# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 022524Orig1s000

# CHEMISTRY REVIEW(S)

| | |
|---|---|
| **Memorandum** | Department of Health and Human Serviced<br>Food and Drug Administration<br>Center for Drug Evaluation and Research |
| **Date:** | 02-JUL-2010 |
| **To:** | NDA 22-524 CMC Review #2 |
| **From:** | Bogdan Kurtyka, Ph.D. |
| **Through:** | Moo-Jhong Rhee, Ph.D.<br>Chief, Branch IV ONDQA Division II |
| **CC:** | Marie Kowblansky, Ph.D. |
| **Subject:** | **CMC recommendation for NDA 22-524 due to recent submission of updated labeling** |

The PDUFA date of (b) (4) is 04-JUL-2010. CMC Review #2 was completed on 24-JUN-2010 with a recommendation of Approval action. However, the Recommendation of Review #2 stated that any labeling amendments submitted to this NDA before the action date would be reviewed and a memorandum with an updated CMC recommendation will be filed.

The sponsor submitted the updated labeling on 01-JUL-2010. The new labeling was reviewed and found adequate from the CMC viewpoint.

Therefore, this amendment does not affect the Review #2's recommendation of "Approval".

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

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/s/

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BOGDAN KURTYKA
07/02/2010

MOO JHONG RHEE
07/02/2010
Chief, Branch IV

# NDA 22-524

## Zuplenz (ondansetron) oral soluble film

## Par Pharmaceutical, Inc.


## Bogdan Kurtyka, Ph.D.

**Review Chemist**

## Division of New Drug Quality Assessment II
## Branch IV


**CMC REVIEW OF NDA 22-526**

## For the Division of Gastrointestinal Products (HFD-180)

# Table of Contents

# CMC Review Data Sheet

1. NDA 22-524

2. REVIEW #: 2

3. REVIEW DATE: 24-JUN-2010

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: CMC Review #1

| Submission(s) Reviewed | Document Date |
|---|---|
| Original Submission | 07-APR-2009 |
| Amendment – Stability update | 22-SEP-2009 |
| Amendment – Stability update | 19-OCT-2009 |
| Amendment – Response to the IR letter | 04-NOV-2009 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Labeling update | 01-JAN-2010 |
| Complete Response | 04-MAY-2010 |
| Labeling update | 22-JUN-2010 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Par Pharmaceuticals, Inc. |
| Address: | 300 Tice Boulevard<br>Woodcliff Lake, NJ 07677 |
| Representative: | Cheryl Elder |
| Telephone: | 201-802-4296 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zuplenz
b) Non-Proprietary Name: Ondansetron oral soluble film
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antiemetic

CMC Review Data Sheet

11. DOSAGE FORM: oral soluble film CODE: 063

12. STRENGTH/POTENCY: 4 mg and 8 mg

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

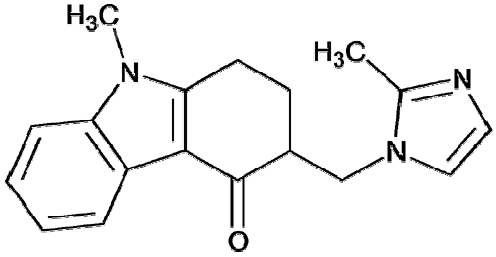
14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAMES, STRUCTURAL FORMULAE, MOLECULAR FORMULAE, MOLECULAR WEIGHTS:

Chemical Name: 9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-2,3-dihydro-1*H*-carbazol-4(9*H*)-one
USAN Name: Ondansetron
CAS Number: CAS-99614-02-5
Structural Formula:




Molecular Formula: $C_{18}H_{19}N_3O$
Molecular Weight: 293.36

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | (b) (4) | 3 | Adequate | 23-OCT-2006 | |
| | | | | 4 | N/A | N/A | |
| | | | | 1 | Adequate | 14-SEP-2009 | |
| | | | | 4 | N/A | N/A | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: N/A**

## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Acceptable | 03/24/2010 | Bogdan Kurtyka |
| Pharm/Tox | N/A | | |
| ONDQA Biopharm | Acceptable, bio-waiver for 4 mg of oral soluble film is granted | 09/10/2009 | Houda Mahayni |
| LNC | N/A | | |
| Methods Validation | N/A, according to the current ONDQA policy | | |
| DMETS | Proprietary name is accepted | 07/22/2009 | Denise Toyer |
| EA | Categorical exclusion is granted (see review) | 11/01/2008 | Bogdan Kurtyka |
| Microbiology | N/A | | |

# The CMC Review for NDA 22-524

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

Previously unresolved labeling issues noted in the CMC Review #1 are now satisfactorily resolved and all facilities are still in compliance with cGMP.

Therefore, from a CMC perspective, this NDA is recommended for "Approval".

Any labeling amendments submitted to this NDA after this review will be subject to further review, and an updated CMC recommendation will be filed through a memorandum

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of CMC Assessments

NDA 22-524 was originally submitted on 07-APR-2009. The application was not approved in the first review cycle due to unresolved labeling issues. A Complete Response Letter was issued on 05-FEB-2010.

An Amendment (Complete Response) to address the labeling deficiencies was submitted on 04-MAY-2010 and all previously noted deficiencies are now satisfactorily resolved.

### A. Description of the Drug Product(s) and Drug Substance(s)

See Review #1.

### B. Description of How the Drug Product is Intended to be Used

See Review #1.

### C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of Zuplenz over the proposed expiration dating period (24 months) when stored as labeled.
Adequate controls for raw materials are in place, manufacturing processes are robust with adequate controls Specifications are also adequate for ensuring the identity, strength, quality, and purity of the drug substance and the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration dating period.

Labeling is now acceptable and the facilities are still in compliance with cGMP. Therefore, this NDA is recommended for "Approval" from a CMC perspective at this time.

However, any labeling amendments submitted to this NDA before the action date will be reviewed and a memorandum with an updated CMC recommendation will be filed.

## III. Administrative

**A. Reviewer's Signature**: *(See appended electronic signature page)*

Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV,
Division of New Drug Quality Assessment II
ONDQA

**B. Endorsement Block:** *(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV,
Division of New Drug Quality Assessment II
ONDQA

**C. CC Block:** entered electronically in DARRTS

6 Page(s) has 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/

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BOGDAN KURTYKA
06/24/2010

MOO JHONG RHEE
06/24/2010
Chief, Branch IV

# NDA 22-524

## Zuplenz (ondansetron) oral soluble film

## Par Pharmaceutical, Inc.

**Bogdan Kurtyka, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment**
**Division of Pre-Marketing Assessment II**
**Branch III**

**CMC REVIEW OF NDA** (b) (4)

**For the Division of Gastrointestinal Products (HFD-180)**

# Table of Contents

# CMC Review Data Sheet

1. NDA 22-524

2. REVIEW #: 1

3. REVIEW DATE: 15-DEC-2009

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original Submission | 07-APR-2009 |
| Amendment – Stability update | 22-SEP-2009 |
| Amendment – Stability update | 19-OCT-2009 |
| Amendment – Response to the IR letter | 04-NOV-2009 |

7. NAME & ADDRESS OF APPLICANT:

| | |
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| Name: | Par Pharmaceuticals, Inc. |
| Address: | 300 Tice Boulevard<br>Woodcliff Lake, NJ 07677 |
| Representative: | Cheryl Elder |
| Telephone: | 201-802-4296 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zuplenz
b) Non-Proprietary Name: Ondansetron oral soluble film
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antiemetic

11. DOSAGE FORM: oral soluble film CODE: 063

12. STRENGTH/POTENCY: 4 mg and 8 mg

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

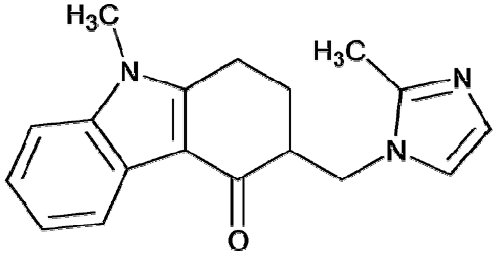
14. Rx/OTC DISPENSED: √ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
√ Not a SPOTS product

16. CHEMICAL NAMES, STRUCTURAL FORMULAE, MOLECULAR FORMULAE, MOLECULAR WEIGHTS:

Chemical Name: 9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]-2,3-dihydro-1*H*-carbazol-4(9*H*)-one
USAN Name: Ondansetron
CAS Number: CAS-99614-02-5
Structural Formula:




Molecular Formula: $C_{18}H_{19}N_3O$
Molecular Weight: 293.36

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | (b) (4) | 3 | Adequate | 23-OCT-2006 | |
| | | | | 4 | N/A | N/A | |
| | | | | 1 | Adequate | 14-SEP-2009 | |
| | | | | 4 | N/A | N/A | |

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1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents: N/A**

## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Acceptable, report attached at the end of this document | 04/30/2009 | Bogdan Kurtyka |
| Pharm/Tox | N/A | | |
| ONDQA Biopharm | Acceptable, bio-waiver for 4 mg of oral soluble film is granted | 09/10/2009 | Houda Mahayni |
| LNC | N/A | | |
| Methods Validation | N/A, according to the current ONDQA policy | | |
| DMETS | Proprietary name is accepted | 07/22/2009 | Denise Toyer |
| EA | Categorical exclusion is granted (see review) | 11/01/2008 | Bogdan Kurtyka |
| Microbiology | N/A | | |

# The CMC Review for NDA 22-262

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Facilities are in compliance with cGMP.

However, issues on labels/labeling have not been resolved. Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of CMC Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

**(1) Drug Substance**

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

**(2) Drug Product**

The drug product has been classified as oral soluble film. The application describes manufacturing and control of two distinct films – 4 mg and 8 mg. Both drug products are dose proportional and are manufactured from in same process. Different dosages come from different surface areas of the film, higher dosage having the area twice larger than the lower strength.

The manufacturing process is identical to both strengths of drug product. (b) (4) The specification of the drug product includes appearance, identification, assay, and content uniformity of active ingredients,

dissolution, impurities, moisture, and microbial limits.
The application includes results of 12 months long-term stability data. The applicant has proposed an 24 month expiration dating period when stored at controlled room conditions. The submitted data support the proposed expiration dating period.
A bioequivalence study was conducted between the 8 mg film and the reference listed drug (Zofran ODT). The applicant requested the bio-waiver for 4 mg formulation based on the fact the two proposed strengths are proportional in the amount of active and excipients, and differ only by size. The dissolution data were reviewed by ONDQA Biopharm reviewer Houda Mahayni with the recommendation that bio-waiver request for 4 mg film is acceptable.

**B. Description of How the Drug Product is Intended to be Used**

Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy: 24 mg given successively as three 8 mg film strips administered 30 minutes before the start therapy.
Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy: one 8 mg film strip given twice a day.
Prevention of nausea and vomiting associated with radiotherapy: The recommended oral dosage is one 8 mg film strip given 3 times a day.
Postoperative nausea and vomiting: 16 mg given successively as two 8-mg film strips 1 hour before induction of anesthesia.

**C. Basis for Approvability or Not-Approval Recommendation**

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of Zuplenz over the proposed expiration dating period (24 months) when stored as labeled.
Adequate controls for raw materials are in place, manufacturing processes are robust with adequate controls Specifications are also adequate for ensuring the identity, strength, quality, and purity of the drug substance and the drug product. The container/closure system is adequate to protect the drug product. Stability data assure that the product will be stable through the expiration dating period. Facilities are in compliance with cGMP.

However, labeling issues are still pending as of this review. Therefore, this NDA is not recommended for "Approval" from a CMC perspective.

## III. Administrative

**A. Reviewer's Signature**: *(See appended electronic signature page)*

Bogdan Kurtyka

**B. Endorsement Block:** *(See appended electronic signature page)*

Moo-Jhong Rhee, Branch Chief, Branch #3, Division 2, ONDQA

**C. CC Block:** entered electronically in DARRTS

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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/

BOGDAN KURTYKA
12/15/2009

MOO JHONG RHEE
12/15/2009
Chief, Branch III

# Initial Quality Assessment
# Branch 3
# Pre-Marketing Assessment Division 2

| | |
|---|---|
| **OND Division:** | Division of Gastroenterology Products |
| **NDA:** | 22-524 |
| **Applicant:** | Par Pharmaceutical, Inc |
| **Stamp Date:** | 4/7/2009 |
| **Received by PAL:** | 4/9/2009 |
| **Review Date:** | 5/11/2009 |
| **PDUFA Date:** | 2/4/2010 |
| **Filing Meeting:** | 5/14/2009 |
| **Proposed Trademark:** | Zuplenz |
| **Established Name:** | Ondansetron |
| **Dosage Form:** | Orally dissolving film strip |
| **Route of Administration:** | oral |
| **Indication:** | antiemetic |
| **PAL:** | Marie Kowblansky, PhD |

| | YES | NO |
|---|---|---|
| **ONDQA Fileability:** | ☒ | |
| **Comments for 74-Day Letter** | | ☒ |

## *A. Summary*

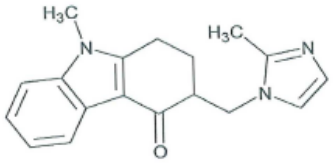
The proposed product, Zuplenz (ondansetron) Orally Dissolving Film Strip (ODFS), is intended as a pharmaceutical alternative to Zofran ODT® (Ondansetron Orally Disintegrating Tablet, NDA 020-781) for the prevention of nausea and vomiting associated with cancer chemotherapy. The product, which is a thin, flexible polymeric film strip containing dispersed ondansetron, is intended to be placed on the tongue for rapid dissolution in the saliva prior to swallowing. It is manufactured in two strengths, 4 mg and 8 mg. The recommended dose for this product ranges from 8 to 24 mg of ondansetron taken up to three times daily. (The 24 mg dose requires three 8 mg films to be taken successively.)

The NDA is being filed as a 505(b)(2) application using NDA 20-781 (ZOFRAN ODT®) as the reference listed drugs. A bioequivalence study was conducted to compare the 8 mg formulation with the reference listed drug. However, because the 4 mg and 8 mg ODFS formulations are proportional in the amounts of active and inactive ingredients (differing solely in the size of the strip) only a dissolution comparison of the two film strip strengths was conducted to support approval of the 4 mg product. This product was developed under (b) (4) and since it is a new formulation of a currently approved drug, it is classified as a type 3 application under the Chemical Classification Code, MAPP 7500.

Because Orally Dissolving Film Strip is not a recognized dosage form in the CDER Standards Manual, the firm was requested in the IND stage of product development to provide justification why the proposed dosage form should not be classified as an Orally Disintegrating Tablet. The firm's justification, submitted in an amendment to (b) (4), was evaluated by FDA, with the conclusion that the ODFS would not be considered the same dosage form as the ODT. (See appended review of the submitted information.) However, the name to be used for this dosage form has not yet been decided and this issue is currently under consideration in the Office of New Drug Quality Assessment.

**Drug Substance**

The drug substance is the racemic form of ondansetron (free base)



which will be manufactured by (b) (4). Only limited information regarding the drug substance is provided in the NDA; reference is made to DMF (b) (4) for complete information regarding the manufacture, characterization, and controls that are used in the process. The material will conform to all USP requirements

| | (b) (4) | USP |
|---|---|---|
| **Identification A (IR)** | Matches Reference i.e. IR spectrum of the test specimen exhibits maxima only at the same wavelengths a that of the a similar preparation of USP reference standard | IR spectrum of the test specimen exhibits maxima only at the same wavelengths a that of the a similar preparation of USP reference standard |
| **Identification B (HPLC)** | Meet Requirements (i.e. the retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay. | The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay. |
| **Water content (Karl Fischer)** | NMT 3.0% | NMT 3.0% |
| **Residue on Ignition** | NMT 0.1% | NMT 0.1% |
| **Chloride content** | NMT 0.02% | NMT 0.02% |
| **Limit of Ondansetron related compound D (HPLC)** | NMT 0.10% | NMT 0.10% |
| **Related Compounds (HPLC)** | | |
| Individual Impurities | NMT 0.1% | NMT 0.1% |
| Total impurities | NMT 0.5% | NMT 0.5% |
| (b) (4) | | |

According to the submission, additional testing will be performed by (b) (4) for residual solvents, heavy metals, optical rotation, polymorphic form (b) (4) by an in-house HPLC method (b) (4), (b) (4) by an (b) (4) method (b) (4), and unidentified (b) (4) by the USP HPLC method (b) (4)

The USP acceptance criteria for all impurities, both identified and unidentified, are 0.1%, (b) (4)

(b) (4)

**Drug Product**

The product is a white, opaque film strip manufactured in two strengths, 8 mg and 4 mg. Both strengths utilize the same formulation and manufacturing process – (b) (4) the films for both strengths are the same thickness and width, differing only in the length, with the 8 mg strip being double the length of the 4mg strip. (The 8 mg strip is 22 mm x 32 mm and the 4 mg strip is 22 mm x 16 mm). The strips are imprinted with information identifying the product and the strength.

The product formulation is given as

| Ingredient | Standard | Use | % w/w |
|---|---|---|---|
| Ondansetron base | USP/in house | Active ingredient | (b) (4) |
| Hydroxypropyl methylcellulose | USP | (b) (4) | |
| Polyethylene oxide | USP/NF | | |
| Erythritol | USP/NF | | |
| Peppermint flavor | In house | | |
| Calcium carbonate | USP | | |
| Sucralose | USP/NF | | |
| Colloidal silicon dioxide | USP/NF | | |
| Titanium dioxide | USP/NF | | |
| Sodium bicarbonate | USP | | |
| Monoammonium glycerrhizinate | USP/NF | | |
| Xanthan gum | USP/NF | | |
| Butylated hydroxytoluene | USP/NF | | |
| (b) (4) | | | |
| **Total Weight**<br>4 mg strip<br>8 mg strip | | | <br>30 mg<br>60 mg |

The percentage of any given ingredient is identical in the 4 mg and 8 mg strip, but the weight in the 8 mg strip is double the weight in the 4 mg strip. Based on the batch formula, the total weights of the 4 mg and 8 mg strips would be 30 and 60 mg, respectively, but losses of flavors during processing result in strip weights of (b) (4).

All excipients are compendial with the exception (b) (4), for which DMFs are referenced.

The manufacturing process consists of (b) (4)

Both strengths of the drug product will conform to the following release and stability specifications

| Test | Release Acceptance Criteria | Stability Acceptance Criteria |
|---|---|---|
| Appearance | White film | White film |
| Identification (HPLC) | Retention time of major peak corresponds to standard | Retention time of major peak corresponds to standard |
| Assay (HPLC)<br>Related compounds<br>(b) (4)<br>Individual unidentified<br>Total impurities<br>dissolution<br>(b) (4)<br>Content uniformity<br>Microbial limits<br>(b) (4) | (b) (4) | |

The proposed specification is generally acceptable for this type of dosage form, with impurities conforming to ICH standards. However, a second identification test should be added. It should be noted from the dissolution acceptance criterion that the rapid dissolution of this product is considerably faster than for most tablet formulations.

Six months of accelerated (40°C/75%RH) and controlled room temperature (25°C/60%RH) stability data have been submitted for three registration batches at each strength. The bulk dispersion was prepared at commercial scale, (b) (4) 4 mg and 8 mg strips, with the result that the strips were produced at approximately (b) (4) of commercial scale (this is within the general guideline that pilot batches for use in stability studies need to be greater than (b) commercials scale). There are no trends in the data indicative of product instability from either storage condition or strength. Twelve months of supporting stability data for a pilot batch of the 8 mg strength are also provided. (b) (4)

Based on the submitted data, (b) (4)

The firm commits to continuing the ongoing stability studies for the registration lots and to place the first three production batches of each dosage strength on stability testing at controlled room temperature conditions (25°C/60% RH). Thereafter, one additional batch of each strength will be added to the stability program each year. Stability data from these batches will be reported in post approval, annual reporting process. The proposed testing schedule is acceptable, but the stability commitment does not include a statement that should any of the test results fall out of specifications, FDA will be notified and the batch will be withdrawn from the market.

In accordance with 21 CFR 25.31(a), Par Pharmaceutical, Inc. requests a claim for categorical exclusion from an environmental assessment because approval of this New Drug Application will not increase the use of the active moiety, ondansetron. Ondansetron ODFS is a new dosage form of ondansetron that substitutes directly for the reference approved product, ZOFRAN ODT® 8 mg Tablets. Ondansetron ODFS will be used for the same indications, at the same dosage levels, and for the same duration as previously approved by the Agency for ondansetron.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

## *B. Critical issues for review*

-- The applicant has not conducted any bioequivalence studies with the 4 mg strength product, relying solely on comparative dissolution studies. The evaluation of these studies should be consulted to the ONDQA/ Biopharm staff for review. (The absence of bioequivalence studies for the 4 mg dose was discussed with Dr. Patrick Marroum, ONDQA Biopharm expert, who agreed that in view of the dose proportionality of the 8 mg and 4 mg formulations, dissolution data would be sufficient.)

-- Since some of the excipients in the product are non-compendial, their specifications will need to be closely scrutinized.

-- A second identity test should be added to the drug product specification.

-- Because Orally Dissolving Film Strip is not a recognized dosage form in the CDER Standards Manual, during the course of the complete review the names of other oral film products that have been approved will need to be surveyed and a dosage form name that is consistent with the approved names will need to be recommended for this product.

-- The stability commitment does not include a statement that should any of the test results fall out of specifications, FDA will be notified and the batch will be withdrawn from the market. The applicant should be requested to make the appropriate revision.

--The USP acceptance criteria for all impurities in the drug substance, both identified and unidentified, are 0.1%, yet the proposed (b) (4) for impurities (b) (4) .

-- Per 16 CFR 1700.14(a)(10) the pouch packaging for the strips is required to be child resistant. An evaluation should be made during the course of the full review to determine whether this issue has been adequately addressed

## *C. Comments for 74-Day Letter -- None*

## *D. Recommendation – From the CMC perspective this application is filable*

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

5/11/2009
Date

Moo-Jhong Rhee, PhD
Branch Chief

**NDA 22- 524** **Manufacturing Sites**

## Drug Substance

(b) (4)
(b) (4)

**DMF** (b) (4)

Responsible Official or Agent:
(b) (4)

## Drug Product (manufacture, packaging, testing)

MonoSolRx (Melton site)
6560 Melton Road
Portage, IN 46368

Registration number: 3004395604
DEA Registration number: RM0339564

Contact: Tayo Adebiyi
Sr. Director, Quality Assurance
219-762-8112
TAdebiyi@monosolrx.com

Microbiological testing at either of the following 2 sites

**Table 2.3.P.3-4 Contract Testing Laboratory –** (b) (4)
(b) (4)

**Table 2.3.P.3-5 Contract Testing Laboratory –** (b) (4)
(b) (4)

**NDA 22-456**

| | Content Parameter | Yes | No | Comment |
|---|---|---|---|---|
| 1 | Is the section legible, organized, indexed, and paginated adequately? | √ | | |
| 2 | Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)? | √ | | |
| 3 | Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready? | √ | | |
| 4 | Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)? | √ | | |
| 5 | Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)? | √ | | |
| 6 | Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)? | √ | | |
| 7 | If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included? | √ | | |
| 8 | Have draft container labels and package insert been provided? | √ | | |
| 9 | Have all DMF References been identified? | √ | | |
| 10 | Is information on the investigational formulations included? | | | |
| 11 | Is information on the Methods Validation included? | √ | | |
| 12 | If applicable, is documentation on the sterilization process validation included? | | | Not applicable |

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? ____YES__√__**

# ONDQA Pre-Marketing Assessment Division II
# Branch III
## General Correspondence

**1. IND number:** (b) (4)
Letter Date: 7/29/2008
Review Date: 9/19/2008

**2 OND Division:** HFD -180

**3. Sponsor Name and Address:** PAR Pharmaceutical

**4. Purpose of Submission:**

In a July 2, 2008 meeting, the firm discussed with FDA their plan to submit a 505(b)(2) application for Ondansetron Orally Dissolving Film Strip, using Zofran® Orally Disintegrating Tablets (NDA 20-781) as the reference listed drug. At that time FDA indicated that "orally dissolving film" is not a recognized dosage form that is defined in the CDER Data Standards Manual and that the orally dissolving film strip and orally disintegrating tablet may need to be considered as the same dosage form in view of FDA's Draft Guidance for "Orally Disintegrating Tablets", which defines an orally disintegrating tablet (ODT) as

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

As such, the firm was informed that it may be necessary to submit the application as a 505(j), not as a 505(b)(2). However, with the firm's preference to file as a 505(b)(2), they were requested to provide justification for this type of application by providing additional information with regard to physical or chemical properties that would differentiate the orally dissolving film strip (ODFS) from the orally disintegrating tablet (ODT).

The current submission is in response to the above request. The applicant has provided samples of the dosage form and lists three key properties that differentiate the orally dissolving film strip from the orally disintegrating tablet:

- The polymeric films that are very thin (typically 50 -150 µm) compared to ODTs.
- The films are flexible and can be bent
- The films are not friable

The applicant presents comparative data (appended to this review) for ODT and ODFS dosage forms, confirming some of these differences, but not friability (friability measurements were not performed on the films). Based on these properties, the firm proposes the following definition for this dosage form: *A thin, flexible, non-friable polymeric film strip containing one or more dispersed active pharmaceutical ingredients which is intended to be placed on the tongue for rapid disintegration/dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract.*

The applicant also argues that to call both these dosage forms ODTs could be confusing to patients if they were substituted at the pharmacy level. An AB rating would allow such an automatic substitution and the patient expecting a tablet would believe that the wrong medication was dispensed.

**5. Recommendation/Comments:**

Based on the difference in physical properties between the ODT and ODFS, and the dissimilarity in appearance between the two dosage forms, it is the reviewer's opinion that the proposed product should be filed as a 505(b)(2) application. This conclusion is further supported by the recent approval of a film dosage form (NDA 22-266), Onsolis (fentanyl buccal soluble film).

With regard to the designation of this dosage form as an Orally Dissolving Film Strip, additional consideration will be required. While the term Film will be appropriate to retain in the name of the dosage form, the term Strip should be deleted by analogy to the recently approved product; it may be more appropriate to substitute Disintegrating for Dissolving, depending on the data submitted in the application. Our current thinking is that the dosage form should either be called "Orally Dissolving Film" or "Orally Disintegrating Film". The most appropriate name for this dosage form will be determined during the review process.

**6. Response to be forwarded to the applicant:**

Please forward the following comments to the applicant:

- *It is acceptable for you to submit the application for the product that is the subject of this PIND as a 505(b)(2) application*

- *With regard to the designation of your dosage form as an Orally Dissolving Film Strip, additional consideration will be required. At the present time we are considering either "Orally Dissolving Film" or "Orally Disintegrating Film", depending on the data submitted in the application. The most appropriate name for this dosage form will be determined during the review process.*

_____

Marie Kowblansky, PhD — September 19, 2008
Pharmaceutical Assessment Lead

_____

Moo-Jhong Rhee, PhD — September 19, 2008
Branch Chief

Cc: Project Manager: J. Grewal

**Table 3. Typical range of values for properties of ODTs and ODFS**

| Test/Characteristic | ODT[1] | ODFS[2] |
|---|---|---|
| Thickness (inches) | 0.136 - 0.245 | 0.00197 - 0.0059 |
| Dimensions (inches)<br>Diameter/length x thickness:<br>Width x length: | 0.322 to 0.649 x 0.136 to 0.245 | 0.875 to 1.0 x 0.5 to 1.5 |
| Calculated Surface Area (sq. in.) | 0.242 - 1.161 | 0.875 - 2.625 |
| Ratio of Diameter (or length) / thickness (inches) | 2 – 3.4 | 85 – 760 |
| Weight (mg) | 27 – 300 | 30 – 150 |
| Disintegration (seconds) | [redacted] (b) (4) | |
| Partially Immersed Disintegration (seconds) | | |
| Friability | | |
| Hardness (compressive, kP) | | |
| Tensile Strength (N/mm) | | |
| Elongation (%) | | |
| Flexibility | No | Yes |

[1]The four ODTS tested were Zofran™ 8 mg, Zomig™ 5 mg, Orapred™ 15 mg and Risperdal™ 1 mg and 4 mg.

[2]The data on film strips was based upon data excerpted from testing performed on various commercialized OTC products and Rx products development at Monosolrx.

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

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/s/
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Marie Kowblansky
5/14/2009 01:40:26 PM
CHEMIST

Shulin Ding
5/15/2009 03:10:04 PM
CHEMIST
On behalf of Moo-Jhong Rhee, Ph.D.