CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022524Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022524 SUPPL # HFD # 180

Trade Name ZUPLENZ

Generic Name ondansetron

Applicant Name Par Pharmaceutical, Inc

Approval Date, If Known July 2, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor's clinical program consisted of the following:

2 bioequivalence studies comparing Zuplenz to Zofran ODT
1 bioavilability study - to demonstrate that the bioavailability of Zuplenz is the same when taken with or without water
2 pilot bioequivalance studies - to inform sample size calculations for the pivotal bioequivalence studies noted above

If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	020781	Zofran (ondansetron) ODT
NDA#	020103	Zofran (ondansetron hydrochloride) tablet
NDA#	020605	Zofran (ondansetron hydrochloride) oral solution
	020007	Zofran (ondansetron hydrochloride) Injection
	020403	Zofran (ondansetron hydrochloride) Injection Premixed
	021915	ondansetron hydrochloride, USP Premix in INTRAVIA plastic container

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Jagjit Grewal
Title: Regulatory Project Manager
Date: 7/2/10

Name of Office/Division Director signing form: Donna Griebel, M.D.

Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/

JAGJIT S GREWAL
07/02/2010

DONNA J GRIEBEL
07/02/2010

3. DEBARMENT CERTIFICATION

Par Pharmaceutical, Inc. 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.

Cheryl A. Elder, Pharm.D.
Senior Director, Regulatory Affairs
Par Pharmaceutical, Inc.

13 Feb 2019
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022524 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zuplenz Established/Proper Name: ondansetron Dosage Form: oral soluble film		Applicant: Par Pharmaceutical, Inc. Agent for Applicant (if applicable):
RPM: Jagjit Grewal, M.P.H.		Division: Division of Gastroenterology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A 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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

NDA 020781 ZOFRAN ODT (ondansetron) orally disintegrating tablet
NDA 020103 ZOFRAN (ondansetron hydrochloride) tablets

Provide a brief explanation of how this product is different from the listed drug.

This application provides for a change in dosage form to an oral soluble film.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☒ No changes ☐ Updated
Date of check: 6/28/10

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ Actions	
• Proposed action • User Fee Goal Date is July 4, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Complete Response 2/5/10

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	☒ Yes ☐ No
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☒ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☒ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	7/14/10
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 7/2/10 Complete Response 2/5/10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/2/10
• Original applicant-proposed labeling	4/7/09
• Example of class labeling, if applicable	8/22/06: Zofran ODT, Zofran tablet, Zofran oral solution 8/22/06: Zofran Injection, Zofran Injection Premixed

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	7/2/10
• Original applicant-proposed labeling	4/7/09
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	7/1/10 & 6/22/10
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 7/22/09 7/2/10; 12/31/09; 7/20/09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 12/23/09 ☒ DMEDP 12/30/09 ☒ DRISK 6/21/10 ☒ DDMAC 1/20/10 ☐ CSS ☒ Other reviews SEALD 1/21/10
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM: 6/18/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 1/6/10 If PeRC review not necessary, explain: • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	7/2/10 PI-PPI discussion email 7/2/10 PI-PPI discussion email 7/1/10 carton-container discussion 6/30/10 PI-PPI discussion email 6/29/10carton-container discussion

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	6/24/10 PI-PPI discussion email 6/16/10carton-container discussion 6/16/10carton-container discussion 6/10/10 carton-container-PMR 5/18/10 acknowledge resubmission 12/23/09 labeling IR 10/05/09 CMC IR 06/18/09 filing communication 04/21/09 acknowledgment ltr
❖ Internal memoranda, telecons, etc.	7/2/10 Sponsor label acceptance 3/17/10 Post CR tcon 3/17/10 Post CR tcon
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	X Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 2/23/09 sponsor accepted preliminary comments in lieu of meeting
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) *(indicates dates)*	7/02/08 pre-IND mtg
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available *(do not include transcript)*	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 7/2/10; 2/5/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7/2/10; 2/4/10
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	co-signed primary reviews 6/24/10; 2/4/10; 12/22/09; 6/10/09
• Clinical review(s) *(indicate date for each review)*	6/24/10; 2/04/10; 12/22/09; 6/10/09 filing review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See clinical review dated 12/22/09, [Section 3.3]

[5] Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None PMHS 1/5/10
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None See CDTL reviews 7/2/10 & 2/4/10 co-signed primary reviews 7/1/10 & 2/1/10
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/1/10; 2/1/10; 6/10/09 filing review
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None 5/17/10
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None co-signed primary reviews 12/11/09; 6/9/10
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 12/11/09; 6/9/09 filing review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	

• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None co-signed primary reviews 7/2/10; 6/24/10; 12/15/09; 5/15/09
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7/2/10; 6/24/10; 12/15/09; 9/10/09 (biopharm); 5/15/09
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Product Quality Review dated 12/15/09, [Section CMC Assessment, IIB, page 43]
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date)*	Date completed: 4/30/09 ☒ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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 ODE’s ADRA.

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

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/s/

JAGJIT S GREWAL
07/14/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, July 02, 2010 3:47 PM
To: 'Luck-barnes, Casilda'
Cc: Grewal, Jagjit
Subject: RE: NDA 022524 Zuplenz (ondansetron) oral soluble film - PI/PPI revisions
Importance: High
Attachments: FDA Revised2 PI 7-2-10.doc; FDA Revised2 PPI 7-2-10.doc

Hello Dr. Barnes,

Upon further review, FDA is proposing additional edits to the package insert label (section 12.3) and patient package insert label. Please review the noted changes (attached) and respond with your acceptance and/or proposed changes.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Luck-barnes, Casilda [mailto:Casilda.Luck-barnes@strativapharma.com]
Sent: Friday, July 02, 2010 1:54 PM
To: Grewal, Jagjit
Subject: RE: NDA 022524 Zuplenz (ondansetron) oral soluble film - PI/PPI revisions

We accept the changes as is. See clean copy. We look forward to the action letter today.

Casilda Barnes, Pharm.D. | Director, Regulatory Affairs
Strativa Pharmaceuticals | 300 Tice Boulevard | Woodcliff Lake, NJ 07677
Phone: 201.802.4031-casilda.luck-barnes@strativapharma.com

From: Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Sent: Friday, July 02, 2010 1:35 PM
To: Luck-barnes, Casilda
Cc: Grewal, Jagjit
Subject: NDA 022524 Zuplenz (ondansetron) oral soluble film - PI/PPI revisions
Importance: High

Hello Dr. Barnes,

Reference is made to your New Drug Application dated April 7, 2009 for NDA 022524 Zuplenz (ondansetron) Oral Soluble Film, 4 mg and 8 mg. We also refer to your Complete Response resubmission dated May 4, 2010 in

response to the FDA Complete Response letter dated February 5, 2010.

Attached are annotated WORD documents containing additional FDA revisions to your proposed package insert label and patient package insert label. Please review the noted changes and respond with your acceptance and/or proposed changes.

Please acknowledge receipt of this email. I can be reached at the below phone number or through email with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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

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/s/

JAGJIT S GREWAL
07/02/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, July 01, 2010 8:47 AM
To: 'Luck-barnes, Casilda'
Cc: Grewal, Jagjit
Subject: RE: NDA 022524 Zuplenz (ondansetron) oral soluble film - carton/container revisions
Importance: High

Hello Dr. Barnes,

In response to your below email, we accept your proposal to utilize the 4 mg trade pouch with the 4 mg physician sample carton until November/December 2010. As stated in your email, you should develop a separate 4 mg physician pouch label, with the text "Physician Sample Not For Sale," to be utilized with the 4 mg physician carton by November/December 2010.

Please submit formal correspondence to your NDA 022524, stating your plans for the 4 mg physician sample labeling and reference this agreement. You should also address the following items within the same submission:

- (b) (4)
- Confirm that the 4 mg physician sample pouch, to be implemented in November/December 2010, will contain only one film per pouch, the dosage form will be stated as "Oral Soluble Film," and the net quantity statement on the pouch will be stated as "1 Film."

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Luck-barnes, Casilda [mailto:Casilda.Luck-barnes@strativapharma.com]
Sent: Tuesday, June 29, 2010 5:19 PM
To: Grewal, Jagjit
Subject: RE: NDA 022524 Zuplenz (ondansetron) oral soluble film - carton/container revisions

Hello Jagjit:

Concerning your comments below Strativa will not be pursuing the 8mg physician sample. When I submit final labeling I will indicate this as well. Concerning the 4mg physician samples we understand the Division's request for submitting the pouch with "physician sample not for sale" statement on the 4mg physician sample pouch. We are agreeing to change this. However, we are requesting that we implement this change post approval in November/December 2010 timeframe. Due to financial printing issues we would like to have the foil/pouch not have the physician sample statement on the pouch for the initial run post approval. The foil pouch would still be attached inside of the tri fold carton that clearly identifies the pouch as a physician sample not for sale. Again

would the Division be agreeable to this scenario.

Casilda Barnes, Pharm.D. | Director, Regulatory Affairs
Strativa Pharmaceuticals | 300 Tice Boulevard | Woodcliff Lake, NJ 07677
Phone: 201.802.4031-casilda.luck-barnes@strativapharma.com

From: Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Sent: Tuesday, June 29, 2010 6:46 AM
To: Luck-barnes, Casilda
Cc: Grewal, Jagjit
Subject: NDA 022524 Zuplenz (ondansetron) oral soluble film - carton/container revisions
Importance: High

Hello Dr. Barnes,

Reference is made to your New Drug Application dated April 7, 2009 for NDA 022524 Zuplenz (ondansetron) Oral Soluble Film, 4 mg and 8 mg. We also refer to your Complete Response resubmission dated May 4, 2010 in response to the FDA Complete Response letter dated February 5, 2010.

We have reviewed your revised carton and container labeling, dated June 22, 2010, and have the following comments:

(b) (4)

4 mg Physicians Sample:

- For the 4 mg Physicians Sample, only the 4 mg carton labeling was submitted. Both the carton labeling and pouch label for the 4 mg strength need to be submitted.

Please review the noted changes and respond with your acceptance and/or proposed changes by 12:00PM Wednesday, June 30, 2010. Additionally, please acknowledge receipt of this correspondence.

I can be reached at the below phone number or through email with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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

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/s/

JAGJIT S GREWAL
07/01/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, June 30, 2010 5:14 PM
To: 'Luck-barnes, Casilda'
Cc: Grewal, Jagjit
Subject: NDA 022524 Zuplenz (ondansetron) oral soluble film - PI/PPI revisions
Importance: High
Attachments: FDA Revised PI Lbl ANNOTATED 6-30-10.doc; FDA Revised PI Lbl CLEAN 6-30-10.doc; FDA Revised PPI-IFU Lbl ANNOTATED 6-30-10.doc; FDA Revised PPI-IFU Lbl CLEAN 6-30-10.doc

Hello Dr. Barnes,

Reference is made to your New Drug Application dated April 7, 2009 for NDA 022524 Zuplenz (ondansetron) Oral Soluble Film, 4 mg and 8 mg. We also refer to your Complete Response resubmission dated May 4, 2010 in response to the FDA Complete Response letter dated February 5, 2010.

Further reference is made to the FDA PI/PPI labeling revision correspondence, dated June 23, 2010, and your email response accepting all proposed changes, dated June 28, 2010. Attached are annotated and clean WORD documents containing additional FDA revisions to your proposed package insert label and patient package insert label. Please review the noted changes and respond with your acceptance and/or proposed changes.

In addition, please be advised that we are revising the description of the pediatric PK studies required under PREA (Studies #1 & #3) to remove the text "compared to standard therapy." Your submission dated June 22, 2010 provided agreement and milestone dates for the required pediatric PREA studies.

Please acknowledge receipt of this email. I can be reached at the below phone number or through email with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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

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/s/

JAGJIT S GREWAL
06/30/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, June 23, 2010 3:41 PM
To: 'Luck-barnes, Casilda'
Cc: Grewal, Jagjit
Subject: NDA 022524 Zuplenz (ondansetron) Oral Soluble Film - FDA proposed PI/PPI label revisions
Importance: High
Attachments: FDA Revised PI Label ANNOTATED 6-23-10.doc; FDA Revised PI Label CLEAN 6-23-10.doc; FDA Revised PPI Label 6-23-10.doc

Hello Dr. Barnes,

Reference is made to your New Drug Application dated April 7, 2009 for NDA 022524 Zuplenz (ondansetron) Oral Soluble Film, 4 mg and 8 mg. We also refer to your Complete Response resubmission dated May 4, 2010 in response to the FDA Complete Response letter dated February 5, 2010.

Attached are annotated and clean WORD documents containing the FDA's revisions to your proposed package insert label and patient package insert label. Please review the noted changes and respond with your acceptance and/or proposed changes by 12:00PM Monday, June 28, 2010. Additionally, please acknowledge receipt of this correspondence.

I can be reached at the below phone number or through email with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

24 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 PHARMACEUTICAL	ZUPLENZ (ONDASETRON) ORALLY-DISSOLVING F

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/s/

JAGJIT S GREWAL
06/24/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, June 16, 2010 11:04 AM
To: 'Luck-barnes, Casilda'
Cc: Grewal, Jagjit
Subject: FW: NDA 022524 Zuplenz (ondansetron) oral soluble film - 8 mg carton/pouch labeling
Attachments: UC 325-62.pdf; PO 325-52.pdf

Hello Casilda,

Upon preliminary review, your attached revised labeling appears to address our comments as emailed to you on June 14, 2010. Please be sure that any labels/labeling for the physician samples are consistent with changes made to the trade labels/labeling.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Luck-barnes, Casilda [mailto:Casilda.Luck-barnes@strativapharma.com]
Sent: Tuesday, June 15, 2010 3:18 PM
To: Grewal, Jagjit
Subject: FW: Zuplenz 8 mg

Hi Jagjit:

I wanted to send you an example of the revision to the carton and pouch to address your concerns for the 8 mg. If you could let me know if this addresses the Agencies comments below we will ensure it is consistent with the 4 mg artwork as appropriate. Once we get your feedback we will revise all artwork to ensure consistency and submit as a single submission for additional comment as necessary.

Regards

Casilda Barnes, Pharm.D. | Director, Regulatory Affairs
Strativa Pharmaceuticals | 300 Tice Boulevard | Woodcliff Lake, NJ 07677
Phone: 201.802.4031-casilda.luck-barnes@strativapharma.com

From: Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Sent: Monday, June 14, 2010 4:29 PM
To: Luck-barnes, Casilda
Cc: Grewal, Jagjit

Subject: FW: Zuplenz carton and container label

Hello Casilda,

We have the following preliminary comments regarding your below email and attached revised labeling.

- We note that the "8 mg" strength is presented in green [redacted] (b) (4), and is somewhat washed-out against the white background and thus, lacks prominence. You should revise the presentation of the strength e.g, by outlining (but NOT with [redacted] (b) (4) Violet), using a more contrasting color or a more contrasting shade of green (i.e., NOT [redacted] (b) (4) Violet or similar blue color), or some other means, to improve the prominence and readability. We also recommend that you de-emphasize the net quantity statement [redacted] (b) (4) (e.g., by unbolding and decreasing the font size), so that it does not detract from more important information (i.e., the strength).

Additionally, please provide all of proposed revisions in a single submission for additional comment. I can be reached at the below phone number or through email with questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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

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/s/

JAGJIT S GREWAL
06/16/2010

Grewal, Jagjit

From: Grewal, Jagjit

Sent: Thursday, June 10, 2010 11:17 AM

To: 'Luck-barnes, Casilda'

Cc: Grewal, Jagjit

Subject: NDA 022524 Zuplenz (ondansetron) Oral Soluble Film - Communication of PREA PMRs and Carton/Container Labeling

Importance: High

Hello Dr. Barnes,

Reference is made to your New Drug Application dated April 7, 2009 for NDA 022524 Zuplenz (ondansetron) Oral Soluble Film, 4 mg and 8 mg. We also refer to your Complete Response resubmission dated May 4, 2010 in response to the FDA Complete Response letter dated February 5, 2010.

Please be advised that Par Pharmaceuticals, Inc. will be responsible for the following required postmarketing studies under the Pediatric Research Equity Act (PREA). Upon review of the required pediatric studies, submit to your NDA a timetable identifying the following milestone dates for each study: **Final Protocol Submission Date, Study Completion Date, and the Final Study Report Submission Date**.

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 compared to standard therapy in pediatric patients ages 4 to <17 years receiving HEC.
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.
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 compared to standard therapy in pediatric surgical patients ages 0 to <17 years. An age-appropriate formulation must be developed for younger pediatric patients.
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.

Additionally, we have the following comments regarding your proposed carton labeling and container labels (pouch):

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 ½ 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. Replace the text (b) (4)" with "1 Film" on the front of the pouch labels. Also, replace the text (b) (4) with "Each film contains" on the back of the pouch labels.

4. Replace the text (b) (4) with "10 Films" on the front and sides of the 10 count carton labeling. A similar revision should be made for the 30 count carton labeling. Also, replace the text (b) (4) with "Each film contains" on the back of the carton labeling (10 and 30 count).

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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

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/s/

JAGJIT S GREWAL
06/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022524

ACKNOWLEDGE CLASS 1 COMPLETE RESPONSE

Par Pharmaceutical, Inc.
Attention: Casilda Barnes, Pharm.D.
Associate Director, Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Dr. Barnes:

We acknowledge receipt on May 4, 2010 of your May 4, 2010 resubmission to your new drug application for Zuplenz (Ondansetron) Oral Soluble Film, 4 mg and 8 mg.

We consider this a complete, class 1 response to our February 5, 2010 action letter. Therefore, the user fee goal date is July 4, 2010.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

JAGJIT S GREWAL
05/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-254 **ADVICE**

Par Pharmaceutical, Inc.
Attention: Cheryl Elder, PharmD
Sr. Director, Regulatory Affairs
300 Tice Boulevard
Woodcliffe Lake, NJ 07677

Dear Dr. Elder:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zuplenz (Ondansetron Oral Soluble Film) 4mg and 8mg.

We also refer to your April 7, 2009 submission, containing the Labeling (package insert and carton and container) for Zuplenz Oral Soluble Film.

We have reviewed the referenced material and have the following comments and recommendations for labeling changes. We request that you provide responses as soon as possible so we can continue to review your labeling.

Preliminary Content Revisions:

1. Update dosage form to "Oral Soluble Film" throughout the label

2. Full Prescribing Information
   a. The DOSAGE FORMS AND STRENGTHS section should include shape, color, and imprinting

   b. The DESCRIPTION section has the following errors; please address the following:
      i. Incorrect structural formula
      ii. Sucralose is missing from the list of excipients
      iii. [redacted] (b) (4) should read "butylated hydroxytoluene"
      iv. [redacted] (b) (4) should read "Hydroxypropyl methylcellulose"
      v. [redacted] (b) (4) should read "polyethylene glycol"
      vi. [redacted] (b) (4) should read "colloidal silicon dioxide"

   c. In the HOW SUPPLIED/STORAGE AND HANDLING section, the reported storage conditions are not consistent with USP definition of controlled room temperature.

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. In the 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 heading "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 (1) INDICATIONS AND USAGE, (2) DOSAGE FORMS AND STRENGTHS, and (3) 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 align 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 the dosage form should be expressed as "8mg" rather than (b) (4).

      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. [see 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. It 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 unbold.

   f. Avoid using acronyms in subsection headings. In subsection 5.2 (b) (4) and unbold. (Refer to the Institute for Safe Medication Practices website at www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.

   g. In section 17: PATIENT COUNSELING INFORMATION, (b) (4)

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 periods 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.

Preliminary Carton and Container Revisions:

1. Insert proprietary name in place of TRADE NAME throughout the label

2. Update dosage form to Oral Soluble Film

3. Revise storage conditions to be consistent with USP definition of controlled room temperature.

If you have any questions, call Frances Fahnbulleh, Regulatory Project Manager, at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA.
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

MATTHEW C SCHERER
12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-524 **INFORMATION REQUEST**

Par Pharmaceutical Companies, Inc.
Attention: Cheryl Elder, PharmD
Senior Director, Regulatory Affairs
300 Tice Boulevard
Woodcliffe Lake, NJ 07677

Dear Dr. Elder:

Please refer to your New Drug Application (NDA) submitted and received on April 7, 2009, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zuplenz (ondansetron) oral soluble film, 4 and 8 mg.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the name of the dosage form:

   Your dosage form has been classified as an "oral soluble film". Please revise your labels and labeling accordingly.

2. Regarding the drug product specification:

   a) Two different specification tables are described in your application, one in Section 2.3.P and one in Section 3.2.P.5.1. Please state clearly which one is the proposed regulatory specification.

(b) (4)

3. Regarding validation of analytical methods:

(b) (4)

(b) (4)

Submit a validation report that is complete and specific for your product.

4. Regarding stability data:

The stability commitment does not include a statement, "Should any of the test results fall out of specifications, FDA will be notified and the batch will be withdrawn from the market". Please revise it accordingly.

If you have any questions, call Frances Fahnbulleh, Regulatory Project Manager, at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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/s/

MOO JHONG RHEE
10/05/2009
Chief, Branch III

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-524

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Par Pharmaceutical
300 Tice Boulevard
Woodcliff Lake, NJ 07677

ATTENTION: Cheryl Elder, Pharm.D.
Sr. Director, Regulatory Affairs

Dear Dr. Elder:

Please refer to your New Drug Application (NDA) dated April 7, 2009, received April 7, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ondansetron Orally-Dissolving Film Strips, 4 mg and 8 mg.

We also refer to your May 1, 2009, correspondence, received May 1, 2009, requesting review of your proposed proprietary name, Zuplenz. We have completed our review of the proposed proprietary name, Zuplenz and have concluded that it is acceptable.

The proposed proprietary name, Zuplenz, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 1, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Denise Toyer, Pharm.D.
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Denise Toyer
7/22/2009 01:04:39 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-524

Par Pharmaceutical Companies, Inc.
Attention: Cheryl Elder, PharmD
Senior Director, Regulatory Affairs
300 Tice Boulevard
Woodcliffe Lake, NJ 07677

Dear Dr. Elder:

Please refer to your new drug application (NDA) dated and received on April 7, 2009 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zuplenz (ondansetron) Orally Disintegrating Film Strip, 4 and 8 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**, therefore, the user fee goal date is February 7, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 8, 2010.

During our filing review of your application, we identified the following potential review issues:

According to the current label for Zofran ODT, gender differences were evident when ondansetron was administered as a single tablet dose. The extent and rate of ondansetron's absorption is greater in women than men, thus resulting in higher plasma levels in women. In the submitted pivotal BE studies, a limited number of female subjects was included: 7 females versus 41 males in the fasting BE study and 12 females versus 36 males in the fed BE study.

We request that you also analyze the data by gender to assess the gender difference in PK with ondansetron ODFS.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

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.

(b) (4)

If you have any questions, call Frances Fahnbulleh, project manager at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
6/18/2009 02:18:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22,524

NDA ACKNOWLEDGMENT

Par Pharmaceutical Companies, Inc.
Attention: Cheryl Elder, Pharm.D.
Senior Director, Regulatory Affairs
300 Tice Boulevard
Woodcliffe Lake, NJ 07677

Dear Dr. Elder:

We have received your new drug application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (Zuplenz) Ondansetron Orally Dissolving Film Strip 4mg & 8mg

Date of Application: April 7, 2009

Date of Receipt: April 7, 2009

Our Reference Number: NDA 22-524

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 6, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-0942.

Sincerely,

{See appended electronic signature page}

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

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/s/

Frances G Fahnbulleh
4/21/2009 10:31:00 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2009

To: Cheryl Elder, Pharm.D. Senior Director, Regulatory Affairs	**From:** Jagjit Grewal, MPH
Company: Par Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: (201) 802-4600	**Fax number:** (301) 796-9905
Phone number: (201) 802-4296	**Phone number:** (301) 796-0846

Subject: PIND (b) (4)2 Ondansetron orally dissolving film strips - Preliminary Meeting Responses

Total no. of pages including cover: 3

Comments:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 25, 2009 at 1:00PM (EST) between Par Pharmaceuticals, Inc. and the Division of Gastroenterology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Jagjit Grewal, RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Document to be mailed: YES ☑NO

Chemistry, Manufacturing, and Controls

Question 1: Does the Agency have any comments on our process validation proposal?

FDA Response:
Process validation is not a review issue. You will need to contact the Office of Compliance to discuss your validation plans.

Question 2: Is the stability data submission plan during the NDA review cycle acceptable to the Agency?

FDA Response:
Your proposed plan to submit at least 6 months of stability data for the (b) (4) batch and 12 months of data for the (b) (4) batch with the initial submission, and to supplement the data no later than four months prior to the PDUFA goal date is acceptable. Data received after that time will not be considered for expiration dating.

Regulatory

Question 1: Does the Agency agree that the proposed content of the application and sources of data are sufficient for the ondansetron ODFS 505(b)(2) NDA?

FDA Response:
The information provided is limited. Upon NDA submission, the following items should also be included in the reports of Study Nos. 01905/08-09, 01906/08-09, and 04795/08-09:

1. **Assay validation report (standard curves for accuracy, precision, recovery, etc.) and in-study assay performance results (QC for interday-/intraday-variations, etc.)**
2. **Dataset of individual pharmacokinetic raw data (SAS format) and statistical output results in electronic format for BE assessment**

In module 5, please include safety data and reports for each bioequivalence study.

Question 2: Does the Agency agree that the data to be included in this NDA are sufficient to support the proposed indications?

FDA Response:
Whether the data are sufficient will be determined at the time of NDA review. We recommend that the available data on the time (in seconds) for ODFS for complete disintegration on top of the tongue be provided for review. This should include individual data and the mean ± standard deviation.

We note that you are developing a 4 mg ODFS, but at this time, you are not proposing an indication for this dosage strength. Please explain.

Additional FDA Regulatory Information:
The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/index.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

****
*** TX REPORT ***
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2009

To: Cheryl Elder, Pharm.D. Senior Director, Regulatory Affairs	**From:** Jagjit Grewal, MPH Division of Gastroenterology Products
Company: Par Pharmaceuticals, Inc.	
Fax number: (201) 802-4600	**Fax number:** (301) 796-9905
Phone number: (201) 802-4296	**Phone number:** (301) 796-0846

Subject: PIND [redacted] (b) (4) Ondansetron orally dissolving film strips - Preliminary Meeting Responses

Total no. of pages including cover: 3

Comments:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 25, 2009 at 1:00PM (EST) between Par Pharmaceuticals, Inc. and the Division of Gastroenterology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Jagjit Grewal, RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on [illegible] to the development plan or additional questions

Linked Applications	Sponsor Name	Drug Name / Subject
(b) (4)	PAR PHARMACEUTICAL COMPANIES INC	Ondanstron (b) (4) 8 and 4 mg.

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/s/

JAGJIT S GREWAL
02/23/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

PIND (b) (4)

Applied Pharma Research S.A.
Authorized Representative: Par Pharmaceuticals Companies, Inc.
Attention: Cheryl Elder, Pharm.D.
Director, Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Dr. Elder:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ondansetron (b) (4); 8 mg and 4 mg.

We also refer to the telecon between representatives of your firm and the FDA on July 2, 2008. The purpose of the meeting was to obtain guidance for the development of your proposed ondansetron product to support approval of a 505(b)(2) new drug application.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 2, 2008

TIME: 10:00AM EST

LOCATION: FDA – White Oak Campus
10903 New Hampshire Avenue, Building 22
Silver Spring, MD 20993

APPLICATION: pIND (b) (4)

DRUG NAME: Ondansetron (b) (4) 8 mg and 4 mg

TYPE OF MEETING: Type B, pre-IND Meeting (teleconference)

MEETING CHAIR: Donna Griebel, M.D.

MEETING RECORDER: Jagjit Grewal, M.P.H.

FDA ATTENDEES:

Donna Griebel, M.D., Division Director, Division of Gastroenterology Products (DGP)
Anil Nayyar, M.D., Medical Reviewer, DGP
Nancy Snow, M.D., Medical Reviewer, DGP
Sushanta Chakder, Ph.D., Pharmacology Reviewer, DGP
Charles Wu, Ph.D., Pharmacology Reviewer, DGP
Tien Mien Chen, Ph.D., Reviewer, Office of Clinical Pharmacology
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment
Jagjit Grewal, M.P.H., Regulatory Project Manager, DGP

EXTERNAL CONSTITUENT ATTENDEES:

Monosolrx LLC.
Pradeep Sanghvi, Ph.D., Vice-President, Pharmaceutical Development
Madhu Hariharan, Ph.D., Senior Director, Pharmaceutical Development
(b) (4)

Applied Pharma Research S.A. (APR)/Labtec
Aldo Donati, Vice President, Applied Pharma Research
Valentina Reiner, Head of Clinical and Regulatory Operations, Applied Pharma Research
Peter Klaffenbach, Managing Director, Labtec GmbH
(b) (4)

Par Pharmaceuticals, Inc.
Eric Mittleberg, Ph.D., Executive Vice President, Pharmaceutical Research & Development
Cheryl Elder, Pharm.D., Director of Regulatory Affairs

BACKGROUND:
Applied Pharma Research S.A. (APR) submitted a pre-IND meeting request dated March 27, 2008 to discuss their proposed ondansetron (b) (4) 8 mg & 4 mg. APR intends to submit a NDA for the proposed ondansetron orally dissolving filmstrip as a 505(b)(2) application using Zofran orally disintegrating tablets 8 mg as the reference listed drug. The FDA granted the sponsor a face-to-face meeting in our letter dated May 13, 2008. APR submitted their meeting background package dated June 2, 2008, and preliminary responses were sent to the sponsor on June 30, 2008. APR requested that the meeting be changed from a face-to-face to a teleconference in their submission dated July 1, 2008. Additionally, APR indicated that they would like to focus the discussion on Question #1a.

Ondansetron orally dissolving filmstrip is proposed for 1) prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$ 50 mg/m2; 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 in patients receiving either total body irradiation, single high-dose fraction to abdomen, or daily fractions to the abdomen; and 4) prevention of postoperative nausea and/or vomiting.

MEETING OBJECTIVES:
1. Identify any potential concerns the FDA may have regarding APR's development plan.
2. Discuss the most efficient and appropriate route to obtain marketing approval of APR's proposed ondansetron product.

DISCUSSION POINTS:

1. Regulatory

   a. Monosolrx intends to submit a 505(b)(2) New Drug Application for Ondansetron 8mg and 4mg Orally Dissolving Film product referencing the Agency's prior approval of the Orange Book Reference Listed Drug, Zofran® 8mg Orally Disintegrating Tablets (NDA 20-781). Does the Agency agree that this is acceptable?

   <u>FDA Response</u>:
   FDA's Draft Guidance for "Orally Disintegrating Tablets" (which can be found on the FDA website) defines an orally disintegrating tablet as

   A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue

   Taking into account the above definition, please provide justification why you believe that your product should be submitted as a 505(b)(2) and not as a 505(j).

   If you can adequately justify that this should be a 505(b)(2) application, it will be acceptable to submit your new drug application using Zofran 8 mg Orally Disintegrating Tablet (NDA 20-781) as the Reference Listed Drug.

Additional Comments:
APR believes that their orally dissolving filmstrip (ODF) is a different dosage form than the orally disintegrating tablet (ODT). FDA stated that the CDER standards manual defines all dosage forms, but orally dissolving filmstrips are not included. APR argued that the orally dissolving filmstrip has different characteristics, properties, and is produced by different processes than orally disintegrating tablets and therefore should be considered as a new dosage form. FDA requested that APR provide a comparison of the characteristics/properties of ODTs and ODFs which would justify consideration of the ODF as a unique dosage form, distinct from the ODT. Quantitative information should be submitted for this purpose, not merely qualitative descriptions. APR agreed to submit this information as a general correspondence to the pIND. Additionally, FDA requested that APR submit a sample filmstrip with its response. APR also agreed to provide a sample filmstrip.

APR plans to submit their IND by mid-August 2008.

APR stated that they intend to submit their NDA as a 505(b)(2), and asked if there are any additional impediments that would prevent submitting the application as a 505(b)(2) NDA. FDA indicated that if the sponsor's proposed product is classified as an orally disintegrating tablet instead of a filmstrip, the sponsor would have to submit the NDA application as a generic because there are already approved orally disintegrating tablets for ondansetron.

In the event that FDA determines that the ODT and ODF dosage forms are the same, and not unique dosage forms, APR inquired whether they can choose the more rigorous NDA route, rather than a generic application. FDA indicated that they would follow up on this issue and provide advice as part of the meeting minutes (see below).

FDA Additional Response:
Per the "Guidance for Industry: Applications Covered by Section 505(b)(2)," 505(b)(2) new drug applications should not be submitted for duplicates of approved products that are eligible for approval under 505(j). Furthermore, 21 CFR 314.101(d)(9) states that the FDA may refuse to file an application that is submitted as a 505(b)(2) for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j).

2. NDA Content

   a. Does the Division agree with, or have additional comment on, Monosolrx's proposal to file the NDAs as an electronic submission in eCTD format?

   FDA Response:
   It is acceptable to submit your NDA in electronic eCTD format. Please refer to the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format –

Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (June 2008) for additional information.

b. Does the Division agree that the proposed content of the filing and sources of data are appropriate for the Ondansetron ODF NDA?

FDA Response:
Your proposed content appears to be acceptable. Please see the guidance document in Question #2a and the below references for additional information:

- **"Guidance for Industry: M4: Organization of the CTD" (August 2001)**
- **FDA eCTD Webpage http://www.fda.gov/cder/regulatory/ersr/ectd.htm**

c. Monosolrx intends to us (b) (4). as the contract clinical facility for pivotal bioequivalence studies. Should all CRFs from the bioequivalence studies be included in the NDA?

FDA Response:
Yes, please include all CRFs from the bioequivalence studies in the NDA.

3. Preclinical Data

a. Monosolrx plans to rely on FDA's previous findings relative to pre-clinical data. Does the Agency agree that no additional pre-clinical data is needed for Ondansetron Orally Dissolving Film 505(b)(2) NDA?

FDA Response:
We agree that no additional pre-clinical data is needed for your proposed application.

b. All inactive components of the ODF formulation are compendial, are considered "Generally Recognized As Safe" when taken orally, or have been previously approved in other CDER approved products at levels greater than or exceeding those proposed in our product for the same route of administration (Oral). Because of this, and because the product is a Oral formulation that is intended to be similar to previously approved Ondansetron ODTs, Monosolrx believes that no additional preclinical studies will be necessary. Does the Division agree with this assessment? If not, what information does the Division foresee needing?

FDA Response:
We agree with your assessment.

4. Clinical Pharmacokinetic Studies to Establish Bioequivalence

   a. The clinical development program will consist of two separate bioequivalence studies (using the highest {8mg} strength) conducted under fed and fasted conditions in normal healthy volunteers. They will be randomized, open-label, single oral dose, two-way cross-over comparative bioequivalence studies in 36 subjects each. Bioequivalence will be assessed based on plasma concentrations of Ondansetron. Does the Agency agree that the proposed clinical development program is sufficient to support a 505(b)(2) New Drug Application?

      FDA Response:
      The proposed clinical development program is sufficient to support a 505(b)(2) NDA.

   b. Does the Agency agree that comparative dissolution testing versus the 4 mg ODT strengths in the Orange Book will support the approval of an additional 4 mg strength (dose proportional to 8 mg formulation) of Monosolrx's Orally Dissolving Film product without additional bioequivalence studies?

      FDA Response:
      We agree with your proposal.

5. Methods for statistical analysis of clinical data

   a. Does the Division agree with Monosolrx's proposal to present comparative pharmacokinetic data and conduct descriptive statistical analyses as outlined in the FDA guidance entitled, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations"?

      FDA Response:
      We agree with your proposal.

   b. Monosolrx plans descriptive statistics to describe adverse events, laboratory findings, and other clinical safety evaluations. No comparative safety analyses are necessary between the ODT and the ODF formulations. Does the Division agree?

      FDA Response:
      We agree that descriptive analyses of these data are acceptable.

6. Studies needed to assess pediatric safety and effectiveness

   a. Although Monosolrx is interested in developing treatments involving Ondansetron that are appropriate for use in pediatric patients, Monosolrx believes that Ondansetron Orally Dissolving Film Strips are eligible for a waiver from pediatric study requirements under

PREA. Does the Division agree that the film strip products are eligible for a waiver under PREA?

FDA Response:
We believe that you should develop a pediatric plan because this formulation is desirable for pediatric use given the lack of need to swallow a pill. We recommend you submit a pediatric plan for use in pediatric patients which should include a pharmacokinetic study. Decisions regarding waiver request or deferral of pediatric studies are made during the review by the Pediatric Review Committee.

7. CMC Data

a. Monosolrx plans to use (b) (4) as the primary source of the Ondansetron base for the film strip product. API from this source has been used in other approved pharmaceutical products in the US. Monosolrx would demonstrate suitability of the Ondansetron base API supply for use in the Orally Dissolving Film product by conducting stability studies for the film strips made with three different lots of the API. Other than this, would the Division require anything beyond authorization to refer to the supplier's DMF for review of the Ondansetron base drug substance suitability?

FDA Response:
No other information will be required.

b. (b) (4)

FDA Response:
Based on the information that you have provided in the briefing package, we agree with this approach, but you will need to fully justify it in the NDA submission.

c. Monosolrx believes that the SUPAC guideline for oral solid dosage forms are relevant to the proposed Oral film strip formulations for use as a guide to Monosolrx for making and reporting post approval scale up and manufacturing changes. Does the Division agree?

FDA Response:
Yes, we agree.

d. Three batches of each of the two strengths of the product at maximum commercial scale will be manufactured as validation batches. Manufacturing process validation will be protocol driven and conducted on only the first three batches of product scheduled for commercial manufacture. Is this plan acceptable to the Division?

FDA Response:
Yes, this plan is acceptable.

e. (b) (4)

FDA Response:
Yes, this plan is acceptable.

f. Monosolrx proposes specifications for the Ondansetron ODF formulation provided in the CMC section of this document. Does the Division agree with these specifications as adequate?

FDA Response:
The specification appears adequate, but will be evaluated within the context of your full NDA submission. As a consequence of our review we may find that additional variables need to be controlled and included in the specification.

g. Dissolution testing will be performed using a slightly modified version of USP Apparatus 2 (b) (4). The specification for dissolution will be similar to the Ondansetron ODT specifications in USP <31>. Is this approach acceptable?

FDA Response:
Yes, this approach is acceptable.

h. The drug product is pouched in foil-foil opaque pouches during bulk storage as well as the final package. We believe this is adequate justification for not performing photostability studies – Does the division agree?

FDA Response:
Photostability studies on the packaged product will not be necessary, but you should address photostability of the product during the manufacturing process, prior to packaging.

i. We propose to submit the NDA based on initial (T0) data plus a minimum of four stability time points (1, 2, 3 and 6 months at RT and 1, 3 and 6 months at accelerated conditions) giving at least six months of stability data. At appropriate time points, (b) (4);

(b) (4) Is this plan acceptable to the Division?

FDA Response:
(b) (4) **the longest expiration date that would be possible is 12 months. Please refer to ICH Guidance Q1E "Extrapolation of Stability Data".**

j. Other than data generated from drug product in batches that are at commercial batch size and a commitment to perform stability on all three validation batches followed by an annual stability batch, would the Division require any additional drug product stability information?

FDA Response:
A forced degradation study should be conducted for the purpose of demonstrating the stability-indicating nature of the assay procedure.

DECISIONS (AGREEMENTS) REACHED:
See Discussion section.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:
1. Classification of APR's proposed orally dissolving filmstrip.

ACTION ITEMS:
1. APR will provide a comparison of the characteristics/properties and justification that the orally dissolving filmstrip is different from an orally disintegrating tablet.
2. APR will provide a sample filmstrip.

ATTACHMENTS/HANDOUTS:
None

Linked Applications	Sponsor Name	Drug Name
(b) (4)	Applied Pharma Research S.A.	Ondanstron (b) (4) 8 and 4 mg.

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/s/

JAGJIT S GREWAL
07/31/2008