# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209410Orig1s000

# OTHER REVIEW(S)

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

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | December 13, 2017 |
| To: | Billy Dunn, MD<br>Director<br>**Division of Neurology Products (DNP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Karen Dowdy, RN, BSN<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Dhara Shah, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Patient Package Insert (PPI) |
| Drug Name (established name): | OSMOLEX ER (amantadine) |
| Dosage Form and Route: | extended-release tablets, for oral use |
| Application Type/Number: | NDA 209410 |
| Applicant: | Osmotica Pharmaceutical US LLC |

## 1 INTRODUCTION

On January 18, 2017, Osmotica Pharmaceutical US LLC submitted for the Agency's review original New Drug Application (NDA) 209410 for OSMOLEX ER (amantadine) extended-release tablets. The extended-release formulation and once daily dosing schedule for OSMOLEX ER (amantadine) extended-release tablets were developed to provide more consistent levels of amantadine throughout the day and to enhance patient compliance by reducing administration from twice to once daily. The proposed indication for OSMOLEX ER (amantadine) extended-release tablets is in:

- the treatment of (b) (4) Parkinson's disease, (b) (4) (b) (4)
- the treatment of drug-induced extrapyramidal reactions.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Neurology Products (DNP) on August 16, 2017 and March 16, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for OSMOLEX ER (amantadine) extended-release tablets.

## 2 MATERIAL REVIEWED

- Draft OSMOLEX ER (amantadine) extended-release tablets PPI received on September 27, 2017 and received by DMPP and OPDP on September 27, 2017.
- Draft OSMOLEX ER (amantadine) extended-release tablets Prescribing Information (PI) received on January 18, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 29, 2017.
- Approved GOCOVRI (amantadine) extended release capsules comparator labeling dated August 24, 2017.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

## 4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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KAREN M DOWDY
12/13/2017

DHARA SHAH
12/13/2017

MARCIA B WILLIAMS
12/13/2017

LASHAWN M GRIFFITHS
12/13/2017

**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

## Memorandum

**Date:** December 12, 2017

**To:** Susanne Goldstein, M.D.
Division of Neurology Products (DNP)

Annie Nguyen, Regulatory Project Manager, (DNP)

Tracy Peters, Associate Director for Labeling, (DNP)

**From:** Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for OSMOLEX ER (amantadine) extended-release tablets, for oral use

**NDA**: 209410

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In response to the DNP consult request dated March 16, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for OSMOLEX ER (amantadine) extended-release tablets, for oral use (Osmolex).

**PI and PPI**: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP on November 29, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DNP on December 5, 2017 and December 8, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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DHARA SHAH
12/12/2017

# MEMORANDUM

**REVIEW OF REVISED LABEL AND LABELING**

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| **Date of This Memorandum:** | November 29, 2017 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | NDA 209410 |
| **Product Name and Strength:** | Osmolex ER (amantadine extended-release) tablets<br>129 mg, 193 mg, 258 mg |
| **Applicant/Sponsor Name:** | Osmotica Pharmaceutical |
| **Submission Date:** | October 18, 2017 |
| **OSE RCM #:** | 2017-155-1 |
| **DMEPA Safety Evaluator:** | Chad Morris, PharmD, MPH |
| **DMEPA Team Leader:** | Lolita White, PharmD |

## 1 PURPOSE OF MEMO

The Division of Neurology Products requested that we review the revised the carton labeling, unit-dose blister foil labels, and container labels for Osmolex ER (amantadine) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

We note, Osmotica did not identify the location of the lot number and expiration date on the carton labeling and container labels images; however, within their cover letter they state "the format for the expiration date will be displayed on the carton labels and container labels in MMM YYYY format within the GS1 datamatrix barcode. The GS1 datamatrix barcode will be placed on the non-coating area marked on the carton labels and container labels." See Appendix A for the proposed GS1 datamatrix barcode.

## 2 CONCLUSION

The revised unit-dose blister foil labels for Osmolex ER (amantadine) are unacceptable from a medication error perspective. The placement of the NDC number on the unit-dose blister foil labels may lead to confusion and result in wrong product medication error.

[a] Morris, C. Label and Labeling Review for Osmolex ER (NDA 209410). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 07. RCM No.: 2017-155.



Reference ID: 4187468

## 3 RECOMMENDATIONS FOR OSMOTICA PHARMACEUTICALS

We recommend the following be implemented prior to approval of NDA:

A. As currently presented, the placement of the NDC number in the center of the unit-dose blister foil labels with no identifier may increase the risk for product identification medication errors. To decrease risk of confusion, we recommend you:
   a. Relocate the NDC number away from the strength, either at the top near the linear barcode or at the bottom near the lot number/expiration date.
   b. Add the letters NDC followed by a colon (NDC:) in front of the NDC number.

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/s/

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JOHN C MORRIS
11/29/2017

LOLITA G WHITE
11/29/2017

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

**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

**Date:** October 11, 2017.

**To:** Billy Dunn, M.D., Director
Division of Neurology Products

**Through:** Dominic Chiapperino, Ph.D. Acting Director
Martin S. Rusinowitz, M.D., Senior Medical Officer
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

**From:** Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

**Subject:** **NDA 209410**: Amantadine Hydrochloride (HCl) Extended Release (ER) Tablets
**Trade Name:** Osmolex ER
**Dosages:** 160 mg, 240 mg, and 320 mg, tablets once daily (QD) oral
**IND Number:** 103538
**Indication:** Treatment of Parkinson's disease
**Sponsor:** Osmotica Pharmaceutical US LLC.
**PDUFA Goal Date:** November 18, 2017

## Materials Reviewed:

- 1.11.4 Abuse related information
- 2.3 Quality overall summary
- 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
- 2.7.4 Summary of Clinical safety
- 5.3.1 Reports of Biopharmaceutic Studies
- 5.3.5 Reports of efficacy and safety studies
- 1.14. Labeling
- NDA 208944; OSE Consult, Tobenkin A; DARRTS Feb 9, 2017.

Table of Contents



# I. Summary

## 1. Background

This memorandum is in response to a consult request by the Division of Neurology Products (DNP), dated January 26, 2017, to evaluate abuse related data submitted by Osmotica Pharmaceutical in NDA 209410 (developed under IND103538) for Amantadine Hydrochloride (HCl) Extended Release (ER) Tablets; Trade Name Osmolex ER.

The proposed indication is for the treatment of Parkinson's disease (PD). The ER formulation and once daily dosing schedule were developed to provide more consistent levels of amantadine throughout the day and to enhance patient compliance by reducing administration from twice to once daily. Amantadine HCl ER is being submitted under 505(b)(2) regulations with reference to NDA 016023 (Symmetrel Syrup; amantadine HCl).



Reference ID: 4165976

Amantadine was initially approved in the USA in 1976. Amantadine HCl is not a controlled substance under the Controlled Substances Act (CSA).

### 2. Conclusions

There is no evidence of abuse associated with amantadine based on the adverse event (AE) profile of Amantadine HCl ER Tablets and Division of Pharmacovigilance's (DPV) review of post-marketing cases in the FDA Adverse Event Reporting System (FAERS). Additionally, there is no evidence in the medical literature for an association between amantadine and drug abuse, dependence or withdrawal. It is recommended that amantadine not be scheduled under the CSA.

### 3. Recommendations (to be conveyed to Sponsor).

Based on our findings we recommend the following:

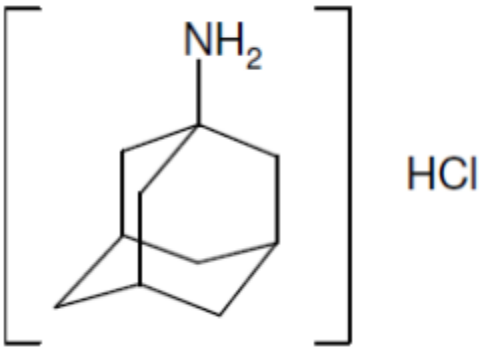
- Amantadine should remain as a non-controlled substance under the Controlled Substances Act (CSA).
- Section 9.0, Drug Abuse and Dependence should not be included in the label of the product.

## II. DISCUSSION

### 1. Chemistry

### 1.1 Substance Information

Chemical Name: Tricyclo[3.3.1.13,7]decan-1-amine, hydrochloride
Amantadine Hydrochloride (Amantadine HCl)
Molecular Structure




Pharmacological Class: Anticholinergic-like agent
Physical Description: White or almost white crystalline powder
Solubility characteristics: At room temperature, amantadine hydrochloride is freely soluble in water, ethanol, and methanol; soluble in chloroform; sparingly soluble in methylene chloride, and practically insoluble in ether.

## 1.2 Product Information

Amantadine HCl ER Tablets, 160, 240, and 320 mg contain an ER tablet core and an immediate-release (IR) layer. The Sponsor describes the formulation and its components as follows:

Drug release from the ER core is controlled by an osmotic pump system. Osmotic pump systems consist of a drug core contained within a semipermeable polymer membrane that is permeable to water molecules but not to the drug with an orifice for drug delivery. Drug release is driven by the osmotic pressure generated within the tablet core upon exposure to water.

## 2. Nonclinical Pharmacology

Amantadine has anticholinergic-like pharmacological activity. The mechanism of action of amantadine in the treatment of PD and drug-induced extrapyramidal reactions is not known. Data from earlier animal studies suggest that amantadine may have direct and indirect effects on dopamine neurons. More recent studies have demonstrated that amantadine is a weak, non-competitive, NMDA receptor antagonist. Although amantadine has not been shown to possess direct anticholinergic activity in animal studies, clinically it exhibits anticholinergic-like side effects such as dry mouth, urinary retention, and constipation. The Sponsor states that Amantadine HCl ER Tablets contains the same active ingredient as the currently marketed Listed Drug (LD), Symmetrel Oral Syrup (amantadine HCl), which is indicated for the same patient population (PD patients), has the same route of administration and duration of treatment, and for which patient daily exposure from Amantadine HCl ER Tablets does not differ significantly from that of the LD. The Sponsor is, therefore, relying on the Agency's prior finding of safety for the LD in lieu of new nonclinical pharmacology, ADME, or toxicology studies for Amantadine HCl ER Tablets.

No abuse related, animal behavioral studies were conducted.

## 3. Clinical Pharmacology

The pharmacokinetic (PK) profile for amantadine from the ER product differs from that of the LD. The partial-AUC bioequivalence (BE) analysis (point-by-point comparison) performed using data from the pivotal BE study (OS320-PKP06; 320 mg ER vs 2x160 mg IR) showed that the exposure to amantadine is within BE limits at some time-points; however, exposure is outside of the BE limits at other time-points. The pivotal BE study results demonstrate that the ER tablet results in plasma levels that fall within the BE limits for Cmax and AUC relative to amantadine syrup at the 320 mg dose level.

## 3.1 Drug/Product Interactions

Examination of Amantadine HCl ER dissolution profiles in 40% ethanol in acidic (0.1 N HCl) or QC (water) media revealed that the 160-mg, 240-mg, and 320-mg tablets maintained their ER properties. The profile maintained its pseudo-zero order characteristic; the release profile was linear from 30 minutes to 120 minutes. The maximum increase in amantadine HCl release induced by the addition of up to 40% ethanol was 37%, 34% and 16% of the amount of amantadine HCl in the ER tablet core for the 160, 240, and 320 mg ER Tablets, respectively. The maximum amount released in 2 hours for the



Reference ID: 4165976

160, 240, and 320 mg ER Tablets was 53%, 66%, and 87%, respectively, of the dose of a 200 mg IR amantadine HCl oral solution dose.

Dissolution media containing up to 40% ethanol does not compromise the release-rate-controlling mechanism of the ER tablet core of Amantadine HCl ER Tablets.

Amantadine HCl ER Tablets do not dose dump in ethanol solutions containing up to 40% ethanol.

In a food effect study of Osmolex ER 320 in 24 healthy male and female volunteers, the ratio of Fed to Fasted values for Cmax and AUC was 108% and 94%, respectively; the 90% confidence intervals were within 80.00 to 125.00%, indicating that no significant food effect was observed.

## 4. Clinical Studies

### 4.1 Adverse Event Profile Through all Phases of Development

This NDA relies on relative bioavailability data from three Phase 1 studies, the FDA's prior findings of safety and efficacy of amantadine HCl syrup, one Phase 1 study of amantadine pharmacokinetics in patients with renal impairment, supplemental safety data from two Phase 3 studies, and relevant safety and efficacy results from the published literature and the public domain.

OS320-PKP04 ( Phase 1 )An Open-label, Balanced, Randomized, Two-period, Two-sequence, Single dose, Bioavailability Study of Amantadine HCl 320 mg Extended Release Tablets Under Fasting and Fed Conditions in Normal, Healthy, Adult, Non-smoking Male and Female Subjects.

Primary Objective: To determine the bioavailability of a formulation of Amantadine HCl 320 mg ER Tablets in healthy volunteers after a single dose administration while fasting and after a high-fat meal. Twenty four (24) subjects were enrolled. No abuse-related AEs were reported.

OS320-PKP05 (Phase1)Relative Bioavailability Study of Amantadine HCl Extended Release Tablets, 160 mg, 240 mg, and 320 mg Compared to 160 mg (16 mL) of Amantadine HCl Syrup (50 mg/5 mL) Under Fasted Conditions.

The study primary objectives were to evaluate dose proportionality between 160, 240, and 320 mg Amantadine HCl ERtablets, and to determine the relative bioavailability of the 160 mg tablet compared to the PK parameters of a reference formulation of 160 mg of Amantadine HCl syrup (50 mg/5 mL), in healthy volunteers after a single dose administration under fasted conditions. The products were administered to 24 subjects; two subjects were withdrawn due to non-abuse-related AEs. Somnolence was reported in one subject in the Amantadine ER group and one in the Amantadine HCl syrup group.

OS320-PKP06(Phase 1) A Steady-State Relative Bioavailability Study of Amantadine HCl Extended-Release Tablets, 320 mg Compared to 320 mg Amantadine HCl Oral Solution.

The study primary objective was to determine the steady-state relative bioavailability after multiple dosing of Amantadine HCl ER Tablets, 320 mg once a day compared to the plasma profiles and pharmacokinetics parameters of an equivalent daily dose of 320 mg Amantadine HCl Oral Syrup (50 mg/5mL) divided into 2 equal doses, in healthy volunteers under fasted conditions.

The following treatment regimens were used:

Amantadine HCl 50 mg/5 mL Oral Syrup (160 mg dose, once daily for 2 days), followed by:

Treatment-A (Test): Amantadine HCl 320 mg ER Tablet (320 mg dose, once daily for 7 consecutive days)

Treatment-B (Reference): Amantadine HCl 50 mg/5 mL Oral Syrup (160 mg twice daily for 7 consecutive days)

A total of 24 subjects were included in this study. One subject was withdrawn due to AEs of visual and hearing difficulty. No abuse related AEs were reported.

OS320-PKP3 (Phase 1) A single dose, randomized, 4-way cross-over design to evaluate the relationship between bioavailability and dose of three controlled release Osmotic Amantadine Tablets versus a reference syrup formulation in 24 healthy subjects under fasted conditions.

Twenty-four subjects were enrolled. In a four period cross over study, separated by a wash-out period of 7 days, 24 subjects received Amantadine ER tablets (160, 240 and 320 mg) as test and Amantadine 320 mg syrup (50mg/mL) as reference preparation. Two subjects in the 240mg ER group experienced somnolence

OS320-3005 (Phase 3) A Multicenter, Randomized, Placebo-controlled, Double-blind, 16-Week Study to Evaluate the Efficacy and Safety of Amantadine HCl Extended Release Tablets in Parkinson's Disease Subjects with Levodopa-Induced Dyskinesias.

This was a randomized, double-blind, placebo-controlled parallel-group, 3-arm, Phase 3, multicenter study. After a Titration Period, the subjects were assigned to fixed dose groups that compared the efficacy and safety of Amantadine HCl ER tablets with placebo in subjects 30 to 85 years of age with PD who had Levodopa-induced dyskinesia (LID).

Eligible subjects were randomized in a 1:1:1 manner into one of three treatment groups:

- Amantadine HCl ER 320 mg,
- Amantadine HCl ER 240 mg, or
- Placebo.

Number of Randomized Subjects: Eighty seven (87); (29 subjects in the Amantadine HCl ER 320 mg group, 30 subjects in the Amantadine HCl ER 240 mg group, and 28 subjects in the Placebo group)
Duration of Treatment: Sixteen (16) weeks.

Hallucinations were reported in 8 subjects; 7 in the Amantadine group (11.8%) and 1 the placebo group (3.6%). Somnolence was reported in 2 subjects in the Amantadine ER group and 2 in the placebo group.

OS320-3006 (Phase 3) A Multicenter, Randomized, Placebo-controlled, Double-blind, 26-Week Study to Evaluate the Efficacy and Safety of Amantadine HCl Extended Release Tablets in Parkinson's Disease Subjects with Levodopa-Induced Dyskinesias.

This was a fixed-dose trial (after a Titration Period) that compared the efficacy and safety of Amantadine HCl ER tablets with placebo in subjects 30 to 85 years of age with PD who had LID. Eligible subjects were randomized in a 1:1:1 manner into one of three treatment groups:

- Amantadine HCl ER 320 mg,
- Amantadine HCl ER 240 mg, or
- Placebo

One hundred and thirty-five (135) subjects were randomized in the study; 46 subjects were assigned to the Amantadine HCl ER 320 mg group, 45 subjects to the Amantadine HCl ER 240 mg group, and 44 subjects to the placebo group. Overall median exposure to the study drug was 180.0 days. The treatment groups were comparable with respect to study drug exposure. Somnolence was reported by 3 subjects in the amantadine groups and 4 in the placebo group. Hallucinations were reported by 8 (8.8%) subjects in the amantadine groups and 2 (4.5%) in the placebo group.

## 4.2 Safety Profile

The Sponsor has not conducted studies specifically addressing the abuse potential of Amantadine HCl ER Tablets.

They have captured abuse-related AEs during Phase 1 and Phase 3 studies. AEs were summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). The Phase 3 clinical program included over 150 unique subject exposures to amantadine with up to 24 weeks of double-blind treatment.

The Phase 1 and Phase 3 clinical trials conducted during development of Amantadine HCl ER do not reveal evidence of abuse-related AEs. There were no reports of euphoria, elevated mood, feeling drunk, or feeling of relaxation. Hallucinations occurred to a greater extent in the Amantadine HCl ER group (8.8%- 11.8%) compared to the placebo group (3.6%-4.5%). Hallucinations are a known side effect of amantadine and did not occur in the context of other abuse-related AEs. Hallucinations are also known to occur in patients with PD. Somnolence occurred to a similar extent in the Amantadine HCl ER and control groups.

The Sponsor has also assessed the abuse potential of amantadine through an evaluation of the current literature. No literature or post-marketing study was found indicating amantadine as a drug of abuse potential.
The expected maximum daily dose of Amantadine HCl ER (320 mg) is lower than the highest recommended dose of amantadine in currently available products (400mg/day).

## 4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

In the Amantadine HCl ER Tablet clinical development program, no subjects had an AE categorized as drug abuse or drug dependence in the analysis of AEs. There were no drug accountability issues.

## 5. Other Relevant Information

DPV, in the Office of Surveillance and Epidemiology, was consulted to look for any historical evidence of amantadine abuse . FDA has not performed a previous review of abuse potential for amantadine. CSS specifically identified Amantadine ER tablets as a drug that must undergo an assessment of studies and other information related to abuse potential because it affects the CNS, is chemically and pharmacologically similar to other drugs with known abuse potential, and produces psychoactive effects.

DPV Consult Review: This review evaluated post-marketing cases in FAERS and literature for an association between amantadine and drug abuse, dependence or withdrawal.

Searches of the FAERS database and the literature identified no cases of abuse or dependence with amantadine therapy. The lack of FAERS postmarket cases of abuse or dependence with amantadine therapy was also supported by a literature search. Although the search of the FAERS database did not identify cases describing amantadine abuse or dependence, nine cases were identified describing amantadine withdrawal. Since there were very few cases with withdrawal symptoms, these findings would not prompt inclusion of withdrawal in Section 9 in the labeling which describes abuse and dependence. Furthermore, the symptoms that were described in the postmarket cases, such as; anxiety, depression, and hallucinations are described in the current amantadine labeling in the PRECAUTIONS section.
DPV Conclusion: 'We did not find evidence of abuse or dependence with amantadine in the post-marketing setting.'

## 6. Regulatory Issues and Assessment

The Sponsor requests that Amantadine HCl ER Tablets not be placed in any schedule of the CSA. Based on the AE profile of Amantadine HCl ER and the consult related to abuse potential by the DPV, we agree with the Sponsor that Amantadine HCl ER does not warrant placement in any schedule of the CSA. Section 9.0, Drug Abuse and Dependence, is not recommended for product labeling.
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SHALINI M BANSIL
10/11/2017

MARTIN S RUSINOWITZ
10/11/2017

SILVIA N CALDERON
10/12/2017

DOMINIC CHIAPPERINO
10/12/2017

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

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

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DATE: August 8, 2017

TO: William H. Dunn, MD
Director
Division of Neurology Products
Office of New Drugs

AND

Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4)

**Inspection Summary**

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of studies OMC-P6-145 (NDA 209410), Non-Responsive conducted at (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude that data from the audited studies (OMC-P6-145, Non-Responsive are reliable. Thus, I recommend that the data from studies

OMC-P6-145, Non-Responsive , and other studies using similar methods, be accepted for further Agency review.

**Inspected Studies:**

**NDA 209410**
**Study Number:** **OMC-P6-145**
**Study Title:** "A Steady-State Relative Bioavailability Study of Amantadine HCl Extended Release Tablets, 320 mg Compared to 320 mg Amantadine HCl Oral Solution"
**Dates of conduct:** 04/26/2016 – 05/09/2016

Non-Responsive

Non-Responsive

**Analytical site:** (b) (4)

OSIS scientist Kara A. Scheibner, Pharmacologist, audited the analytical portion of the above studies at (b) (4)

The inspection included a thorough examination of study records, analytical facilities, laboratory equipment, method validations, sample analyses, and interviews with the firm's management and staff. In addition, SOPs, training records, and equipment maintenance records were reviewed, and electronic data from Analyst (including audit trails), Watson, Validation (in-house method validation program), and Dosage (in-house sample analysis program) were reviewed and evaluated. Finally, I verified that (b) (4) updated and improved processes following discussions conducted during the last inspection in (b) (4).

One concern noted prior to the inspection was the large number of sample repeats in studies OMC-P6-145, Non-Responsive

(b) (4). I reviewed all repeat records carefully, and concluded that the number of repeats counted all samples reassayed, including those due to batch failures; 1 of 10 in study OMC-P6-145, Non-Responsive Individual sample repeats in all three studies were minimal, and were due to samples requiring dilution (>ULOQ), samples lost in processing, and samples with an unexpected internal standard responses. I verified all repeats, including those from failed batches, and did not observe any discrepancies or samples reassayed without justification.

At the conclusion of the inspection, I did not observe objectionable conditions and did not issue Form FDA 483.

**Conclusion:**

After reviewing inspectional findings, I conclude that data from the audited studies are reliable. Therefore, I recommend that the data from studies OMC-P6-145 (NDA 209410), Non-Responsive be accepted for further review.

Based on the inspectional findings, studies using similar methods conducted between the last inspection (b) (4)) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Kara A. Scheibner, Ph.D.
Pharmacologist

**Final Classification:**

**NAI** - (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au/Scheibner

Draft: KAS 08/07/2017
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KARA A SCHEIBNER
08/09/2017

SEONGEUN CHO
08/09/2017

**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

| | |
|---|---|
| **Date of This Review:** | July 7, 2017 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | NDA 209410 |
| **Product Name and Strength:** | amantadine hydrochloride<br>Extended-Release tablet |
| **Product Type:** | Single ingredient product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Vertical Pharmaceuticals, LLC |
| **Submission Date:** | January 18, 2017; April 13, 2017 |
| **OSE RCM #:** | 2017-155 |
| **DMEPA Primary Reviewer:** | Chad Morris, PharmD, MPH |
| **DMEPA Team Leader:** | Lolita White, PharmD |



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## 1 REASON FOR REVIEW

As part of the approval process for NDA 209410 amantadine HCl, the Division of Neurology Products (DNP) requested The Division of Medication Error Prevention and Analysis (DMEPA) to review the carton labeling, unit-dose blister foil labels, and container labels submitted on January 18, 2017, and the Prescribing Information submitted on April 13, 2017 for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

**Table 1. Materials Considered for this Label and Labeling Review**

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Human Factors Study | C (N/A) |
| ISMP Newsletters | D (N/A) |
| FDA Adverse Event Reporting System (FAERS)* | E (N/A) |
| Other | F |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the carton labeling, unit-dose blister foil labels, container labels, and Prescribing Information (PI) for amantadine hydrochloride extended-release tablet for areas of vulnerability that may lead to medication areas. We identified areas of the carton labeling, container labels, and PI that can be improved to increase the prominence and readability of important product information.

Full Prescribing Information

- Product identifier information necessary to facilitate identification of the product (e.g. imprint code, tablet shape, tablet color, shape) is not presented in Section 16. The lack of this important product identifier information might lead to wrong product or wrong strength medication errors.

All Carton labeling, foil-backed blister labels, and Container labels

- The colors used to differentiate the 240 mg and 320 mg strengths are too dark and decrease the readability of the strengths. In addition, the (b) (4) color used to



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differentiate the 320 mg strength (b) (4). The differentiation of strengths can be improved to reduce the risk of wrong strength medication errors.
- The format of the expiration date is not clearly defined, which may lead to a degraded drug product medication error.
- The dosage form is more prominent than the established name and may contribute to risk of wrong drug medication errors.

10-count unit-dose blister pack carton labeling only

- There NDC number as presented lacks prominence which may increase the risk of product selection medication errors.

30- and 90-count bottle container labels only

- The net quantity and RX Only statement are located in close proximity to the strength statement. This presentation contributes to the lack of prominence of the strength statement, which may pose risk of wrong strength medication errors.

We provide recommendations to help minimize the potential for medication errors to occur with the use of the product in Sections 4.1 and 4.2.

## 4 CONCLUSION & RECOMMENDATIONS

We find the Prescribing Information, carton labeling, foil-backed blister labels, and container can be improved to improve readability, facilitate identification of dosage forms, increase the prominence, and clarify important information to ensure the safe use of the product. We provide recommendations to the Division of Neurology Products in Section 4.1 and to Vertical Pharmaceuticals in Sections 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this application.

### 4.1 RECOMMENDATIONS FOR THE DIVISION OF NEUROLOGY PRODUCTS

- As currently presented in Section 16 of the full Prescribing Information, important information to facilitate identification of the product is not provided. The lack of this information may contribute to wrong product or wrong strength medication error. Specifically, the required information to define imprinting, shape, color, and coating are not listed. In accordance with 21 CFR 201.57(c)(17), we recommend adding the imprint codes, shape, color, and coating information to Section 16.

### 4.2 RECOMMENDATIONS FOR VERTICAL PHARMACEUTICALS

We recommend Vertical Pharmaceuticals implement the following prior to the approval of this NDA:

All Carton labeling, foil-backed blister labels, and Container labels

- As currently presented, the deep shades of the (b) (4) backgrounds for the 240 mg and 320 mg, respectively, do not provide adequate contrast and decrease the

readability of the strength statements and increase the risk for wrong strength medication errors. For example, the [redacted] in the background of the 320 mg product should be lighter to increase contrast and improve readability. [redacted] For example, the [redacted] background color used to highlight the 240 mg product strength [redacted] We recommend increasing the contrast of the background colors used to differentiate the strengths to provide adequate contrast and we recommend the use of unique colors [redacted] to better differentiate the product strengths and decrease risk of wrong strength medication error.

- The format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format similar to either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).
- As currently presented, the dosage form is too prominent. The proprietary name and established names should be the most prominent information on the label. In accordance with 21 CFR 201.10 (g) (2), decrease the font size and prominence of the dosage form statement and increase the prominence of the established name ensuring the established (proper) name is at least ½ the size of the proprietary name.
- The NDC # lacks prominence due to the small font size and due to its close proximity to the bolded net quantity and package type statements. Since the NDC # is often used as an additional verification prior to dispensing, it is an important safety feature and should be more prominent. Consider increasing the font size of the NDC # and debold the net quantity and package type statements.

<u>30- and 90-count bottle container labels</u>

- The net quantity and Rx only statement are located in close proximity to the strength statements. The presentation contributes to the lack prominence of the strength statement which may lead to confusion and pose risk of wrong dose medication error. Consider relocating the strength statement above the net quantity and Rx only statements. In addition, debold the net quantity and Rx only statements so they do not decrease the prominence of the product strength.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Osmolex ER that Vertical Pharmaceuticals submitted on April 13, 2017, and the listed drug (LD).

**Table 2. Relevant Product Information for Osmolex ER and Symmetrel syrup**

| **Product Name** | **Osmolex ER** | **Symmetrel** (syrup, NDA 016023) |
|---|---|---|
| **Initial Approval Date** | N/A | 02/14/1968 |
| **Active Ingredient** | Amantadine HCl | Amantadine HCl |
| **Indication** | • Treatment of (b) (4) Parkinson's disease, (b) (4) (b) (4)<br>• Treatment of drug-induced extrapyramidal reactions | • Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus.<br>• Treatment of parkinsonism<br>• Treatment of drug-induced extrapyramidal reactions |
| **Route of Administration** | Oral | Oral |
| **Dosage Form** | Extended-release tablet | Syrup |
| **Strength** | 160 mg, 240 mg, 320 mg | 50 mg/5 mL |
| **Dose and Frequency** | (b) (4) | Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus<br>• Adults - 200 mg daily or 100 mg twice daily<br>• 1 to 9 years of age – 2 to 4 mg/lb/day (4.4 to 8.8 mg/kg/day), not to |



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<table>
<tr><td></td><td>(b) (4)</td><td>exceed 150 mg per day<br>• 9 to 12 years of age – 100 mg twice daily<br>Treatment of parkinsonism<br>• 100 mg once daily to 400 mg daily in divided doses<br>Treatment of drug-induced extrapyramidal reactions<br>• 100 mg twice daily to 300 mg daily in divided doses<br>Dosing in renal impairment<br>CREATININE CLEARANCE (mL/min/1.73m$^2$) — SYMMETREL DOSAGE<br>30-50 — 200 mg 1st day and 100 mg each day thereafter<br>15-29 — 200 mg 1st day followed by 100 mg on alternate days<br><15 — 200 mg every 7 days</td></tr>
<tr><td>How Supplied</td><td>• Unit-dose cards of 10 tablets<br>• Bottles of 30 and 90 tablets</td><td>480 mL bottle</td></tr>
<tr><td>Storage</td><td>Store at (b) (4) excursions permitted to 15-30°C (59-86°F).</td><td>Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F).</td></tr>
<tr><td>Container Closure</td><td>Foil backed blisters and (b) (4) bottles</td><td>Child-resistant bottle</td></tr>
</table>

## APPENDIX B. PREVIOUS DMEPA REVIEWS

### B.1 Methods

On May 17, 2017, we searched the L: drive and AIMS using the term, Osmolex, to identify reviews previously performed by DMEPA.

### B.2 Results

Our search did not identify previous labels and labeling reviews.

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LOLITA G WHITE on behalf of JOHN C MORRIS
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