CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209410Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209410
Supporting document/s:	1
Applicant's letter date:	JAN 18, 2017
CDER stamp date:	JAN 18, 2017
Product:	Amantadine extended release tablets
Indication:	Parkinson's disease
Applicant:	Osmotica Pharmaceutical US LLC
Review Division:	Division of Neurology Products
Reviewer:	LuAnn McKinney, DVM, DACVP
Supervisor:	Lois M. Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Anhtu Nguyen, Pharm D

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209410 are owned by Osmotica Pharmaceutical or are data for which Osmotica Pharmaceutical has obtained a written right of reference. Any information or data necessary for approval of NDA 209410 that Osmotica Pharmaceutical does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 209410.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Osmotica Pharmaceutical has submitted this NDA for Osmolex® (amantadine HCl extended release tablets) indicated in the treatment of (b) (4) Parkinson's disease, (b) (4) , and in the treatment of drug-induced extrapyramidal reactions.

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Osmotica Pharmaceutical is relying on the Agency's finding of safety for the RLD Symmetrel® 50 mg/5 mL Oral Syrup (NDA 16023, approved on FEB 14, 1968).

1.2 Brief Discussion of Nonclinical Findings

1.2 Brief discussion of Nonclinical findings:

No nonclinical studies were submitted to this NDA.

1.3 Recommendations

1.3.1 Approvability

This NDA is approvable from a nonclinical perspective.

1.3.2 Labeling

1. Labeling largely reflects that approved for the RLD; however, the following are recommended to be included:

   A) Comparisons to the recommended human dose (RHD) should be based on the Osmolex® maximum RHD (MRHD) of 400 mg/day (247 mg/m^2)

   B) Section 8.1 should reflect the findings described in the publications summarized under Reproductive and Developmental Toxicology.

2 Drug Information

2.1 Drug

CAS Registry Number: 665-66-7

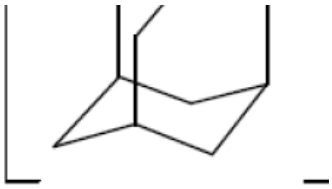
Generic Name: Amantadine HCl extended release tablets

Code Name: 1-amantadine Hydrochloride

Chemical Name: adamantan-1-amine, hydrochloride; Tricyclo[3.3.1.1^{3,7}]decan-1-amine, hydrochloride

Molecular Formula/Molecular Weight: $C_{10}H_{17}N \cdot HCl$/ 187.7

Structure or Biochemical Description (sponsor's figure)



2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 103538
Symmetrel® (NDA 016023)
With reference to:
Type 2 DMF: (b) (4)
Type 3 DMF: (b) (4)
Type 4 DMF: (b) (4)

2.3 Drug Formulation

Osmolex ® is to be formulated as 160 mg, 240 mg, and 320 mg of Amantadine HCL, ER, in layered tablets consisting of a drug core contained within a polymer membrane that is permeable to water but not to the drug. Upon exposure to water, water enters the core and drug is released through an orifice in the membrane. There are no novel excipients in the drug product; all excipients are at levels less than those listed in the Inactive Ingredient Database (IID), and impurities are within acceptable limits.

2.4 Comments on Novel Excipients

The amounts of all excipients in the drug product are at or below the approved levels as listed in FDA's Inactive Ingredient Database (IID).

2.5 Comments on Impurities/Degradants of Concern

The drug product contains no new impurities/degradants above the qualification threshold.

2.6 Proposed Clinical Population and Dosing Regimen

The clinical population is adult patients with Parkinson's disease and elderly adult patients with Parkinsonian symptoms. Osmolex® may be administered as adjunctive therapy with levodopa; the proposed maximum recommended human dose (MRHD) of Osmolex® is 400 mg of amantadine HCL, administered once daily.

2.7 Regulatory Background

IND 103538 was submitted on APR 14, 2009.
NDA 209410 was submitted on JAN 18, 2017.
No nonclinical studies were required to be submitted to either the IND or this NDA.

3 Studies Submitted

None

4 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted to this NDA; however, labelling of the RFD (Symmetrel®) reflects publications of studies that predate the GLP regulations, by Vernier et al. (Toxicol Appl Pharmacology, **15**, 642-665, 1969) and Lamar et al. (Abstracts: Annual Meeting, Soc. of Tox, 1970). Vernier et al. (1969) reported that oral administration of amantadine to male and female rats at a dose of 32 mg/kg/day resulted in impaired fertility, but no fetal abnormalities were observed.

Lamar et al. (1970) reported that when amantadine was administered to Harlan Sprague Dawley rats at 0, 50 or 100 mg/kg/day 5 days prior to mating and through Gestation Day (GD) 6, decreased numbers of implants and increased absorptions were found at the HD.

Lamar et al. (1970) further reported that oral administration of amantadine to pregnant Harlan SD rats from GDs 7 to 14 resulted in marked fetal malformations at the MD and HD (50 and 100 mg/kg/day, respectively) of edema, malrotated hindlimbs, missing tail, stunting, brachygnathia, and ribs and sections of the lumbar and sacral spinal column were found to be absent at both dose levels. On a milligrams per meter squared basis, the high dose (100 mg/kg/day) is 2.4-times the MRHD and the the lowest adverse effect level (LOAEL) of 50 mg/kg/day is approximately equal to (1.2-fold) the MRHD; the NOEL of 37 mg/kg/day is less than (0.9-fold) the MRHD.

In a third publication (Kakinai et al. Mod Clin, **3**, No.12, 782-795, 1970) of a non-GLP study of amantadine administered orally to pregnant ICR mice from GD 7 to GD 12, increased fetal loss and reduced fetal weights were found at the highest dose of 40 mg/kg/day which, on a mg per meter squared basis, is one-half the MRHD.

An additional non-GLP study of amantadine in pregnant Wistar rats was conducted by the same laboratory (Yo et al. Mod Clin, **4**, No.1, 44-55, 1970). Oral administration of amantadine from GD 9 to GD 14, increased fetal loss and reduced fetal weights at the highest dose of 120 mg/kg/day (3.0-fold the MRHD). In both the rat and mouse studies, when 5/15 females per group carried to term and the litters were observed through post-natal day 21, reduced litter sizes and birth weights were the reported differences from controls.

5 Integrated Summary and Safety Evaluation

Osmolex® is an oral extended release tablet formulation of amantadine HCl intended for the treatment of (b) (4) Parkinson's disease (b) (4) and in the treatment of drug-induced extrapyramidal reactions. As a 505(b)(2) application, approval relies largely on the findings of safety for the reference listed drug(RLD), Symmetrel®, an orally administered amantadine HCl syrup. The application relies on a finding of bioequivalence (C_{max} and AUC) of Osmolex® and the RLD. Because the use and indication are the same as the RLD, and the drugs are found to be bioequivalent, no nonclinical studies were required.

Although not conducted according to current standards, developmental and reproductive toxicity studies were cited in the Symmetrel® label and are found in the published literature. On a body surface area basis, embryolethality and malformations were seen in rats administered doses roughly equal to (1.2-fold) the recommended human dose of 400 mg per day. At similar doses reduced fertility was seen in male and female rats. At doses less than (0.5-fold) the MRHD, administration of amantadine to mice was associated with fetal loss and decreased fetal weight.

From a nonclinical perspective, the application is approvable.

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

/s/

LUANN MCKINNEY
10/12/2017

LOIS M FREED
10/12/2017
I agree that the application is approvable, from a nonclinical standpoint.