) (4)

(b) (4) Since (b) (4) ceased operations prior to this inspection, inspections of the clinical and analytical portions were conducted at (b) (4)

Following the inspections (April 19 - 22, 2010), Form FDA 483 was issued. (b) (4) responded to the Form FDA 483 observations in a letter dated May 3, 2010. The observations, (b) (4) response, and our evaluations follow:

(b) (4)

**1. The firm failed to conduct adequate incurred sample reproducibility (ISR) assessment.**

Specifically, out of the 1,656 plasma samples analyzed for 46 subjects, only 24 samples from subjects 1 to 14 (1.4% of total samples) were re-assayed for ISR. Out of those 24 samples, 6 deviated from the original value by 22% to 72%.

It should be noted that 75% of ISR samples (18 out of 24) passed, which approaches the recommended 67% of ISR samples needing to pass for small molecules.

Since 100% of the study runs were accepted based on quality control samples (QCs) and calibrators meeting acceptance criteria (95% QCs and 100% standard curves passed for all runs), the above finding should not significantly affect the study outcome. However, the firm must improve their ISR procedure (see firm's response below).

**2. The firm's SOP for ISR is insufficient.**

Specifically, the SOP only requires 5% of total study samples (but not less than 24) for ISR assessment regardless of the number of samples in the study. The agency requires a minimum of 10% for ISR assessment in smaller studies, and a minimum of 5% for larger studies.

During the inspection and in their written response, the firm stated that their ISR SOP has been updated to require at least 10% of ISR samples for studies with 1000 or fewer samples, and at least 5% for studies with 2000 or more samples. DSI accepts their response.

**3. The firm failed to fully report and discuss all data generated during assay validation.**

Specifically, the firm failed to include results from method validation run "P&A-IV" for assessing sensitivity, dilution integrity and re-injection reproducibility. Even though the standard curve was acceptable and 15 out of 18 run acceptance QCs passed, results from the run were not used.

In their response, the firm included results from the rejected batch, and there was no adverse impact on method validation results. DSI accepts the firm's response.

**4. The firm failed to follow the protocol.**

Specifically, vital signs were not measured at the protocol-specified times at 1 hour pre-dose and at 24 hours post-dose. For 44 out of 48 subjects, vital sign checks deviated at least 90 minutes from the scheduled pre-dose and post-dose times.

Although the firm should have followed the protocol, this finding should not adversely affect study outcome. In their response, the firm acknowledged the finding and promised to provide clearer language for vital sign measurement procedures and timings in the protocol. DSI accepts their response.

**Conclusion:**

Following DSI's evaluation of the inspectional findings and the firm's response, DSI recommends that the inspected clinical and analytical portions be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.  
Pharmacologist

**Final Classification:**

Page 4 - NDA 22-524, Zuplenz (Ondansetron) Orally  
Dissolving Film Strip 8 mg

cc:

OC DSI GLPBB/Yau/Kadavil/Rivera-Lopez/CF

OND ODEIII DGP/Fahnbulleh

OTS OCP DCPIII/Fang

Draft: JAK 5/17/10

Edit: MKY 5/17/10

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JOHN A KADAVIL

05/17/2010

Dr. Martin Yau signed the paper copy on May 17, 2010. Original signed copies are available in the DSI file.

## SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-524
APPLICANT	Par Pharmaceutical Resources, Incorporated
DRUG NAME	ZUPLENZ (ondansetron)
SUBMISSION DATE	April 7, 2009
SEALD REVIEW DATE	January 20, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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DEBRA C BEITZELL  
01/21/2010

LAURIE B BURKE  
01/21/2010

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** January 20, 2010

**To:** Frances Fahnbulleh, Regulatory Project Manager  
Division of Gastroenterology Products (DGP)

**From:** Kathleen Klemm, Regulatory Review Officer  
Sheetal Patel, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**CC:** Shefali Doshi, Regulatory Review Officer, DDMAC  
Robert Dean, DTC Group Leader, DDMAC  
Lisa Hubbard, Professional Group Leader, DDMAC

**Subject:** NDA 22-524  
DDMAC labeling comments for ZUPLENZ (ondansetron) Oral Soluble Film

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DDMAC has reviewed the proposed product labeling (PI), carton and container labels, and patient labeling for ZUPLENZ (ondansetron) Oral Soluble Film (Zuplenz) submitted for consult on June 7, 2009, and offers the following comments.

The version of the draft PI and patient labeling used in this review is titled, "1.12.10 FinalDRAFTLabel22524(3).doc" and was sent via email from Frances Fahnbulleh to Kathleen Klemm and Sheetal Patel on January 12, 2010.

DDMAC's comments on the PI and patient labeling are provided directly on the marked up version of this document, attached below. DDMAC's comments will also be inserted in the draft PI in the DGP eRoom. DDMAC's comments on the carton and container labels are also attached below.

Thank you for the opportunity to comment on this proposed material.

If you have any questions on the comments for the PI or carton and container labels, please contact Katie Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions on the comments for the patient labeling, please contact Sheetal Patel at 301.796.5167 or Sheetal.Patel@fda.hhs.gov.

Carton and Container Labels

DDMAC has reviewed the following proposed carton and container labels, and offers the following comments:

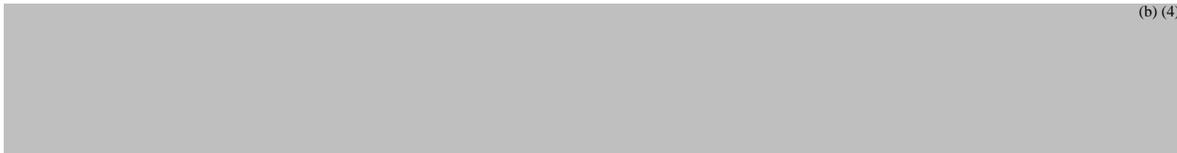


These documents were obtained via the DGP eRoom and were last modified on September 29, 2009.

General Comments

DDMAC recommends that the proposed carton and container labels be revised to present the dosage strength in direct conjunction and in equal prominence with the display of the dosage form.

[4mg-pouch-po-324.52.pdf](#) and [Singlepouch-po-325-52.pdf](#)



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KATHLEEN KLEMM

01/20/2010



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs - Immediate Office  
Pediatric and Maternal Health Staff  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**M E M O R A N D U M**

**Date:** December 23, 2009

**From:** Amy M. Taylor, MD, MHS, Medical Officer  
Pediatric and Maternal Health Staff

**Through:** Lisa Mathis, MD, OND Associate Director  
Pediatric and Maternal Health Staff, Office of New Drugs

**To:** Donna Griebel, MD, Director  
Division of Gastroenterology Products

**Re:** Pediatric plan for CINV

**Sponsor:** Par Pharmaceutical Companies, Inc.

**Drug:** Ondansetron Orally Dissolving Film Strip (Zuplenz) 4 and 8 mg

**Indications:** Proposed Adult Indications in the NDA

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin  $\geq 50\text{mg}/\text{m}^2$
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Prevention of nausea and vomiting associated with radiotherapy, either total body irradiation or single high-dose fraction or daily fraction to the abdomen
- Prevention of postoperative nausea and vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and /or vomiting will occur

postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ondansetron ODFS is recommended even where the incidence of postoperative nausea and/or vomiting is low.

#### Proposed Pediatric Indication in the NDA

- Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in pediatric patients 4 years and older

(b) (4)

#### **Dosage form and route of administration:**

Orally Dissolving Film Strip 4 and 8 mg

#### **Dosing regimen (proposed in the NDA):**

Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy

- Adults: 24 mg given successively as three 8 mg film strip administered 30 minutes before the start of single-day highly emetogenic chemotherapy.
- Pediatrics: none proposed

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

- Adults: 8 mg film strip given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8 mg film strip should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy
- Pediatrics: For pediatric patients 12 years 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 film strip given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4 mg film strip should be administered 3 times

a day (every 8 hours) for 1 to 2 days after completion of chemotherapy

#### Prevention of nausea and vomiting associated with radiotherapy

- Adults: the recommended adult oral dosage is one 8 mg film strip given 3 times a day.
  - For total body irradiation, one 8 mg film strip 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 film strip 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 film strip should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.
- Pediatrics: none proposed

#### Prevention of postoperative nausea and vomiting

- Adult: The recommended dosage is 16 mg given successively as two 8 mg film strip 1 hour before induction of anesthesia. Each film strip should be allowed to dissolve completely before administering the next film strip.
- Pediatrics: none proposed

**Document ID Number:** NDA 22-524 Associated IND (b) (4)

**Consult Question:** The Division of Gastroenterology Products requests PMHS' assistance in evaluating whether the CINV-HEC indication should be required or waived for Zuplenz ondansetron oral soluble film in the pediatric population.

#### **Background**

The sponsor, Par Pharmaceutical Companies, Inc. has submitted an original 505(b)(2) NDA for an orally dissolving film strip (ODFS) formulation of ondansetron (proposed trade name Zuplenz). The sponsor's proposed indications are chemotherapy-induced nausea and vomiting (CINV) - highly and moderately emetogenic (HEC and MEC respectively), post-operative nausea and vomiting (PONV) and radiotherapy-induced

nausea and vomiting (RINV) in adults and CINV- MEC in pediatric patients aged 4 years and above. (b) (4)

The application was received on April 7, 2009 and the PDUFA date is February 7, 2010.

**Drug product and indications**

Ondansetron is approved for marketing in several oral formulations and for injection. Approved adult indications are for prevention of CINV (both HEC and MEC), prevention of PONV and prevention of RINV. Approved pediatric indications are for CINV and PONV for the injection formulation and CINV (moderately emetogenic) for the oral tablet, oral solution and orally disintegrating tablet.

Zofran® (ondansetron HCl)

Formulation/ strength	Approved Pediatric Indication(s)	Clinical Studies
I.V (2 mg/ml)	CINV 6 month and older PONV 1 month and older	<ul style="list-style-type: none"> <li>• PK in pediatric cancer patients (1 month to 18 years)</li> <li>• PK in surgery patients (1 month to 12 years)</li> <li>• Open-label noncomparative trials in pediatric cancer patients (6 months to 18 years)</li> <li>• Placebo-controlled trials in pediatric surgical patients (1 month to 12 years)</li> </ul>
Oral Tablet (4 mg and 8 mg) Oral Solution (4 mg/5 mL) Orally Disintegrating Tablet (4 mg and 8 mg)	CINV-MEC 4 years and older	<ul style="list-style-type: none"> <li>• No pediatric pharmacokinetic data in labeling</li> <li>• Open-label, uncontrolled trials in pediatric cancer patients (4 to 18 years)</li> </ul>

The product which is the subject of this NDA is, according to the sponsor, a thin, flexible, non-friable polymeric film strip containing dispersed ondansetron and is intended to be

placed on the tongue for rapid dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract. The sponsor states that ondansetron ODFS will serve as a pharmaceutical alternative of an effective and safe anti-emetic therapy for patients who may have difficulty swallowing and/or holding down tablets or who may prefer a thin film to other oral forms.

The sponsor is relying on FDA’s previous finding for Zofran® Injection (NDA 20-007), Zofran® Tablets (NDA 20-103), Zofran® Oral Solution (NDA 20-605) and Zofran ODT® Orally Disintegrating Tablet (NDA 20-781) to support their application.

**Sponsor’s Proposed Pediatric Plan**

The pediatric plan included in the NDA contains the following:

- A request for a partial waiver for patients under 4 years of age
- [REDACTED] (b) (4)
- A request for a deferral of study in patients 4 to 11 years of age
- [REDACTED] (b) (4)

*Reviewer’s comment: Please refer to my Review from July 2009 for a full evaluation of the sponsor’s proposed pediatric plan.*

*The following is a chart of the Review Division’s current recommended pediatric plan. The recommended plan is schedule for review by the Pediatric Review Committee (PeRC) on January 6, 2010.*

**Overall Pediatric Plan Recommendations under PREA**

Indications	Age Groups			
	0-1 mo.	1 mo. - <4 years	4-11 years-old* <sup>+</sup>	12-17-old* <sup>+</sup>
CINV-HEC	----	?	?	?
CINV-MEC	----	PK studies and adequate well-controlled clinical study for safety and efficacy. Use age-appropriate formulation.	Fulfills PREA requirement as OSF = Zofran ODT for BE	Fulfills PREA requirement as OSF = Zofran ODT for BE
RINV	Add waiver: sponsor must submit request and justification			
PONV	For all age groups, PK studies and adequate well-controlled clinical study for safety and efficacy. Use age-appropriate formulations.			

\*OSF = oral soluble film, ODT = oral disintegrating tablet, BE = bioequivalence  
<sup>+</sup> Due to BE, the CINV-MEC indication will follow the Zofran ODT label and be considered “appropriately labeled for ages ≥ 4 years-old”.

**Prevention of chemotherapy induced and radiation induced nausea and vomiting in pediatric patients**

Chemotherapy-induced nausea and vomiting (CINV) is a common cause for poor compliance. (Cohen 2007) CINV is classified as acute (less than 24 hours after a

chemotherapy dose), delayed (24 hours up to seven days after a chemotherapy dose) and anticipatory CINV (usually one to four hours before chemotherapy, but can occur several days prior to chemotherapy). The incidence of CINV is related to the specific chemotherapy agent. With highly-emetogenic agents such as cisplatin ( $> 50 \text{ mg/m}^2$ ), more than 90% of patients develop nausea and vomiting. Moderately emetogenic agents such as methotrexate ( $50\text{-}250 \text{ mg/m}^2$ ) have a 10-30 % incidence. (Antonarakis 2004, Cohen 2007) Patient characteristics that are associated with a higher risk of CINV include female sex, age greater than 3 years, anxiety, motion sickness, and poor control with previous chemotherapy. Several classes of drugs have been used to prevent and treat CINV. These include 5-HT<sub>3</sub> blockers such as ondansetron and granisetron, dopamine antagonists such as metoclopramide and chlorpromazine, and corticosteroids.

**Written requests issued**

(b) (4)

(b) (4)

**Related Products**

Aloxi (palonosetron HCl) IV formulation is approved in adults for CINV (acute HEC and acute and delayed MEC) and acute PONV. The oral capsule is approved for CINV (acute MEC) in adults. There are no approved pediatric indications.

(b) (4)

Kytril (granisetron) IV formulation is approved in adults and pediatric patients 2 years and older for CINV and PONV in adults. There are no approved pediatric indications for the oral tablet or solution.

(b) (4)

Anzemet (dolasetron mesylate) IV formulation is approved for pediatric patients 2 years to 16 years for CINV and PONV. The tablet formulation is approved for CINV-MEC and PONV for patients 2 years to 16 years. Of note, dolasetron was withdrawn from the market in Europe due to safety concerns. The FDA assessed the cardiac safety concerns in 2007 and added the following to the labeling:

Rare cases of sustained supraventricular and ventricular arrhythmias, cardiac arrest leading to death, and myocardial infarction have been reported in children and adolescents.

### **Answers to Division's Question**

**1. The Division of Gastroenterology Products requests PMHS' assistance in evaluating whether the CINV-HEC indication should be required or waived for Zuplenz ondansetron oral soluble film in the pediatric population.**

PMHS recommends requiring pediatric studies in pediatric patients with cancer age 1 month to 17 years undergoing HEC. Pediatric patients do receive highly emetogenic chemotherapy, and thus there should be a sufficient number of patients in certain centers for enrollment in a study.

PMHS agrees with the Division's current plan to require PK, safety and efficacy studies in pediatric patients with cancer age 1 month to less than 4 years undergoing moderately emetogenic chemotherapy (MEC). Currently, for oral ondansetron, there is no approved indication for pediatric patients with cancer undergoing highly emetogenic chemotherapy (HEC) for any pediatric age group. PREA requires a pediatric assessment of all indications approved in the NDA in question. In this case, the sponsor is proposing separate indications for MEC and HEC in adults in the NDA. In addition, the dosing regimen proposed in adults is different, with a higher daily dose for HEC.

The required studies for HEC should include a PK study and an adequate and well controlled trial for safety and efficacy. It may be possible to extrapolate efficacy in pediatric patients undergoing HEC from adequate and well controlled efficacy studies in pediatric patients undergoing MEC *if* there is no history of discordance of efficacy between HEC and MEC in this class of drugs in adults (i.e. there is no history of efficacy being established for MEC and failing to be established HEC). The Division should request justification from the sponsor for extrapolating efficacy in pediatric patients undergoing HEC from adequate and well controlled efficacy studies in pediatric patients undergoing MEC. If a determination is made by the Division that efficacy can be extrapolated from MEC to HEC, a PK/PD study and a safety study is still needed because the total daily dose for HEC is expected to be higher than the total daily dose needed for MEC. As with MEC, and age appropriate formulation would be needed for the younger patients.

In addition to the PREA requirement, this application by a new Sponsor may be an opportunity to assess efficacy of ondansetron for nausea and vomiting caused by other etiologies. There is significant usage and reference of the use of antiemetics, especially ondansetron, in children for undifferentiated nausea and vomiting in the Emergency Department. Although not the focus of this review,

PMHS would like the opportunity to discuss issuing a WR for this product if the new sponsor has the opportunity to be granted a non-pediatric exclusivity with approval of this NDA.

### References

Alhashimi D, Al-Hashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents (Review) *The Cochrane Library* 2009, Issue 3

Antonarakis ES, Hain RDW. Nausea and vomiting associated with cancer chemotherapy: drug management in theory and in practice. *Arch Dis Child* 2004;89:877-880

Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. *Anesth Analg* 1990;70:160-7

Cohen IT. An overview of the clinical use of ondansetron in preschool age children. *Therapeutics and clinical risk management* 2007;3(2):333-339

Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. *Br J Anaesth* 1999;83:104-17

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/s/  
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AMY M TAYLOR  
01/05/2010

LISA L MATHIS  
01/05/2010  
Concur



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 30, 2009

To: Donna Griebel, MD, Director  
Division of Gastroenterology Products

Through: Kristina Arnwine, PharmD, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Lori Cantin, RPh., Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Labels and Labeling Review

Drug Name(s): Zuplenz (Ondansetron) Oral Soluble Film  
4 mg and 8 mg

Application Type/Number: NDA 022524

Applicant: Nycomed

OSE RCM #: 2009-937

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## 1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Products for assessment of labels and labeling for Zuplenz (Ondansetron) Oral Soluble Film, 4 mg and 8 mg.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis<sup>1</sup> (FMEA) to evaluate the labels and labeling submitted as part of the November 4, 2009, submission (Appendix A thru E; no image of insert labeling).

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved on to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 (*Comments to the Division*) for discussion during the review team's label and labeling meetings. Section 3.2 (*Comments to the Applicant*) contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Nitin Patel, OSE Regulatory Project manager, at 301-796-5412.

### 3.1 COMMENTS TO THE DIVISION

DMEPA's suggestions for revisions to the package insert labeling have been made on the working draft copy of the package insert in your Division's e-room and are subject to discussion during the review team's label and labeling meetings. Our suggested revisions are:

- Revisions to the dosage form designation to reflect the correct dosage form (e.g., "oral soluble film" or "film") for the product. In several instances, the Applicant had referred to the dosage form as (b) (4).
- Spelling out of the full phrase for the abbreviation "ODT" the first time it is used in the running text of the package insert labeling.
- Spelling out of the full phrases for abbreviations related to frequency of administration (e.g., b.i.d and t.i.d). In June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone symbols, abbreviations, and dose designations in prescribing. As part of this campaign, FDA agreed not to approve such symbols, abbreviations, and dose designations in labeling because they can be carried over to the prescribing practice.
- Addition of dosage units when omitted (e.g., (b) (4) should read as 4 mg to 8 mg).

Additionally, we note that the Applicant has included the FDA-approved Patient Labeling as a numbered subsection under section 17. SPL (Structured Product Labeling) no longer allows for patient labeling to be a numbered subsection under section 17. The Applicant can choose to append this information to the package insert, or this information may accompany the package insert as a separate document. The reader will be notified of the existence of the FDA-approved Patient Labeling in two places in the package insert labeling:

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

1. At the line at the end of Highlights that says "See 17 for Patient Counseling Information and FDA-approved Patient Labeling."
2. At the beginning of section 17, where the first line should read "See FDA-approved Patient Labeling."

### 3.2 COMMENTS TO THE APPLICANT

#### *Pouch Labels and Carton Labeling*

1. The colors used to present the 4 mg and 8 mg strengths use the same colors as the trade dress (blue and green). Using the same color for the trade dress as well as to display the strength minimizes the effect of color to differentiate the two strengths. Revise the labels and labeling to ensure the two strengths are well differentiated by the use of unique colors that are not present in your trade dress.
2. The prominence of the established name is not commensurate to the proprietary name. Increase the prominence of the established name so that it appears at least  $\frac{1}{2}$  as large as the proprietary name and ensure its prominence is commensurate with the prominence of the proprietary name taking into account all pertinent factors including typography, layout, contrast, and other printing features.
3. Revise the container labels and carton labeling to accurately reflect the correct dosage form for the product. For example, on the pouch label (b) (4) should be stated as "1 Soluble Film", and on the carton labeling (b) (4) should be stated as "10 pouches each containing 1 soluble film".

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

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

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/s/

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LORI G CANTIN  
12/30/2009

DENISE P TOYER on behalf of KRISTINA C ARNWINE  
12/30/2009

DENISE P TOYER  
12/30/2009

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

## **Division of Gastroenterology Products**

**Application Number:** NDA 22-524

**Name of Drug:** Zuplenz (Ondansetron) Oral Soluble Film

**Applicant:** Par Pharmaceutical Companies, Inc.

### **Material Reviewed:**

**Submission Date(s):** April 7, 2009

**Receipt Date(s):** April 7, 2009

**Submission Date of Structure Product Labeling (SPL):** April 7, 2009

**Type of Labeling Reviewed:** WORD

### **Background and Summary**

Par Pharmaceutical Companies, Inc. has submitted an original 505(b) (2) NDA for Ondansetron Oral Soluble Film (Zuplenz). The sponsor has developed a new dosage form of ondansetron, using a thin film technology. Ondansetron Oral Soluble Film will serve as a pharmaceutical alternative antiemetic therapy for patients who may have difficulty swallowing and/or holding down tablets, or who may prefer a thin film to other oral forms.

The proposed indications are:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin  $\geq 50\text{mg/m}^2$
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
3. Prevention of nausea and vomiting associated with radiotherapy, either total body irradiation, or single high dose fraction or daily fractions to the abdomen
4. Prevention of post-op nausea and vomiting

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

## Review

The following issues/deficiencies have been identified in your proposed labeling.

### Format Revisions:

1. **Highlights of Prescribing Information**
  - a. Highlights, excluding the boxed warning, must be limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11 paper, single spaced, 8 point type with ½ inch margins on all sides, in a two-column format). Your request for waiver of Highlights' one-half page requirement is acknowledged.
  - b. Initial approval date should reflect original approval date of active ingredient. Label does not reflect original approval date of active ingredient, ondansetron. (Refer to 21 CFR 201.57(3)), The verbatim statement "Initial U. S. Approval" followed by the four digit year in which FDA initially approved a new molecular entity. (i.e., 1991)
  - c. Under **INDICATIONS AND USAGE**: All headings must be in bold type. Subheading "Prevention of Postoperative Nausea and Vomiting: the information should be concisely summarized without repetition, and presented in an easily accessible format( e.g., bulleted, tabular).
  - d. Each summarized statement should be located under the appropriate Highlights heading and must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The subheading "**WARNINGS AND PRECAUTIONS**" should be shifted to the right column, above the three bullet points describing warnings and precautions.
  - e. There should be white spaces between each major heading in the Highlights; a space should be inserted: above **INDICATIONS AND USAGE**, above **DOSAGE FORMS AND STRENGTHS**, and above **CONTRAINDICATIONS**.
  - f. Bullet points under **INDICATIONS AND USAGE**, **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**, **DRUG**

INTERACTIONS and USE IN SPECIFIC POPULATIONS should be shifted to the left to fall in sequence with the set margins.

- g. Under **DOSAGE AND ADMINISTRATION**:
  - i. Tabular format should be used to enhance accessibility of information (e.g., when there are different dosing regimens for different indications).
  - ii. Under **DOSAGE FORMS AND STRENGTHS**, the strength and potency of dosage form should be expressed in metric system, which is correct except for the hyphen in (b) (4). Remove the hyphen so it reads “8mg” under each indication.
  - iii. The date of the most recent revision of the labeling must be presented at the end of Highlights, and must appear in bold type. 21 CFR 201.56(5) (e) (5)

2. Full Prescribing Information (FPI):

- a. The right column (**ADVERSE REACTIONS**) begins at the same level as the **FULL PRESCRIBING INFORMATION: CONTENTS \***, this heading should be shifted down to begin on the same line as **INDICATIONS AND USAGE**.
- b. Remove all periods after numbers for section and subsection headings.
- c. Section headings must be in bold type and should be in upper-case letters.
- d. Subsection headings must be indented and not bolded and should be in regular text, or non uppercase letter.
- e. Create subsection headings that identify the content. Avoid using the words “General”, “Other”, “Miscellaneous” for a subsection heading. In subsection 5.4, change (b) (4) to “Effect on Peristalsis”, and un-bold.
- f. Avoid using acronyms in subsection headings. In subsection 5.2 (b) (4) changes, and un-bold. (Refer to the Institute for Safe Medication Practices website at [www.ismp.org/Tools/abbreviationslist.pdf](http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.
- g. In section 17: **PATIENT COUNSELING INFORMATION**, the label refers to a (b) (4) label; this section should be labeled as (17.1) Information for Patient and (17.2) FDA- Approved Patient Labeling.

3. Overview of Full Prescribing Information:
  - a. All headings and subheadings should be named and numbered correctly as outlined under 21 CFR 201.56(d)(1), therefore, remove all decimals after each heading number.
  - b. The use of subheadings to organize information in the FPI is encouraged. Each subheading that is used must be assigned a decimal number that corresponds to its placement and order in the FPI. Do not number headings within a subsection (e.g., do not use 14.3.1); use headings within a subsection without numbering.
  - c. Identifying numbers must be presented in bold print, and must precede the headings and subheadings by at least a space of 2 square m's.
4. Preliminary Carton and Container Revision:
  - a. Insert proposed proprietary name throughout label to replace (TRADE NAME)
  - c. Update dosage form to Oral Soluble Film
  - d. Revise storage conditions to be consistent with USP definition of controlled room temperature.

### **Recommendations**

Please address the identified deficiencies/issues and re-submit labeling by December 28, 2009. This updated version of labeling will be used for further labeling discussions.

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Frances Fahnbulleh, PharmD  
Regulatory Project Manager  
Division of Gastroenterology Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

Supervisory Comment/Concurrence:

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Matthew Scherer, MS  
Acting Chief, Project Management Staff  
Division of Gastroenterology Products

Drafted: FGF/11- 13 -09

Revised/Initialed: 12/18/09

Finalized: 12/22/09

Filename: CSO Labeling Review Template (updated 1-16-07).doc

**CSO LABELING REVIEW OF PLR FORMAT**

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

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/s/

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FRANCES G FAHNBULLEH  
12/23/2009  
RPM labeling review

MATTHEW C SCHERER  
12/23/2009

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # <b>22-524</b>	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Zuplenz Established/Proper Name: Ondansetron Dosage Form: Orally Dissolving Film Strip Strengths: 4mg and 8mg		
Applicant: Par Pharmaceutical Companies, Inc. Agent for Applicant (if applicable):		
Date of Application: April 7, 2009 Date of Receipt: April 7, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: February 7, 2010 (Sunday)		Action Goal Date (if different): February 5, 2010 (Friday)
Filing Date: June 6, 2009 Date of Filing Meeting: May 14, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>category 3</b>		
Proposed Indication(s): Prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> <b>505(b)(2)</b>
<b>Refer to Appendix A for further information.</b>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> <b>Standard</b> <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <b>No</b> Resubmission after refuse to file? <b>No</b>		
Part 3 Combination Product? <b>No</b>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other: <b>Standard</b>	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): (b) (4)	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments: N/A	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO   <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes</b>, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p><b>Note:</b> If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</p>			
<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p> <p>If yes, please list below:</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</p>			
<b>Format and Content</b>			
<p><b>Do not check mixed submission if the only electronic component is the content of labeling (COL).</b></p> <p><b>Comments:</b> eCTD format</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>			
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><b>Forms include:</b> 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); <b>Certifications include:</b> debarment certification, patent certification(s), field copy certification, and pediatric certification.</p> <p><b>Comments:</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission</b>, does it follow the eCTD guidance? (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not</b>, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>BLAs/BLA efficacy supplements only:</b> N/A</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<b>PREA</b>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Comments:</b>	

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide (listed as FDA approved patient labeling) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES NO  YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

ATTACHMENT

## MEMO OF FILING MEETING

**DATE:** May 14, 2009

**NDA/BLA #:** 22-524

**PROPRIETARY/ESTABLISHED NAMES:** Zuplenz (Ondansetron) Orally Dissolving Film Strip

**APPLICANT:** Par Pharmaceutical Companies, Inc.

### BACKGROUND:

Par Pharmaceutical Companies, Inc. has submitted an original 505(b)(2) NDA for Ondansetron ODFS (Zuplenz). This molecular entity is already approved and the sponsor has now developed a new dosage form of ondansetron, using a thin film technology. Ondansetron ODFS (orally dissolving film strip) will serve as a pharmaceutical alternative of an effective and safe antiemetic therapy for patients who may have difficulty swallowing and /or holding down tablets, or who may prefer a thin film to other oral forms. The proposed indication for use includes: Prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting.

### REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frances Fahnbulleh	Y
	CPMS/TL:	Cristi Stark Brian Strongin	N Y
Cross-Discipline Team Leader (CDTL)	Nancy Snow		Y
Clinical	Reviewer:	Helen Sile	Y
	TL:	Nancy Snow	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	

OSE	Reviewer:	DMEPA : Lori Cantin	N
	TL:	TBD	N
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Lanyan (Lucy) Fang	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	N/A (NAI)	NAI
	TL:	Mike Welch	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Charles Wu	Y
	TL:	Sushanta Chakder	Y
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka	Y
	TL:	Marie Kowblansky	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	N/A	
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		
Other reviewers	DDMAC, DRISK		No

**OTHER ATTENDEES:**

Donna Griebel, Director DGP  
Anne Pariser, Deputy Director, DGP  
Joyce Korvick, Deputy Director/Safety

<p>505(b)(2) filing issues?</p> <p><b>If yes, list issues:</b></p>	<p><input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p>Per reviewers, are all parts in English or English translation?</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b> NONE</p>	<p><input type="checkbox"/> Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Receipt of partial waiver and deferral requests acknowledged in 74-day letter; advice letter to follow.</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical study site(s) inspections(s) needed?</p> <p><b>If no, explain:</b> No clinical data; Biopharm sites to be inspected</p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO (No clinical data; Biopharm sites to be inspected)</p>
<p>• Advisory Committee Meeting needed?</p> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p><input type="checkbox"/> YES  Date if known:  <input checked="" type="checkbox"/> NO  <input type="checkbox"/> To be determined</p> <p>Reason:  This is not an NME</p>
<p>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Review issues conveyed in 74-day letter</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed? YES.</p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b> N/A</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>• Establishment(s) ready for inspection?</p> <p>▪ Establishment Evaluation Request (EER/TBP-EER)</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> Not Applicable</p>

submitted to DMPQ?  <b>Comments:</b> OC found all manufacturing and testing facilities listed in application to be acceptable as confirmed by the Establishment Evaluation System.	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
• Sterile product?  <b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>FACILITY (BLAs only)</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Donna Griebel

**GRMP Timeline Milestones:** See attached timeline below

**Comments:**

**TIMELINE**

<b><i>Letter Date of Application</i></b>	<b><i>April 7, 2009</i></b>
<b><i>Receipt Date of Application</i></b>	<b><i>April 7, 2009</i></b>
<b><i>Filing Meeting</i></b>	<b><i>May 14, 2009</i></b>
<b><i>60-Day Filing Date</i></b>	<b><i>June 5, 2009</i></b>
<b><i>74 Day Letter Date</i></b>	<b><i>June 19, 2009</i></b>
<b><i>Team Meeting #1</i></b>	<b><i>June 10, 2009</i></b>
<b><i>Team Meeting #2</i></b>	<b><i>July 15, 2009</i></b>
<b><i>Team Meeting #3 (Mid-Cycle Meeting)</i></b>	<b><i>September 14, 2009</i></b>
<b><i>Team Meeting #4</i></b>	<b><i>October 12, 2009</i></b>
<b><i>Team Meeting #5 (Wrap-up Meeting)</i></b>	<b><i>December 2, 2009</i></b>
<b><i>Division Goal Date(Final Reviews signed off in DFS)</i></b>	<b><i>December 5, 2010</i></b>
<b><i>Labeling Meeting #1</i></b>	<b><i>December 29, 2009</i></b>
<b><i>Labeling Meeting #2</i></b>	<b><i>January 6,2010</i></b>
<b><i>Labeling Meeting #3</i></b>	<b><i>January 11,2010</i></b>
<b><i>Labeling Meeting #4</i></b>	<b><i>January 20,2010</i></b>
<b><i>Labeling Meeting #5</i></b>	<b><i>January 2,2010</i></b>
<b><i>Labeling Meeting #6</i></b>	<b><i>January 29,2010</i></b>
<b><i>PDUFA goal date</i></b>	<b><i>February 5, 2010</i></b>

**\*\*Schedule will be adjusted/updated as deemed necessary\*\***

<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>X Review issues have been identified for the 74-day letter. List (optional):</p> <p>X Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
X	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

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Frances G Fahnbulleh  
6/17/2009 04:14:02 PM  
CSO

Revised RPM filing review

Brian Strongin  
6/18/2009 09:43:50 AM  
CSO