CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022524Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tamara Johnson, MD, MS/Nancy Snow, DO
Pharmacology Toxicology Review	Charles Wu, Ph.D./ Sushanta Chakder, Ph.D.
CMC Review	Bogdan Kurtyka, Ph.D./Moo Jhong Rhee, Ph.D.
Biopharmaceutics Review ONDQA	Houda Mahayni, Ph.D./Patrick Marroum, Ph.D.
Clinical Pharmacology Review	Insook Kim, Ph.D./Dilara Jappar, Ph.D/Sue-Chih Lee, Ph.D.
DDMAC	Kathleen Klemm/Sheetal Patel
DSI	John Kadavil, Ph.D./Martin Yau, Ph.D.
CDTL Review	Sue-Chih Lee, Ph.D.

OSE/DMEPA	Lori Cantin, R.Ph., PharmD/Kristina Tolivar, PharmD/Denise P. Toyer, PharmD
OSE/DRISK	John Hubbard, MPAS, PA-C/Sharon Mills, BSN,RN,CCRP/Mary Willy, Ph.D.
SEALD	Debbie Beitzell, BSN/Laurie Burke, RPh, MPH
Pediatric and Maternal Health Staff	Amy M. Taylor, MD, MHS/Lisa Mathis, MD

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

Division Director Summary Review

1. Introduction

This is a Class I Resubmission response to a CR letter dated February 5, 2010. In this 505(b)(2) application, Par Pharmaceutical, Inc. proposes a new ondansetron oral dosage form – oral soluble film, in 4 mg and 8 mg doses. The applicant references the Agency's previous findings of safety and efficacy in the ondansetron NDAs Zofran Tablet (NDA 20103) and Zofran ODT (orally disintegrating tablet NDA 20781). This NDA relied upon demonstration of bioequivalence of Zuplenz to Zofran ODT. Zofran ODT was itself approved based on demonstration of bioequivalence of Zofran ODT to Zofran tablets. The proposed indications for Zuplenz are:

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Prevention of postoperative nausea and/or vomiting.

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

Although the bioequivalence data in the original NDA submission appeared to support approval of Zuplenz, inspection of the "pivotal" bioequivalence trial Protocol OND/CR/020/08-09 (site in India) and the analytical site (b) (4) could not be conducted during the first review cycle due to a Department of State Travel Advisory. Because establishment of the safety and efficacy of the proposed product hinged on the bioequivalence study that could not be inspected, a CR letter was issued. The inspections were conducted April 19-22, 2010, and the applicant has resubmitted the NDA.

The CR letter February 5, 2010 cited the inability to inspect the sites and unresolved product labeling as the only CR issues. In this review cycle, I will limit my comments to new

information in the resubmission. Please refer to the appended Division Director Summary Review from the original review cycle for a summary of each discipline's review recommendations and conclusions.

2. Background

Ondansetron is a 5-HT3 receptor antagonist. Multiple ondansetron products are currently marketed, including generics and oral dissolving tablets.

3. CMC

I concur with the conclusions reached by the Chemistry Reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. See appended original Division Director Review for more details. In this resubmission, the Chemistry Reviewers have found the labeling acceptable. The facilities are still in compliance. I concur with their recommendation for approval.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the Pharmacology/Toxicology Reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concurred with the Clinical Pharmacology reviewers in the first review cycle that the bioequivalence data appeared to support approval of Zuplenz; however, the inability to inspect the bioequivalence trial Protocol OND/CR/020/08-09 clinical and analytical sites in (b) (4). Approval hinged on completion of the inspection, a satisfactory inspection report for the sites, and resolution of product labeling. The DSI inspections were conducted April 19-22, 2010 at (b) (4) Because the (b) (4) (where the clinical portion of the study was conducted) ceased operations prior to inspection, the clinical and analytical portions of the inspection were both conducted at (b) (4) The DSI report comments on both analytical issues and clinical trial conduct. A 483 was issued, citing 4 issues, and DSI accepted the responses received to each. DSI concluded that the clinical and analytical data were acceptable for review.

The 4 issues cited by DSI were:

1. Failure to conduct adequate incurred sample reproducibility (ISR) assessment. Out of 1,656 plasma samples analyzed from 46 subjects, only 24 samples from 14 subjects (1.4% of total samples) were re-assayed for ISR. Of those, 6 deviated from the original value by 22% to 72%. The DSI inspector noted that 75% of ISR samples (18/24) passed, which approaches the recommended 67% of ISR samples needed to pass. The inspectors concluded that 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), this inspection finding should not significantly

affect the study outcome. They noted that the firm must improve their ISR procedure, and the firm indicated that they had done so.

2. The SOP for ISR was insufficient. The SOP only required 5% of total study samples (but not less than 24) for ISR assessment, regardless of the number of samples in the study. FDA 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 accepted the response.

3. Failure to fully report and discuss all data generated during assay validation. Results from method validation run "P&A-IV" were not included 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 to the 483, the firm included results from the rejected batch, and there was no adverse impact on method validation results. DSI accepted the firm's response.

4. Failure to follow the study 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 schedule. The inspectors determined that this 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 timing in protocols. DSI accepted the response.

I concur with the Clinical Pharmacology reviewer and the CDTL that in light of the favorable recommendation of the DSI inspectors, the bioequivalence data can be used to support the approval of this 505b2 NDA. I concur with their recommendation for approval and their recommendations for labeling, including clarification of the drug interaction with tramadol and the addition of information on the drug interaction with apomorphine (as a Contraindication, see Section 12 Labeling below, and as a Drug Interaction).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Please refer to the appended Division Director Summary review from the original review cycle. I concur with the Clinical Reviewers' recommendation for approval and with their recommendations regarding labeling. Those recommendations were incorporated in the final approved product labeling.

8. Safety

Please refer to the appended Division Director Summary review from the original review cycle. I concur with the Clinical Reviewers' recommendations regarding labeling (see Section 11 Other Regulatory Issues and Section 12 Labeling below).

9. Advisory Committee Meeting

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

10. Pediatrics

Please refer to the appended Division Director Summary review from the original review cycle.

The proposed product is a new dosage form. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The original application was discussed at a PeRC meeting on January 6, 2010. The summary recommendations from the PeRC meeting can be found in the appended Division Director Summary Review.

The reviewers have determined that FDA should waive the pediatric study requirement for the indication 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 because necessary studies are impossible or highly impracticable. This is because there are too few children with radiotherapy-induced nausea and vomiting to study.

We are waiving the pediatric study requirement for children less than 4 years of age for the following indications:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$50 mg/m^2; and
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. This is because there are age-appropriate formulations of alternative antiemetic products for these indications.

We are deferring submission of pediatric studies for the following indications and age groups:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$50 mg/m^2 in children ages 4 to less than 17 years; and

- prevention of postoperative nausea and/or vomiting in children ages 0 to less than 17 years

because this product is ready for approval for use in adults and the pediatric studies have not been completed.

This product is appropriately labeled for use in ages 4 to 17 years for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Therefore, no additional studies are needed in this pediatric age group.

The pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are:

1664-1 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:	June 2011
Study/Trial Completion:	June 2012
Final Report Submission:	December 2012

1664-2 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:	December 2013
Study/Trial Completion:	June 2015
Final Report Submission:	December 2015

1664-3 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:	June 2011
Study/Trial Completion:	June 2012
Final Report Submission:	December 2012

1664-4 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:	December 2016
Study/Trial Completion:	December 2017
Final Report Submission:	June 2018

11. Other Relevant Regulatory Issues

The Clinical Pharmacology reviewers selected two sites for inspection by Division of Scientific Investigations (DSI) – the bioequivalence study site in India and the bioanalytical site in (b) (4). Due to a Department of State Travel Advisory for (b) (4), those site inspections could not be scheduled by DSI during the original review cycle. The inspection was completed on April 22, 2010, prior to resubmission of this NDA. The DSI inspectors recommended that the bioequivalence data can be used to support the approval of this 505b2 NDA. See Section 5 Clinical Pharmacology above for details.

The CDTL notes in her review that a recent thorough QT study in another product in this class, dolasetron, demonstrated a QT prolongation effect for that 5HT3 receptor antagonist. Thorough QT studies have been conducted for the 5HT3 receptor antagonists palonosetron and the granisetron patch. Those studies revealed no significant QT prolongation. There are no thorough QT study data in the reference listed product label (Zofran ODT), however, the labels do refer to "...transient ECG changes including QT interval prolongation have been reported" in the Adverse Reactions and Precautions sections of the label (non-PLR). This information will be included in the Zuplenz label (in Warnings and Precautions). There is a long marketing history of ondansetron products. Ondansetron was the first 5HT3 product in the class to be approved. The Division will discuss in a Regulatory Briefing whether to require the makers of the ondansetron products, in particular the intravenous ondansetron product, to conduct a thorough QT study of ondansetron. The reviewers will not make a thorough QT study a PMR for this 505b2 NDA, for the new oral formulation.

12. Labeling

Labeling negotiations had not been completed at the time of the initial CR regulatory action for this NDA. The DMEPA reviewers found the proposed proprietary name, Zuplenz, acceptable in the initial review, dated July 20, 2009, again after a re-evaluation December 30, 2009, and in an updated review July 1, 2010.

DDMAC's labeling recommendations for the proposed carton and container labels and the package insert were incorporated. Dr. Johnson, the Clinical Reviewer noted in her review that she did not agree with DDMAC's recommendation to include the dosage for each population and indication in the Patient Instructions for Use, because she was concerned that it would create a large document that could be confusing to patients, and might lead patients to select a dose based on preference. I discussed this issue with her and concurred with her recommendation.

Dr. Johnson also disagreed with the SEALD reviewers' recommendations to change label references (b) (4) to "adverse reactions". Dr. Johnson argued that because this is a 505b2 application, the applicant "must stay consistent with the Zofran ODT labeling because they do not have rights to the data that determined the causal relationship between ondansetron and the adverse event." I discussed this issue with the Director of SEALD, and I concur that in light of the constraints of a 505b2 application, we are unable to evaluate the original data to determine which and whether the currently labeled "events" could be reasonably determined to be "reactions". We will be reviewing the PLR conversion of the Zofran label, and will be able to appropriately address this issue for the ondansetron product labels in the future, in the context of that review (when it is completed).

SEALD further recommended that the Highlights section be revised to shorten it to a half page length. This was done, and in doing so, DMEPA reviewers recommended clarifying the language describing the indications and the dosage instructions. Their recommendations were incorporated in the Highlights section. In addition, SEALD recommended that the reference to hypersensitivity in the Contraindication Section should clearly describe the type of hypersensitivity reaction. This was addressed by stating that the reactions included anaphylaxis and bronchospasm (in both the Contraindication section and in the Warnings and Precautions section).

DRISK was consulted to review the proposed Patient Package Insert (PPI). They recommended simplified wording where possible, removed redundant information, and ensured that it met the criteria specified in FDA's Guidance for Useful Written Consumer Medication Information.

As discussed earlier in this review, the Clinical Pharmacology reviewers modified the label to incorporate and/or clarify drug interaction information for apomorphine and tramadol. Concomitant use of apomorphine was added as a Contraindication and was added to the Drug Interaction Section.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment – In light of the satisfactory results of the site inspections and satisfactory resolution of remaining labeling issues, the applicant has adequately addressed the issues cited in the February 5, 2010 Complete Response letter. I concur with the CDTL that the risk and benefit characteristics of Zuplenz appear similar to those of the approved and currently marketed reference ondansetron product, Zofran ODT, and that the labeling of the product appropriately describes the benefits and risks.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None

- Recommendation for other Postmarketing Requirements and Commitments

See Section 10. Pediatrics above and the Approval letter for the list of required studies under Section 505B(a) of the Federal Food, Drug and Cosmetic Act. There are no additional PMRs or PMCs.

13 Pages of Appendix 1 that contains the "2/5/10 Division Director Summary Review Complete Response Recommendation" has been removed as a duplicate copy of the original 2/5/10 Summary Review that is located in the "Medical Review" section of this redacted Approval Package.

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

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

/s/

DONNA J GRIEBEL
07/02/2010