CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209410Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	2/16/2018
From	Gerald D. Podskalny, DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209410
Applicant	Osmotica Pharmaceutical
Date of Submission	1/18/2017
PDUFA Goal Date	2/18/2018 with extension for major amendment
Proprietary Name / Established (USAN) names	Osmolex Extended Release/Amantadine Extended Release
Dosage forms / Strength	Oral 129 mg, 193 mg and 258 mg tablets (Base)
Proposed Indication(s)	1. The treatment of Parkinson's disease and (b) (4) 2. Drug-induced extrapyramidal reactions
Recommended:	APPROVAL

1. Introduction

Osmotica Pharmaceutical US LLC (Osmotica) developed an extended-release dosage form of amantadine tablets for once daily oral administration for treatment of Parkinson's disease, (b) (4) and drug-induced extrapyramidal disorders. Osmotica is relying on the FDA's previous finding of safety and effectiveness for NDA 16023 - Symmetrel (Amantadine HCL) Syrup as the reference drug.

2. Background

Osmolex ER (Amantadine extended release) tablets contain 129 mg, 193 mg, or 258 mg of amantadine, which correspond to 160 mg, 240 mg, or 320 mg of amantadine hydrochloride. The strengths are expressed as the base to conform with the United States Pharmacopeia's salt policy to use the name of the active moiety instead of the salt for drug products.

The applicant submitted a 505(b)(2) New Drug Application (NDA) that relies on FDA's previous findings of safety and efficacy for Symmetrel (NDA 16023, Endo Pharmaceuticals), and on the toxicology, genotoxicology, reproductive toxicology information in the approved label for Symmetrel. The NDA for Symmetrel syrup was withdrawn (FR notice 8/20/2010) by the sponsor, but not for reasons of safety or effectiveness. Following withdrawal of the Symmetrel syrup ND, several reference standard amantadine syrup products were listed in the Orange Book, including the product manufactured by Wockhart (A075060) used in the applicants bridging relative bioavailability studies.

This NDA includes relative bioavailability information from three Phase 1 studies, a study of amantadine pharmacokinetics in patients with renal impairment, safety data from two incomplete (terminated early) Phase 3 studies, and relevant safety and efficacy results from the

published literature and the public domain (e.g., Federal Register Notices and the Symmetrel label).

The approved indications for Symmetrel are as follows:

- Symmetrel is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalatic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levodopa, (-)-3-(3,4- dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established.
- Symmetrel is indicated in the treatment of drug-induced extrapyramidal reactions. Although anticholinergic-type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with the anticholinergic antiparkinson drugs.

The applicant has not requested the indication held by Symmetrel for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza-A virus.

The original indication for amandine ER developed under IND 103538 was for the treatment of levodopa-induced dyskinesia (LID). However, the applicant stopped both Phase 3 studies (b) (4). The applicant is seeking approval for the treatment of (b) (4) Parkinson's disease, (b) (4) and the treatment of drug-induced extrapyramidal reactions by bridging through relative bioavailability to the FDA's findings for Symmetrel.

Amantadine ER Tablets have been formulated in 3 strengths: 160 mg, 240 mg, and 320 mg. The Amantadine ER tablet strengths expressed as the base instead of the hydrochloride salt are 129 mg (160 mg salt), 193 mg (240 mg salt), 258 mg (320 mg salt) and the 129 mg tablet plus the 193 mg tablet =322 mg (400 mg salt). I will refer to the tablet strengths as the salt to remain consistent with the designations in the applicant's submission. The applicant conducted three bioavailability studies in healthy volunteers comparing amantadine ER to approved amantadine HCl syrup.

The FDA review team is presented in Tables 1 and 2.

Table 1. Review Team

Role/Reviewer	Review Discipline
Reviewer:LuAnn McKinney, DVM, DACVP Supervisor: Lois M. Freed, PhD	Pharmacology/Toxicology
Reviewer: Susanne Goldstein, MD CDTL: Gerald David Podskalny, DO, MPHS	Clinical
Reviewer: Bilal AbuAsal, PhD Team Lead: Sreedharan Sabarinath, PhD; Kevin Krudys, PhD	Clinical Pharmacology
Reviewer: Chad Morris, PharmD, MPH	Division of Medication Error Prevention and

Team Lead: Lolita White, PharmD	Analysis (DMEPA) Label and Labeling Review
Reviewer: Shalini Bansil, M.D.,	Controlled Substance Staff
Reviewer: Dhara Shah, PharmD, RPh Team Lead: Aline Moukhtara, MPH	Office of Prescription Drug Promotion (OPDP)

3. CMC/Device

Table 2. Quality Review Team and Roles

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Benjamin Stevens
Drug Product	Thomas Wong	Wendy Wilson-Lee
Process	Yuesheng Ye	Nallaperumal Chidambaram
Microbiology	Yuesheng Ye	Nallaperumal Chidambaram
Facility	Ephram Hunde	Ruth Moore
Biopharmaceutics	Om Anand	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia A. Walters	N/A
Application Technical Lead	Martha Heimann	N/A
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental	N/A	N/A

Drug Substance (DS)

The drug substance (DS), amantadine HCL, is supplied to the applicant by (b) (4) . (b) (4) Drug Master File (DMF (b) (4) for amantadine was reviewed by Govindaraj Kumaran (FDA) on May 6, 2015. The applicant cross-referenced the (b) (4) DMF in this application. The FDA reviewer concluded the DMF was adequate. There were no recent changes to the DMF and all noncompendial analytical procedures were adequately described and validated. The reviewer noted that the DS batches met the USP specification. (b) (4)

Drug Product (DP)

Thomas Wong, PhD, is the OPQ Drug Product (DP) reviewer for this application.

The DP contains an amantadine extended-release tablet core with an outer immediate-release layer. Drug release from the extended-release core is controlled by an osmotic pump system. Osmotic pump systems consist of a drug core inside of a semipermeable polymer membrane that is permeable to water molecules but not to the drug. The semipermeable polymer membrane has a laser drilled orifice for drug delivery. Drug release is driven by the osmotic pressure generated within the drug core upon exposure to water.

The strength of each tablet expressed as the base was rounded to the nearest milligram. All excipients in the formulation are compendial except the coating materials. Dr. Wong noted that the applicant provided adequate information about these coating materials. The DP specifications proposed by the applicant were acceptable. The levels of excipients were compendial except for the coating materials, which the reviewer concluded were adequate. The acceptance criteria for (b) (4) (known impurity) and the (b) (4) were within the qualification limit. Dr. Wong concluded these levels met the ICH Q3B and the levels were acceptable. The applicant used validated non-compendial assay methods for identification, content, uniformity, related compounds and (b) (4) which were acceptable. The results of the batch analysis for three registration size batches for each tablet strength of DP found that all results were within the product specifications.

The DP is packaged in unit-dose blister package for prescriber samples only or High Density Polyethylene (HDPE) bottles of 30 or 90 count. The DMFs for the packaging components were reviewed and minor deficiencies were corrected in the applicant's response to the reviewer's information request.

The DP reviewer noted that there are no impurities above the ICH Q3B (R2) identifiable level (0.2%) observed after storage for up to 30 months at 25°C/40%RH. The impurities identified in the finished product are the same as those reported for the API. There were no adverse trends observed in assay and impurities levels, and the proposed packaging components offer sufficient product protection. The DP reviewer noted that amantadine was not subject to photo-degradation based on the results of U-V testing. Dissolution testing found the DP remained within the acceptance criteria.

CDTL Comment:
Dr. Wong confirmed that the levels of excipients and impurities remain acceptable at the maximum recommended dose of 400 mg daily of Amantadine ER (a 140 mg tablet plus a 240 mg tablet) taken daily.

Shelf-life
The DP reviewer concluded that "The proposed expiry dating of 30 months for all strengths of the Amantadine HCl ER Tablets when packaged in HDPE bottles with 30- and 90-counts and in aluminum foil blisters and stored at 20°C to 25°C (68°F to 77°F)] is justified by the available 18-months real stability data."

The applicant agreed to revise the Post-Approval Stability Protocol and Commitment recommended by OPQ. The long-term (25°C/60% RH) stability studies for the first three commercial batches in each container-closure configuration will be studied up to 36 months, and an additional 3 or 6 months beyond the expiry point. The applicant agreed to include

40°C/75% RH storage conditions in the protocol for the first three commercial batches. The applicant included a commitment to assess the stability of one commercial batch per year for each strength and packaging configuration manufactured per year.

Osmotica claimed a categorical exclusion under 21 CFR §25.31(a) from the requirement to prepare an Environmental Assessment. The applicant stated that no extraordinary circumstances exist that warrant the preparation of an environmental assessment and action on the NDA for the DP would not increase the use of the active moiety.

Manufacturing Process

The Primary Process Reviewer is Yuesheng Ye, Ph.D. In his review, Dr. Ye noted (b) (4)

(b) (4)

There were other minor deficiencies or requests for clarification that were resolved through requests sent to the applicant. There are no unresolved process concerns.

(b) (4)

Microbiology

The applicant's proposal to conduct microbial examination of the finished product according to current USP <61> and <62> limits testing at the time of release for the first three commercial batches and on all annual stability batches is acceptable to the microbiology reviewer.

Biopharmaceutics

Dissolution Testing

The applicant provided comparative dissolution profiles of registration stability and clinical batches. The dissolution methods are acceptable to the reviewer. The biopharmacology

reviewer concluded the dissolution acceptance limits originally proposed by the applicant were "permissive and therefore not acceptable." The applicant agreed to the revised dissolution acceptance criteria recommended by the FDA and provided updated drug product specifications and stability protocol (Table 3).

Table 3. Final Dissolution Methods and Acceptance Criteria

Dissolution Method			
900 mL of Water @37.0 ± 0.5oC using USP Apparatus 2 (paddle) 50 rpm			
Acceptance Criteria			
Time (hour)	% Release		
	160 mg	240 mg	320 mg
0.5	NLT (b) (4)%	NLT (b) (4)%	NLT (b) (4)
1	NMT (b) (4)%	NM (b) (4)%	NMT %
2.5	(b) (4) %	(b) (4) %	(b) (4) %
4	%	%	%
6	NLT (b) (4)%	NLT (b) (4)%	(b) (4) %

Source: OPQ Review

Support for The Extended Release Claim

The biopharmacology reviewer concluded the totality of the information the applicant demonstrate that the amantadine ER drug product met the criteria cited in 21 CFR 325.25 (f) to support the extended-release claim by showing:

- Similar pharmacokinetic steady-state parameters/performance between the proposed ER drug product and amantadine HCl oral syrup in humans (Study OS320-PKP06), with established bioavailability profiles and ruling out the occurrence of dose-dumping
- Extended-release characteristics in humans to provide dosing benefit with respect to dosing frequency.

In Vitro Alcohol Dose Dumping:

There was a 20% to 25% increase of amantadine at intermediate time points without an increase in the total amount of amantadine release at 8 hours in 40% alcohol. The amantadine ER label will advise against taking amantadine ER with alcohol. In patients with advanced PD, the consumption of 40% ethanol alone would increase the risk for GI and psychiatric adverse events.

The Biopharmaceutics review team recommends approval.

Facilities review/inspection

The Primary Facilities Reviewer is Ephrem Hunde, Ph.D.

Table 4. Drug Substance Manufacturers

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			last inspection was initially OAI, downgraded to VAI	Approve
			Low	Approve
			last inspection was initially OAI, downgraded to VAI	Approve

Source: FDA OPQ Review

(b) (4) facilities were given high risk scores in the reviewer's risk table because of Official Action Indicated OAI status, downgraded to Voluntary Action Indication (VAI) given to both firms following inspections in (b) (4). Neither firm had recent product recalls or Field Alert Reports in recent years. All of the firms involved in the manufacture of the DS (Table 4) were recommended for approval.

Table 5. Drug Product Manufacturers

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
Osmotica Pharmaceutical US LLC 895 Sawyer Road Marietta, GA 30062	3009078927	TTR • DP manufacturing, release and stability testing; • Packaging and labeling in HDPE bottles	Medium process risk (b) (4)	Approve

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			Medium risk for facility component	Approve
			Low	Approve

Source: FDA OPQ Review

The reviewer categorized all firms involved in the manufacture of the DP (Table 5) as having a low to medium initial risk assessment. All firms involved in the manufacture of the DP were recommended for approval.

The Office of Product Quality Recommendation
The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 209410 for Osmolex ER (amantadine extended release) tablets. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

CDTL Comment:
Martha Heimann Ph.D., the technical lead for the Amantadine ER NDA, recommended approval of the application. There are no unresolved issues or disagreements expressed in the OPQ reviews. There are no outstanding consults or special labeling recommendations.

4. Nonclinical Pharmacology/Toxicology

The applicant did not include results from new nonclinical studies in the NDA and no new studies were required during the IND stage of development. The application was submitted as a 505(b)(2) NDA relying on the FDA's finding of safety and effectiveness reflected in labeling for the reference product (Symmetrel syrup), and on published medical literature. Dr. McKinney reviewed the proposed labeling and information supporting reproductive and developmental toxicology from publications. The reproductive toxicology studies were published in 1969 and 1970, before implementation of GLP regulations.

Based on calculations using body surface area, embryolethality and malformation were seen in rats at doses that are 1.2-fold the maximum recommended dose in humans per day (400 mg). Reduced fertility was observed in male and female mice following administration of 0.5-fold the maximum recommended daily dose in humans. The findings from the reproductive toxicology findings are known and described in labeling for the reference product. The

nonclinical sections of labeling for amantadine ER will closely follow the language in the nonclinical section for Symmetrel.

The recommendation from the nonclinical review team is that **the NDA is approvable,** with labeling modifications.

5. Clinical Pharmacology/Biopharmaceutics

Bilal AbuAsal, Ph.D. is the primary Clinical Pharmacology reviewer for this application.

The mechanism of action underlying the ability of amantadine to improve the symptoms of PD, (b) (4) and drug-induced extrapyramidal disorders is not known.

The scientific bridge to the FDA's finding of safety and effectiveness for Symmetrel syrup (reference listed drug=RLD) is based on bioequivalence (BE) primarily supported by the results of Study OS320-PKP06. Amantadine ER is not manufactured in tablet strengths that match the minimum (100 mg daily) and maximum (400 mg divided bid) recommended daily dose of Symmetrel syrup. The exposure to amantadine from once daily dosing with the available dose strengths of Amantadine ER tablets (i.e., 240 mg and 320 mg of amantadine HCl) is bracketed by the exposures obtained from the "usual dose" (i.e., 200 mg daily) and the highest dose (i.e., 400 mg daily) of Symmetrel Syrup. However, the combination of a 160 mg tablet plus a 240 mg tablet of Amantadine ER can match exposures of the maximum daily dose (200 mg b.i.d.) of Symmetrel syrup.

Multiple Dose Relative Bioavailability

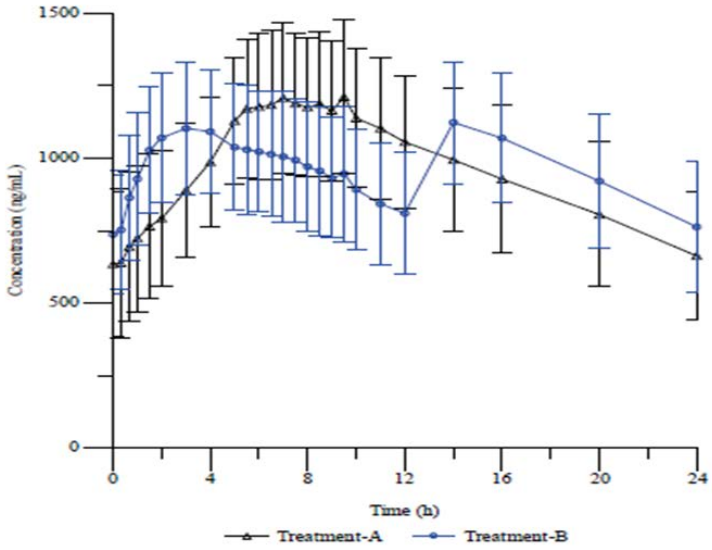
The applicant's pivotal relative bioavailability Study OS320-PKP06 was a 2-treatment, 2-period, 2-sequence, multiple oral dose crossover study with a 2-day titration period in healthy subjects treated for 7 days (excluding titration) under fasting conditions. Steady state relative bioavailability was determined after subjects received Treatment A (Amantadine ER 320 mg once daily for 7 days) or Treatment B (Amantadine syrup 160 mg twice daily for 7 days) (Figure 1). The reviewer concluded that Amantadine ER is bioequivalent to amantadine syrup on a "per mg" basis.

The OCP reviewer also compared the concentration/time profiles of different dose strengths of Amantadine ER with the lowest and highest daily dose of Symmetrel (see Figure 2). The amantadine concentration-time profiles for the 240 mg and 320 mg (salt) doses of Amantadine ER are within the profiles for Symmetrel 100 mg and the 200 mg administered twice daily. As expected, the 160 mg dose of Amantadine ER is higher than the lowest dose of Symmetrel 50 mg twice daily, which may be an effective dose for some patients treated for PD. The OCP reviewer recommended that Amantadine ER 160 mg daily should not be used in patients who cannot tolerate more than 50 mg of amantadine IR b.i.d.

The highest daily dose of Symmetrel (400 mg daily divided dose) can be matched by combining a 160 mg tablet with a 240 mg tablet of Amantadine ER for a total daily dose of 400 mg taken once daily. The OCP and the applicant agree to include a maximum

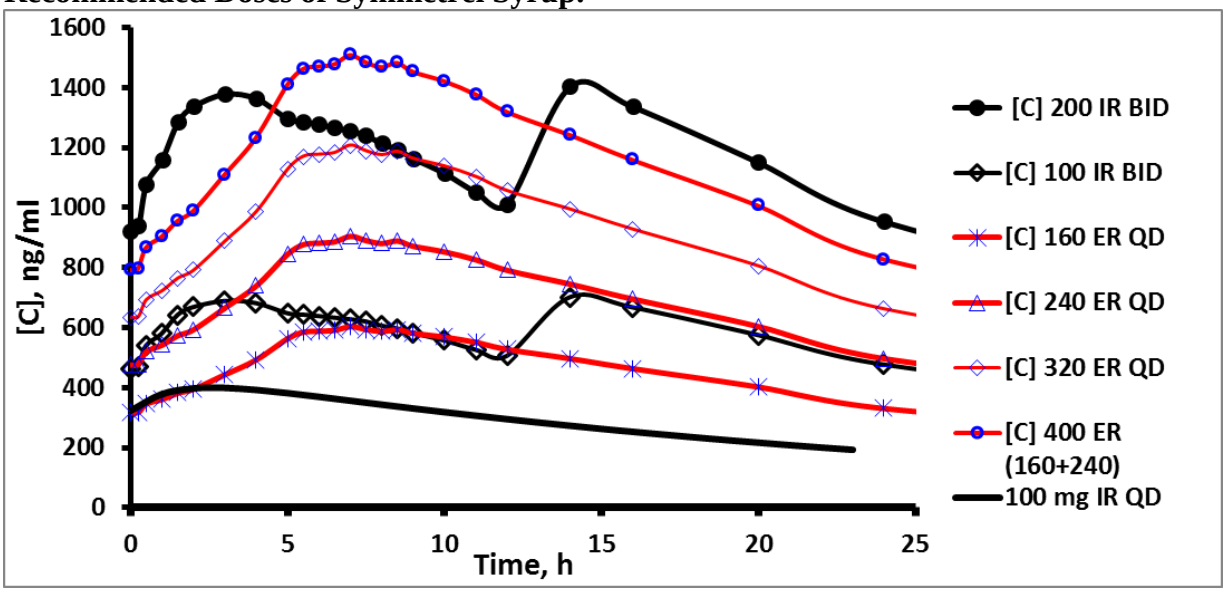
Amantadine ER dose of 400-mg/day in labeling based on the OCP's modeling of the 400 mg/day Amantadine ER and Symmetrel.

Figure 1: Mean plasma concentration-time profiles following oral administration of 320-mg AMANTADINE ER tablets once daily (Treatment-A: 320 mg amantadine HCl ER tablets) or SYMMETREL syrup twice daily (Treatment-B: 160 mg amantadine HCl) for 7 days in healthy volunteers, Study OS320-PKP06



Source: FDA Clinical Pharmacology Review

Figure 2: Comparison of the Steady State PK Profiles of Amantadine from the Proposed Amantadine ER doses (160 mg, 240 mg, 320 mg and 160+240 mg) with the Recommended Doses of Symmetrel Syrup.



Source: FDA Clinical Pharmacology Review

In Figure 2, the lowest dose of 100 mg once daily (QD), usual dose of 100 mg twice daily (BID) and maximum dose of 200 mg BID are shown for Symmetrel Syrup is marked as IR and Amantadine ER tablets as ER respectively.

Dr. AbuAsal noted the difference in median Tmax values following oral administration of 160 mg b.i.d. of amantadine syrup (Tmax=2-3 hours) and Amantadine ER 320 mg daily (Tmax=7.5 hours), but questioned the clinical meaningfulness of this difference in Tmax.

CDTL Comment:
The difference in Tmax between amantadine syrup and Amantadine ER is not clinically meaningful because the clinical effects of amantadine on the symptoms of PD is not immediate. In addition, patients treated with amantadine for PD are titrated to an effective and tolerated dose. It may take one to several weeks to titrate patients to a 200 mg to 400 mg daily dosage of amantadine syrup including time to observe patients for an effect on the symptoms of PD.

Dosing of Amantadine ER in the morning is not expected to impact efficacy, but patients may experience adverse effects closer to Tmax (median 7.5 hours) in the early afternoon. Common adverse reactions associated with use of amantadine include agitation and irritability. It may be preferable that patients experience CNS adverse reactions during the daytime rather potentially interfering with sleep at night.

Single Dose Relative Bioavailability and Dose Proportionality
Study OS320-PKP05 single oral dose, randomized, laboratory-blinded, four-treatment, four-period, four-sequence, crossover design study in healthy male and female volunteers. The results of the study demonstrated dose proportionality between Amantadine HCl ER tablets, 160 mg, 240 mg, and 320 mg.

ADME

Absorption
Median Tmax for plasma amantadine was around 7.5 hours from amantadine ER. Time to reach steady-state is approximately four days after dose initiation in subjects with normal renal function. Ingestion of high-fat, high-calorie meal did not affect the PK of amantadine.

The steady-state exposures (Cmax, AUC0-24) were bioequivalent with the immediate release formulation on a milligram (mg) to mg basis (i.e., 320 mg amantadine ER given once daily and160 mg Symmetrel syrup given twice daily).

Exposure
The mean AUC0-24, ss (ng.h/ml) and Cmax (ng/ml) based on Study OS320-PKP06 healthy subjects after daily dose of 320 mg oral dose at steady state were 9946.7 (33.6) and 536.1 (31.3) respectively. The steady-state exposures (AUC0-Tau) were 20-30% higher than after single dosing (accumulation ratio ~1.2-1.3-fold).

Distribution
The volume of distribution and level of protein binding is expected to be consistent with values for described in the immediate release amantadine (Symmetrel) label. Amantadine is 67% bound to plasma proteins. The volume of distribution from after intravenous administration was 3-8 L/Kg.

Metabolism
Metabolism accounts for only 5-15% of the total clearance for amantadine. However, only the parent compound is believed to be active. Eight metabolites of amantadine have been identified in human urine. One metabolite, an N-acetylated compound, was quantified in human urine.

Elimination

- Amantadine is mainly eliminated renally and around 85% of the administered dose is excreted unchanged in urine by glomerular filtration and tubular secretion. The elimination half-life is about 16 hrs.
- Amantadine is neither a substrate nor an inhibitor of CYP1A2, 2B6, 2C19, 2C8, 2C9, 2D6, 2E1, 3A4, and 3A5 based on in vitro studies.
- In vitro studies showed that amantadine is a week inhibitor of OCT2; however, amantadine is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1 and OAT3 under the conditions examined.
- Amantadine is not a substrate of any of the transporters evaluated under these experimental conditions. Amantadine is reported to be poor substrate to MATE1 based on in-vitro studies, while, in-vivo amantadine clearance increased by 33 % in the presence of quinidine, OCT2 inhibitor.

Age
Amantadine accumulates as renal function declines with aging. (b) (4)

Hepatic Impairment
No dose reduction is recommended in patients with hepatic impairment.

Dosing in Patients with Renal Impairment
Amantadine in primarily eliminated by the kidneys. Patient with impaired renal function will experience accumulation of amantadine. Improper dosing of amantadine in patients with impaired renal function has been associated with fatal overdose.

(b) (4)

Table 6: Dosing Regimens for Patients with Impaired Renal Function Proposed by the Applicant

Source: Adamas

The reviewer noted several limitations in the applicant's model and recommendations regarding dosing in patients with renal impairment:

- The applicant used (b) (4) for the calculation of the creatinine clearance instead of the baseline value (-1 day)
- The applicant proposed (b) (4) which is unnecessary and inconsistent with the dosing recommendations for approved drug products of amantadine (Symmetrel).

The Office of Clinical Pharmacology (OCP) revised the dosing recommendations for patients with impaired renal function using the data from Study OS320-PKP07 and modifying the applicant's base model to target an exposure range based on renal function data from patients with normal and mildly impaired renal function (Table 7).

Table 7. FDA Proposed dosing regimens recommended for patients with impaired renal function

Estimated GFR (mL/min/1.73 m2)	Osmolex ER Dosing regimen
Normal and mild ≥60	Once every 24 hours
Moderate 30 to 59	Once every 48 hours
Severe 15 to 29	Once every 96 hours
ESRD <15	Contraindicated

Source: FDA Clinical Pharmacology Review

Thorough QT Study

A thorough QT Study was not required for this 505(b)(2) application relying on the FDA's finding of safety and effectiveness for Symmetrel Syrup.

Office of Study Integrity and Surveillance (OSIS) Inspection

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data (b) (4) without an on-site inspection based on a recent inspectional outcome that was classified as No Action Indicated (NAI).

Recommended Action by The Office of Clinical Pharmacology
The office of clinical pharmacology considers the PK bridging study between the reference listed drug Symmetrel Syrup and Osmolex ER tablets to be acceptable to support this 505(b)(2) application.

6. Clinical/Statistical- Efficacy

The Amantadine ER tablet clinical development program included two randomized, double-blind, placebo-controlled, Phase 3 studies (Study OS320-3005 and Study OS320-3006) that were intended to support amantadine ER tablets for the 240 mg/day and 320 mg/day strengths for the treatment of dyskinesia in patients with Parkinson's disease (PD) treated with levodopa. Neither study was designed to provide evidence of effectiveness for the treatment of Parkinson's disease (PD), (b) (4). The applicant terminated both Phase-3 studies (b) (4) " Efficacy results from these two studies do not support were not used to support the indications requested in this application. This 505(b)(2) application relies on bioequivalence to bridge the new product to the reference product Symmetrel and to the FDA's previous finding of safety and efficacy for the treatment of PD, (b) (4) and drug-induced extrapyramidal disorders.

7. Safety

Studies 3005 and 3006 included a large proportion of patients who discontinued or were discontinued early resulted in a large amount of missing safety data. In addition, the clinical trials population did not include patients with drug-induced extrapyramidal syndromes (EPS); therefore, studies 3005 and 3006 cannot provide new safety information in patients with EPS.

The extent of the missing safety data is suggested by the difference in the number of patients randomized in studies 3005 and 3006 (combined) in Table 8 and the patients in the Per Protocol (PP) population. The PP population is only 52% of the population randomized in both studies.

Table 8. Controlled Studies 3005 and 3006 - Analysis Population

	Actual Treatment for Period 01						
	Amantadine 240 mg		Amantadine 320 mg		Placebo		ALL
	Study Identifier		Study Identifier		Study Identifier		
	OS320-3005	OS320-3006	OS320-3005	OS320-3006	OS320-3005	OS320-3006	
Randomized Population	30	45	29	46	28	44	222
Safety Population	30	45	29	46	28	44	222
Intent-To-Treat Population	30	45	29	46	28	44	222
Completers Population	17	27	19	27	18	25	133
Per-Protocol Population	18	14	16	25	16	26	115

Source: CDTL

The mean duration of exposure to amantadine ER in the two studies was lower than expected. In Study 3005, patients should have on study drug for 112 days, including the Titration (2

weeks), Maintenance (12 weeks) and Taper (2 weeks). Study 3006 included a 2-week Titration Phase, a 22-week Maintenance Phase and a 13-day Tapering Phase before stopping study drug. The mean and median exposure in days in Study 3006 (Table 9) was only slightly longer the duration of study 3005 which is unexpected because Study 3006 enrolled 50% more patents and the maintenance phase was 10 weeks longer.

Table 9. Summary of Exposure (Days) in Studies 3005 and 3006

Statistics	Amantadine 320 mg	Amantadine 240 mg	Placebo
N	75	75	72
Mean	120	126	123
Std Dev	57	58	58
Median	113	119	114
Min	11	13	14
Max	204	210	232

Source: CDTL

The majority of the early discontinuations occurred in the Maintenance phase of both studies (Table 10).

Table 10. Discontinuation by Study Epoch and Arm Safety Population in Studies 3005 and 3006

	Study Identifier								
	OS320-3005				OS320-3006				All
	Actual Treatment for Period 01				Actual Treatment for Period 01				
Discontinuation Epoch	**Amantadine 240 mg**	**Amantadine 320 mg**	**Placebo**	**All**	**Amantadine 240 mg**	**Amantadine 320 mg**	**Placebo**	**All**	
Titration Period	2	1	2	5	1	1	5	7	12
Maintenance Period	10	9	8	27	15	17	13	45	72
Taper Period	1	0	0	1	2	1	1	4	5
All	13	10	10	33	18	19	19	56	89

Source: CDTL

The two most common reasons for early discontinuation were because of an adverse event or caused by the applicant ending the study early (Table 11). In total, 89 of the 222 patients enrolled in both studies ended participation early.

Table 11. Reasons (Reviewer Recoded) for Discontinuation from Randomized Population in Studies 3005 and 3006

Discontinuation Reason Standardized Term	Amantadine 240 mg	Amantadine 320 mg	Placebo	All
Adverse event	9	13	6	28
Lack of efficacy	2	0	3	5
Lost to follow-up	0	0	1	1
Non-compliance with study drug	0	0	2	2
Physician decision	1	0	0	1
Protocol deviation	2	1	1	4
Screen failure*	0	0	1	1
Study terminated by sponsor	11	9	8	28

Discontinuation Reason Standardized Term	Amantadine 240 mg	Amantadine 320 mg	Placebo	All
Withdrawal by subject	6	6	7	19
All	31	29	29	89

*The applicant withdrew this patient as a Screen Failure because their Screening creatinine level met exclusion criteria
Source: CDTL

Table 12 shown when patients discontinued from the two studies by duration. The bin that included the end of the Taper period, plus at least 1 day is highlighted for both studies (Tables 12-Study 3005 and Table 13-Study 3006). Slightly over half of the patients enrolled in the Safety Population completed the protocol specified duration of dosing including the end of the Taper period.

Table 12. Study 3005: Exposure-Number of Patients by Treatment Duration (in days) on Study Drug

Treatment Duration (days) Binned 2	Amantadine 240 mg	Amantadine 320 mg	Placebo	Actual Treatment for Period 01 = All
1 to 10	0	1	1	2
11 to 20	2	1	1	4
21 to 30	1	1	0	2
31 to 40	2	0	0	2
41 to 50	2	1	4	7
51 to 60	1	3	0	4
61 to 70	1	1	1	3
71 to 80	2	0	0	2
81 to 90	2	2	2	6
91 to 100	0	3	0	3
101 to 110	1	1	2	4
111 to 120	14	14	12	40
121 to 130	1	1	2	4
131 to 140	1	0	2	3
161 to 170	0	0	1	1
All	30	29	28	87

Source: CDTL

Table 13. Study 3006: Exposure-Number of Patients by Treatment Duration (in days) on Study Drug

TRTDUR Binned	Amantadine 240 mg	Amantadine 320 mg	Placebo	TRT01A = All
1 to 10	0	1	1	2
11 to 20	1	0	2	3
21 to 30	2	3	2	7
31 to 40	1	0	0	1
41 to 50	2	2	3	7
51 to 60	0	4	1	5
61 to 70	1	1	1	3
71 to 80	1	2	2	5
81 to 90	2	1	1	4

91 to 100	1	0	2	3
101 to 110	1	0	1	2
111 to 120	1	2	0	3
121 to 130	0	2	0	2
131 to 140	1	1	1	3
151 to 160	1	0	0	1
161 to 170	2	1	2	5
171 to 180	2	7	3	12
181 to 190	22	16	18	56
191 to 200	1	2	2	5
201 to 210	3	1	0	4
211 to 220	0	0	1	1
All	45	46	43	134

Source: CDTL

Serious Adverse Events

One patient died in Study 3005. This was the only reported death in the clinical trials program for amantadine ER. The patient was a 70-year-old male patient who died 31 days after starting 240 mg of amantadine ER. He presented to the emergency department with toxic megacolon. He died from sepsis and postoperative hypotension following extensive abdominal surgery two weeks after stopping amantadine ER. The patient's death did not seem related to treatment with amantadine ER.

Eight patients (5%) in the amantadine ER group (5 patients on 320 mg/day and 4 patients on 240 mg/day), not including the patient who died, suffered a serious adverse event compared to eight (11%) in the placebo group. In Dr. Goldstein's review and upon review of narratives for the patients who experienced a serious adverse event, there was no indication that amantadine caused the serious adverse event.

Twenty-two (15%) patients treated with amantadine ER in studies 3005 and 3006 discontinued from the studies because of an adverse event, compared to 6 (8%) in the placebo group. Hallucinations and confusion were the most common adverse events reported in patients (n=14, 63%) who discontinued in the amantadine ER group, compared to a single patient (13%) in the placebo group. One patient in the placebo group withdrew because of impulse control disorder but no patients treated with amantadine ER withdrew because of an impulse control disorder.

Table 14. Studies 3005 and 3006 All Pooled Treatment Emergent Adverse Reaction ≥2% and more common on Amantadine ER than on placebo

Body System or Organ Class	Dictionary-Derived Term	Amantadine 240 mg N=75 %	Amantadine 320 mg N=75 %	Placebo N=72 %
Psychiatric disorders	Hallucination[1]	9	13	4
Gastrointestinal disorders	Nausea	8	9	4
Gastrointestinal disorders	Dry mouth	7	9	0
Nervous system	Dyskinesia	11	5	8

Body System or Organ Class	Dictionary-Derived Term	Amantadine 240 mg N=75 %	Amantadine 320 mg N=75 %	Placebo N=72 %
disorders				
General disorders and administration site conditions	Oedema peripheral	3	11	1
Nervous system disorders	Dizziness	5	7	0
Vascular disorders	Hypertension	3	7	0
Gastrointestinal disorders	Constipation	4	5	3
Infections and infestations	Urinary tract infection	5	5	4
Musculoskeletal and connective tissue disorders	Arthralgia	5	4	0
Infections and infestations	Nasopharyngitis	3	5	0
Nervous system disorders	Headache	4	4	1
Musculoskeletal and connective tissue disorders	Muscle spasms	4	4	1
Psychiatric disorders	Confusional state	5	3	1
Psychiatric disorders	Anxiety	3	4	3
Musculoskeletal and connective tissue disorders	Back pain	3	3	0
Vascular disorders	Hypotension	4	1	1
Gastrointestinal disorders	Vomiting	1	3	0
Musculoskeletal and connective tissue disorders	Osteoarthritis	1	3	0
Investigations	Haemoglobin urine present	1	3	1
Renal and urinary disorders	Dysuria	1	3	0
Metabolism and nutrition disorders	Decreased appetite	1	3	0
Psychiatric disorders	Nightmare	3	1	0
Investigations	Blood cholesterol increased	3	1	0

Body System or Organ Class	Dictionary-Derived Term	Amantadine 240 mg N=75 %	Amantadine 320 mg N=75 %	Placebo N=72 %
Nervous system disorders	Parkinson's disease	4	0	1

1=Hallucinations, Hallucinations visual, hallucinations auditory and Illusions
Preferred terms were recoded from verbatim terms from the applicant's ISS dataset.
Source: CDTL

Table 14 shows the most frequently reported adverse reaction were G.I. or central nervous system related. There was a clear relationship to dose for hallucinations, dry mouth, edema, and hypertension.

Electrocardiograms (ECG)
Six randomized patients had a normal QT interval at screening but developed an abnormal QT during the study (QT ≥ 450 msec) including one patient in the amantadine ER 320 mg group, three in the amantadine 240 mg group and two in the placebo group. None of abnormalities were clinically significant in the opinion of the investigator/applicant. Four patients had an QTcF (Fridericia) that was normal at screening but became abnormal (≥ 60 msec) during the study, three were in the placebo group and one was in the amantadine ER 240 mg group.

The QT interval abnormalities did not suggest that amantadine ER was associated with an increased incidence of QT or QTcF prolongation. Higher doses of amantadine ER 320 mg/day was not associated with an increased frequency of prolonged QT interval. Only two-third of patients treated with amantadine ER had an ECG by Visit 7 (Table 15). Less than half of the patients randomized in study 3006 (N=133) had an ECG at Visit 9 (End of Study). The large amount of missing ECG data in studies 3005 and 3006 limits the ability to use the data to base labeling recommendations.

Table 15. Patients with ECG Data by Visit Studies 3005 and 3006

Actual Treatment	Screening	Visit 2	Visit 7	Visit 9 (study 3006 only)	Early Termination	Unscheduled
Amantadine 240 mg	75	75	51	29	26	5
Amantadine 320 mg	75	75	49	27	29	8
Placebo	72	72	46	26	27	1

Source: CDTL

Clinical Laboratory
The number of laboratory investigations declined as patients withdrew early from the respective studies. Review of the available laboratory data found no patient had an elevation of bilirubin elevated to greater that 2 X the upper limit of normal (UMN). Another patient had a postbaseline elevation of AST between 2 and 5 X UMN. There were no cases that met Hy's Law criteria. The hematology, electrolytes and glucose testing did not reveal a pattern of abnormality associated with amantadine ER.

8. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application. Amantadine has a long marketing history in the U.S. This application relies on previous FDA finding of safety and effectiveness for amantadine.

9. Pediatrics

The applicant included a request for a full waiver from PREA requirement to conduct studies in the pediatric population. The applicant's justification for requesting a PREA waiver is that studies in children are impracticable. The PeRC granted the request for a full waiver.

10. Other Relevant Regulatory Issues

Clinical Site Inspections
OSI inspections of the clinical sites were not requested for the clinical study sites because both studies were terminated before completion and not necessary to support approval.

Bioequivalence Study Site Inspection
The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for their recommendation is that OSIS recently inspected (b) (4) The outcome from this on-site inspection was a classification of No Action Indicated (NAI).

Controlled Substance Staff
There is no evidence of abuse associated with amantadine based on the adverse event (AE) profile of Amantadine HCl ER Tablets and on a 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. CSS recommends that amantadine remains as a non-controlled substance under the Controlled Substances Act (CSA), and that Section 9 (Drug Abuse and Dependence) is not included in the label of the product.

11. Labeling

Proprietary Name Review
DMEPA found the proposed proprietary name (Osmolex ER) acceptable.

Carton Container Labels
Comments from OPQ and DMEPA were forwarded to the applicant. The applicant submitted revised Carton and Container labels resulting in no additional comments from OPQ or DMEPA.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval

Risk Benefit Assessment
The applicant has successfully bridged amantadine ER tablets to the reference listed product and it is therefore appropriate to rely on FDA's finding of efficacy and safety for Symmetrel Syrup to support this 505(b)(2) application.

The ability to interpret the efficacy and safety information submitted in the application from the applicant's controlled clinical studies investigating amantadine ER for the treatment of dyskinesia in patients with PD treated with levodopa is limited because of the large amount of missing data. These studies do not provide new efficacy information that is adequate for inclusion in labeling, and did not identify unique adverse reactions associated with amantadine ER that are not already described in labeling for the referenced product.

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

/s/

GERALD D PODSKALNY
02/16/2018

ERIC P BASTINGS
02/16/2018