CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209410Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approve

NDA 209410
Review # 1

Drug Name/Dosage Form	Osmolex ER (amantadine) extended release tablets
Strength	129 mg, 193 mg, 258 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Osmotica Pharmaceutical US
US agent, if applicable	N/A

Quality Review Team

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

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	01/18/2017	All
SD-004	03/01/2017	Facilities
SD-009	04/13/2017	Product/Labeling
SD-011	05/05/2017	Process, Product
SD-013	07/19/2017	Biopharmaceutics, Product, Process
SD-017	10/03/2017	Biopharmaceutics, Product
SD-019	10/06/2017	Drug Substance
SD-020	10/10/2017	Process, Product

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)		Adequate	5/6/2016	Reviewed by G. Kumaran
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	IV			N/A [1]	N/A [1]	

[1] Adequate information in application or no significant changes to information since previous reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	103538	Development of amantadine extended release tablets
NDA	16023	Symmetrel Syrup is cross-referenced under 505(b)(2)

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 209410 for Osmolex XR (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.

II. Summary of Quality Assessments

A. Product Overview

Amantadine Hydrochloride was initially approved in 1966, as Symmetrel tablets, for prophylaxis and treatment of infections caused by influenza A virus strains. It was approved in 1973 for treatment of parkinsonism and drug-induced extrapyramidal reactions. In the current 505(b)(2) NDA, the applicant seeks approval of extended-release (ER) tablets for treatment of (b) (4) and drug-induced extrapyramidal reactions. The applicant does not seek approval for the influenza A indications.

Proposed Indication(s) including Intended Patient Population	Treatment of patients with Parkinson's disease and adult patients with drug-induced extrapyramidal reactions
Duration of Treatment	Chronic
Maximum Daily Dose	322 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The (b) (4) active ingredient (API) used to manufacture commercial product will be supplied by (b) (4). Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to (b) (4) drug master file (DMF) (b) (4). The DMF was most recently reviewed(Review-15) by Govindaraj Kumaran dated 05/06/2016, and was found to be Adequate. There have been no significant changes to DMF after Review-15. The NDA itself includes the drug product manufacturer's acceptance specification. The (b) (4) drug substance complies with USP and EP monograph requirements. Noncompendial analytical procedures are adequately described and validated. The applicant adequately addressed issues related to the acceptance specification that were identified during the

pre-NDA meeting the limit for individual unknown impurities was revised from not more than (NMT) (b) (4)% to NMT (b) (4)% consistent with ICH recommendations and the specificity of the GC related compounds method for process impurities and potential degradants was validated. In addition, the applicant confirmed that they will revise the specification per requirements of USP <232> and USP <233> when the USP updates the drug substance monograph; this change will be submitted in an Annual Report.

(b) (4)

Drug Product

The proposed products are extended-release (ER) tablets that contain 129 mg, 193 mg, or 258 mg of amantadine (as 160 mg, 240 mg, or 320 mg of amantadine hydrochloride). The tablets are intended to be taken once daily in the morning and provide for controlled release of the drug over an 8 to 12-hour interval.

Note: The applicant originally proposed to label the product based on content of amantadine hydrochloride. Consistent with USP Salt Policy and recent approval of a related amantadine extended-release product (Gocovri Capsules), the product will be labeled based on the active moiety. In some sections of the integrated quality review, the product and dosage strengths are identified based on the hydrochloride salt.

Amantadine ER tablets comprise an ER core controlled by an osmotic pump system and an immediate-release (IR) outer layer. The osmotic pump system relies on a semipermeable polymer membrane with an orifice for drug delivery. (b) (4)

(b) (4)

(b) (4) All excipients used to manufacture Amantadine ER Tablets are compendial grade or equivalent quality and commonly used in ER solid oral dosage forms.

The to-be-marketed formulations of amantadine ER tablets 129 mg, 193 mg, and 258 mg were used in relative bioavailability studies versus amantadine hydrochloride syrup.

(b) (4)

. In vivo dose proportionality across strengths was established in Study OS320-PKP05.

Amantadine ER Tablets meet the criteria cited in 21 CFR 325.25(f) to support an extended-release claim based on the totality of the information, including a similar pharmacokinetic steady-state performance between the proposed drug product and amantadine HCl oral syrup in humans, with established bioavailability profiles and a reduction in dosing frequency. Results from in vitro alcohol-induced dose dumping studies showed an increase in drug release at early dissolution time points in the presence of 40% alcohol (e.g., approximately 20-25% increases at 2-2.5 hours). This finding was conveyed to the clinical and clinical pharmacology review teams for consideration with respect to risk assessment and labeling.

The drug product manufacturing process involves (b) (4) to produce the finished tablets. Briefly, these include:

- (b) (4)

Based on the applicant's risk assessment and data provided in the original NDA, acceptable risk mitigation strategies were demonstrated for most unit operations; however, some gaps were identified by the review team. In response to information requests, the applicant has clarified how critical process parameters (b) (4)

(b) (4)

(b) (4)

The proposed regulatory specification for Amantadine ER Tablets includes test parameters that are typical for an extended-release product. In general, the analytical procedures are straightforward and supported by adequate method validation studies. The proposed acceptance criteria for most test parameters are considered suitable. At the Agency's request, the applicant revised the dissolution method (b) (4) with acceptance criteria of not more than (NMT) (b) (4) % of drug released from the 129 mg tablets, and NMT (b) (4) % released from 193 mg and 258 mg tablets. The applicant also (b) (4) the acceptance criteria for the (b) (4) -hour time points.

Amantadine ER Tablets are packaged in 30- or 90-count white, opaque HDPE bottles with desiccant and induction sealed, (b) (4) closures or (b) (4) aluminum unit dose blisters. Based on stability data provided in the application, a 30-month shelf life is granted for all package configurations when stored at controlled room temperature.

Methods Verification

Amantadine Hydrochloride is a well characterized small molecule that is subject to a USP monograph, and the analytical procedures for the finished product are straightforward. Thus, this is considered a low risk product from an analytical perspective, and methods verification studies were not requested.

Facilities

All facilities that will be involved in commercial manufacture and testing of Osmolex XR (amantadine) extended-release tablets are currently acceptable.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment (see Attachment)

Martha Heimann

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ATTACHMENT I: Final Risk Assessment

Final Risk Assessment for Amantadine Extended-release Tablets NDA 209410

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	Impurities due to: (b) (4)	**L**	Applicant demonstrated compatibility with excipients. In response to Agency concerns about (b) (4)	Acceptable	Verification of (b) (4) will be performed during commercial process validation
Physical stability (solid state)	Formulation, raw materials, process parameters, scale/equipment/site	**L**	Drug substance is highly soluble at physiological pH and has no known polymorphs.	Acceptable	
Content uniformity	Low dose, particle size/shape, segregation, flow property	**L**	(b) (4)	Acceptable	
Microbial limits	Formulation, raw materials, process parameters, moisture	**L**	Tested at release and on stability.	Acceptable	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Alcohol dose dumping	Formulation, solubility of rate controlling excipient and/or API	**H**	Some increase (about 20 -25% at 2 – 2.5 hours) in dissolution in media containing 40% ethanol. Referred to clinical and clinical pharmacology review teams for consideration of warning in product labeling. Dissolution profile is not significantly affected by pH changes.	Acceptable	
Dissolution	Particle size, moisture, hardness, size, shape, film coat, formulation, process parameters	**M**	(b) (4)	Acceptable	

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LABELING

I. Package Insert (Seq. #0008)

1. *Highlights of Prescribing Information*

OSMOLEX ER™ (amantadine (b) (4) extended release tablets, for oral use

----------DOSAGE FORMS AND STRENGTHS----------

(b) (4)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Osmolex ER/ (amantadine hydrochloride
Dosage form, route of administration	Oral
Controlled drug substance symbol (if applicable)	N/A. Not a controlled substance
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	(b) (4)

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	No special instruction for product preparation is needed.

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

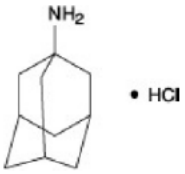
- Tablets containing (b) (4): Round, biconvex, white coated tablets, imprinted on one side with a black "VP" over "075"
- Tablets containing (b) (4) Round, biconvex, green coated tabled, imprinted on one side with a black "VP" over "076"
- Tablets containing (b) (4) Round, biconvex, blue coated tablets, imprinted on one side with a black "VP" over "077"

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	(b) (4)
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	All information is stated in this section. See photocopy above.

4. *Section 11 Description*

11 DESCRIPTION

(b) (4) 1-adamantanamine hydrochloride. (b) (4). It has the following structural formula:



(b) (4) USP is a stable white or nearly white crystalline powder, freely soluble in water and soluble in alcohol and in chloroform.

(b) (4)

Inactive ingredients: cellulose acetate, colloidal silicon dioxide, copovidone, magnesium stearate, microcrystalline cellulose, (b) (4) polyethylene glycol, sodium chloride.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Provided. See photocopy above
Dosage form and route of administration	Dosage form is provided. Route of administration is not provided. See photocopy above
Active moiety expression of strength with equivalence statement (if applicable)	(b) (4)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients are provided. (b) (4)
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Anti-Parkinson
Chemical name, structural formula, molecular weight	Provided.
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	See photocopy above

5. ***Section 16 How Supplied/Storage and Handling***

16 HOW SUPPLIED/STORAGE AND HANDLING

OSMOLEX ER is available as:

(b) (4) mg Tablets

- Unit-dose cards of 10: NDC 68025-075-11
- Bottles of 30: NDC 68025-075-30
- Bottles of 90: NDC 68025-075-90

(b) (4) mg Tablets

- Unit –dose cards of 10: NDC 68025-076-11
- Bottles of 30: NDC 68025-076-30
- Bottles of 90: NDC 68025-076-90

(b) (4) mg Tablets

- Unit –dose cards of 10: NDC 68025-077-11
- Bottles of 30: NDC 68025-077-30
- Bottles of 90: NDC 68025-077-90

Store at (b) (4) excursions permitted to 15-30°C (59-86°F).

Dispense in a tight container as defined in the USP.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	(b) (4)
Available units (e.g., bottles of 100 tablets)	Provided
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The visual description of the tablets should be provided in the How Supply section
Special handling (e.g., protect from light)	Not applicable
Storage conditions	Provided. To avoid confusion, the storage temperature should be written as 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30° C (59°F to 77°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided.

Reviewer's Assessment of Package: Acceptable.

All deficiencies (b) (4) will be resolved in the Labeling review meetings with the full multidisciplinary team.

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Osmolex Established name: Amantadine HCl Font size and prominence are acceptable.	Proprietary name: Osmolex Established name: Amantadine HCl Font size and prominence are acceptable.
Dosage strength	(b) (4)	
Net contents	Provided	Provided
"Rx only" displayed prominently on the main panel	Not in the blister but provided in bottle container.	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Not in the blister but provided in bottle container.	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Provided. To avoid confusion, the storage temperature should be written as 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30° C (59°F to 77°F).	Provided. To avoid confusion, the storage temperature should be written as 20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30° C (59°F to 77°F).
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available		

Reviewer's Assessment of Labels: Acceptable.

All deficiencies (b) (4) will be resolved in the labeling review meetings with the full multidisciplinary team.

List of Deficiencies:

There is no further deficiency other than those listed in the Reviewer's Assessment.

Overall Assessment and Recommendation:

The information presented in the prescribing information and container labels are adequate except the deficiencies listed in the Reviewer's Assessment. These deficiencies will be resolved in the labeling review meetings with the full multidisciplinary team. This NDA is recommended for approval after the deficiencies have been adequately addressed.

Thomas Wong

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
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BIOPHARMACEUTICS REVIEW	
Application No.	NDA 209410-ORIG-1
Type of Submission	505(b)(2)
Applicant/Sponsor	Osmotica Pharamceuticals
Product Name	Osmolex® ER (Amantadine Hydrochloride Extended Release) Tablets
Dosage Form/Strength	Extended Release Tablets, 160 mg, 240 mg and 320 mg
Route of Administration	Oral
Intended Use	Treatment of Parkinson's Disease
Submission Date	01/08/2017 (Original Submission) 07/19/2017 (Quality Amendment Response to IR)
Primary Reviewer	Om Anand, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

1. EXECUTIVE SUMMARY

NDA 209410 for Osmolex® ER (Amantadine Hydrochloride Extended Release) Tablets, 160 mg, 240 mg and 320 mg is a 505(b)(2) submission; The Listed Drug (LD) is Symmetrel Syrup (approved in NDA 016023). The Applicant has developed a new extended-release dosage form, Amantadine Hydrochloride (HCl) Extended Release (ER) Tablets, for once daily (QD) oral administration for treatment of Parkinson's disease.

Formulation:

Each of the Amantadine HCl ER Tablet strengths contains an extended release core and an immediate release layer (see Appendix 1). Drug release from the extended release core is controlled by an osmotic pump system. Osmotic pump systems consist of a drug core contained within a semipermeable polymer membrane (b) (4) that is permeable to water molecules but not to the drug with an orifice for drug delivery. (b) (4)

Review Summary:

The Biopharmaceutics review is focused on the evaluation of the data supporting the proposed dissolution method and acceptance criterion, potential of alcohol-induced dose-dumping and the "Extended Release" claim.

Dissolution method: The drug substance, amantadine HCl, is highly soluble and the drug product is formulated for extended release. The selection of the dissolution conditions is adequately justified. The proposed in vitro dissolution test is adequate for quality control. The approved dissolution method and the acceptance criteria agreed to with the Applicant are as follows:

Dissolution Method			
900 mL of Water @37.0 ± 0.5°C 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)%	NMT (b) (4)%	NMT (b) (4)%
2.5	(b) (4)%	(b) (4)%	(b) (4)%
4	(b) (4)%	(b) (4)%	(b) (4)%
6	NLT (b) (4)%	NLT (b) (4)%	NLT (b) (4)%

In vitro alcohol dose dumping: The results from the in vitro alcohol- induced dose dumping studies showed an increase in drug release at earlier time points in the presence of 40 % alcohol (e.g., approximately 20-25% increases at 2-2.5 hours). This study finding has been conveyed to the OND and OCP review teams for consideration with respect to risk assessment and labeling.

Extended-Release (ER) claim: The proposed drug product meet the "Extended Release" claim based on the totality of the data/information, according to the criteria cited in 21 CFR 325.25(f), mainly:

- Similar pharmacokinetic steady-state performance between the proposed drug product and amantadine HCl oral syrup in humans, with established bioavailability profiles and ruling out the occurrence of dose-dumping.
- Extended-release characteristics in humans provides dosing benefit.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 209410 for Osmolex® ER (Amantadine Hydrochloride Extended Release) Tablets, 160 mg, 240 mg and 320 mg is recommended for **APPROVAL.**

2. List of submissions reviewed:

eCTD sequence #	Received date	Document
0001	01/18/2017	Original NDA submission
0012	07/19/2017	Quality/Response to Quality/Biopharmaceutics Information Request
0016	10/03/2017	Response to Information Request (revised dissolution acceptance criteria)

3. Highlight Key Outstanding Issues from Last Cycle: None

4. Concise Description Outstanding Issues Remaining: None

5. BCS designation:

The drug substance, Amantadine HCl, is highly soluble across the physiologic pH range (pH 1 to pH 8.0; Table 1) and is considered a BCS Class (b) (4) compound by the Applicant. Note that the Applicant did not provide supportive information regarding the permeability for the statement. In addition, the drug substance Amantadine HCl has not been evaluated by the FDA's BCS committee. Furthermore, BCS designation is not applicable for this ER formulation/drug product.

Table 1: Aqueous solubility of Amantadine HCl as a function of pH

pH	Molar Solubility	Mass Solubility
1	Very soluble (4.81 mol/L)	Very soluble (728 g/L)
2	Very soluble (4.81 mol/L)	Very soluble (728 g/L)
3	Very soluble (4.81 mol/L)	Very soluble (728 g/L)
4	Very soluble (4.81 mol/L)	Very soluble (728 g/L)
5	Very soluble (4.80 mol/L)	Very soluble (726 g/L)
6	Very soluble (4.71 mol/L)	Very soluble (712 g/L)
7	Very soluble (3.94 mol/L)	Very soluble (596 g/L)
8	Very soluble (1.50 mol/L)	Very soluble (227 g/L)
9	Soluble (0.21 mol/L)	Soluble (32 g/L)
10	Slightly soluble (0.025 mol/L)	Slightly soluble (3.8 g/L)

6. Dissolution method development:

(b) (4)

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(b) (4)

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Reviewer's assessment:

These studies demonstrated that the dissolution method for Amantadine HCl ER Tablets is discriminating with regards to:

- The critical material attribute (b) (4)
- The critical material attribute (b) (4)
- The critical process parameters (b) (4) and,
- The critical process parameters (b) (4)

Overall, the proposed dissolution method is suitable for batch release and stability testing of Osmolex® ER (Amantadine Hydrochloride Extended Release) Tablets 160 mg, 240 mg and 320 mg.

The analytical method used for the dissolution testing will be evaluated by the CMC reviewer.

7. Multi-media dissolution testing

The dissolution profile of Amantadine HCl ER Tablets in 0.1 N HCl, pH 4.5 and pH 6.8 was characterized for all three strengths; Figures 12-14, below provide these dissolution characterization.

Figure 12: Dissolution profiles of Amantadine HCl ER Tablets in 0.1N HCl

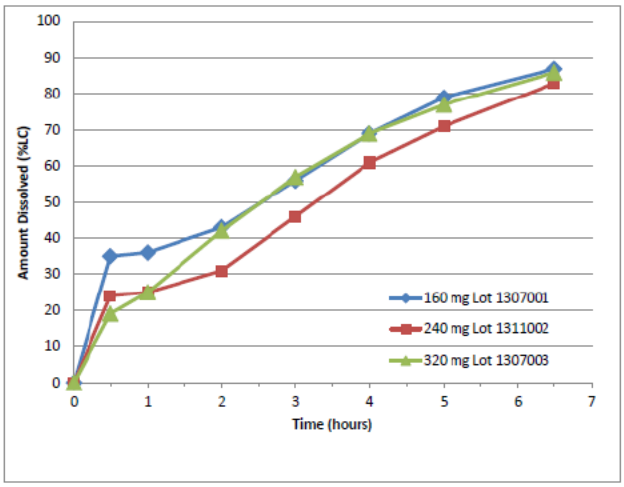


Table 5: Summary of comparison of Amantadine HCl ER Tablets dissolution profiles in 0.1 N HCl

Media	Comparison	f_2 Value
0.1 N HCl	160 mg vs 240 mg	51
	160 mg vs 320 mg	56
	240 mg vs 320 mg	57

Figure 13: Dissolution profiles of Amantadine HCl ER Tablets in pH 4.5 acetate buffer

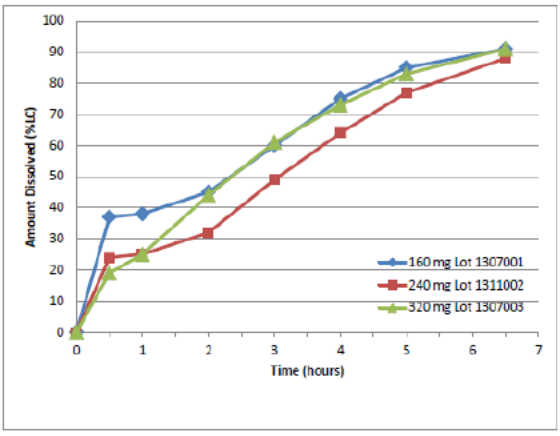


Table 6: Summary of comparison of Amantadine HCl ER Tablets dissolution profiles in pH 4.5 acetate buffer

Media	Comparison	f_2 Value
pH 4.5 acetate buffer	160 mg vs 240 mg	48
	160 mg vs 320 mg	53
	240 mg vs 320 mg	55

Figure 14: Dissolution profile of Amantadine HCl ER Tablets in pH 6.8 phosphate buffer

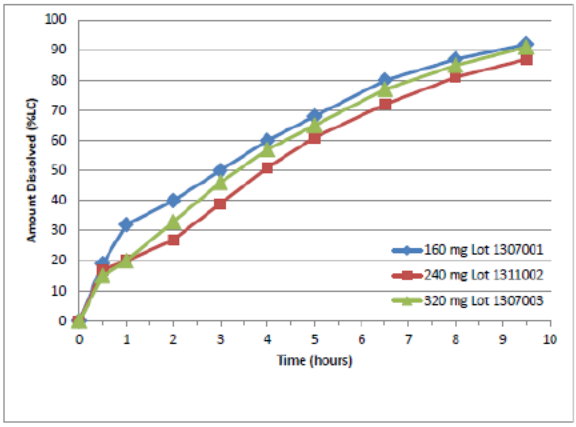


Table 7: Summary of comparison of Amantadine HCl ER Tablets dissolution profiles in pH 6.8 phosphate buffer

Media	Comparison	f_2 Value
pH 6.8 phosphate buffer	160 mg vs 240 mg	53
	160 mg vs 320 mg	63
	240 mg vs 320 mg	66

Tables 5-7 provide comparison (*f*2: similarity factor) of dissolution profiles across various strengths and in various pHs. (b) (4) , the comparability factor values were not expected to be greater than 50. However, as noted in Tables 5-7 above, the *f*2 values are greater than 50 in most of the cases, indicating that the dissolution profiles in various pHs were similar for all three strengths.

The multimedia dissolution testing also demonstrates that the extended release formulation does not dose-dump or increase in dissolution in various pH conditions.

8. Setting of the dissolution acceptance criterion

Comparative dissolution profiles of registration stability and clinical batches:
The proposed commercial formulation is identical to the formulation used in the relative bioavailability and clinical studies. Three registration lots for each of the three each strengths (1307001, 1408001 and 140804 for the 160 mg strength, 1307002, 1311002 and 1408002 for the 240 mg strength and 1307003, 1408003, and 1408005 for the 320 mg strength) have been manufactured and packaged in 30- and 90-count HDPE bottles. Among them, batches 1408001 (160 mg), 1408002 (240 mg) and 1408003 (320 mg) were used in dose proportionality study (Study OS320-PKP05); batch 1408003 (320 mg) was used in multiple dose study, comparing amantadine bioavailability to amantadine HCl syrup (Study OS320-PKP06) and food effect study (Study OS320-PKP04); batch 1408001 (160 mg) was used in renal impairment study (Study OS320-PKP07). Figures 15-17 provide the dissolution profiles of the clinical and the registration batches. The Applicant provided detailed dissolution data from clinical and stability batches.

Figure 15: Dissolution profile of Amantadine HCl ER tablets, 160 mg in water (QC method)

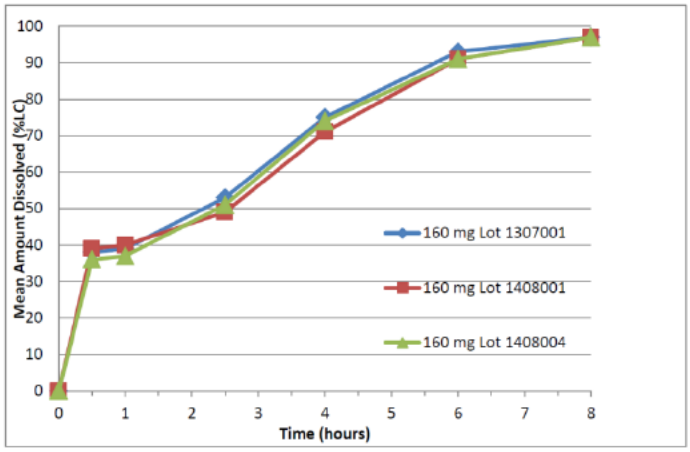


Figure 16: Dissolution profiles of Amantadine HCl ER tablets, 240 mg in water (QC method)

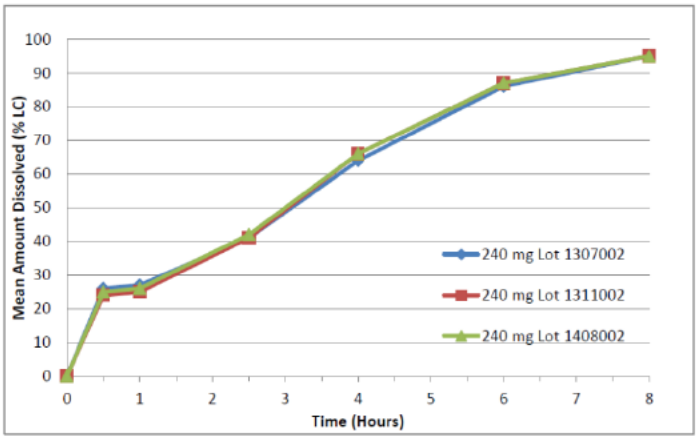


Figure 17: Dissolution profile of Amantadine HCl ER tablets, 320 mg in water (QC method)

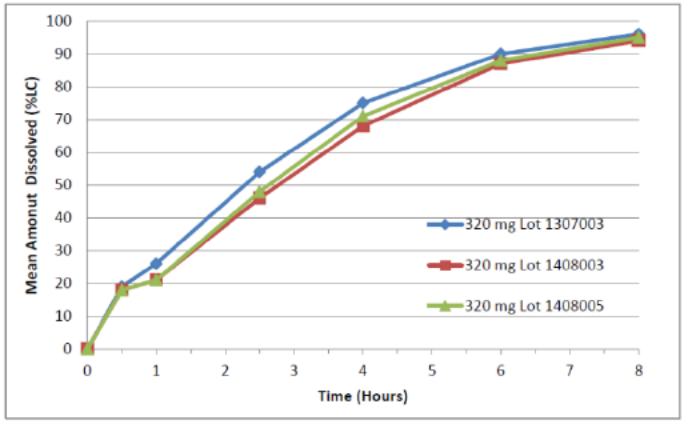


Table 8 summarizes the Applicant's proposed dissolution acceptance criteria, (b) (4)

(b) (4)

Table 8: Proposed dissolution acceptance criteria

Time (hour)	% Release		
	160 mg	240 mg	320 mg
(b) (4)			

(b) (4)

Reviewer's comments:

- There is no apparent change in the dissolution of the stability batches.
- The proposed dissolution acceptance limits are permissive, based on the provided data, and therefore not acceptable. In addition, the proposed dissolution acceptable criterion (b) (4) The Division of Biopharmaceutics communicated with the Applicant during the review cycle and recommended that the Applicant implement the recommended dissolution acceptance criteria (Table 9) for their proposed ER product.

Information Request (IR) conveyed to the Applicant on 9/28/2017:

The proposed dissolution acceptance limits are permissive and therefore not acceptable. Therefore, based on the provided overall dissolution data, we recommend that you implement the following dissolution acceptance criteria for your proposed product at release and on stability.

Table 9: Recommended dissolution acceptance criteria:

Time (hour)	% Release		
	160 mg	240 mg	320 mg
0.5	NLT (b) (4)%	NLT (b) (4)%	NLT (b) (4)
1	NMT %	NMT %	NMT %
2.5	(b) (4) %	(b) (4) %	(b) (4) %
4	%	%	%
6	NLT (b) (4)%	NLT (b) (4)%	NLT (b) (4)%

(b) (4). Please provide a revised drug product Specification Table and update your stability protocol accordingly.

The Applicant's response (dated 10/03/2017): The Applicant agreed to the revised dissolution acceptance criteria recommended by the FDA and provided updated the drug product specifications (3.2.P.5.1) and the stability protocol (3.2.P.8).

9. In vitro alcohol dose dumping studies: Effect of alcohol on the dissolution profile of Amantadine Hydrochloride Extended Release Tablets, 160 mg, 240 mg, and 320 mg

The dissolution profiles of Amantadine HCl ER Tablets, 160 mg, 240 mg and 320 mg, in ethanol-containing media were determined over a 2-hour period with 15-minute sampling intervals and compared to the corresponding profiles in media without alcohol. In addition, the dissolution profile of the 160-mg tablet was characterized over an 8-hour period in ethanol-containing media. Drug release for all product strengths at ethanol levels of 0%, 5%, 20% and 40% in 0.1N HCl (pH 1.2) and in water (media of the drug product (QC) dissolution method) were measured.

Dissolution profile data of Amantadine HCl ER tablets dissolved in acidic (0.1N HCl) and in QC media (water) dissolution media containing 0%, 5%, 20% and 40% ethanol are presented below in Figures 18 and 19, respectively. As shown in Figure 18 and Figure 19, levels of ethanol up to 20% in acidic and in water did not significantly affect the release profile of the 320-mg tablets. In 40% ethanol, the amount dissolved (%) increased to 52% LC for the acidic media ($f2$ = 49) and to 54% LC for the QC media ($f2$=50) in 2 hours [Table 10].

Table 10: Summary of comparison of Amantadine HCl dissolution profiles (up to 2 hours) for 160 mg, 240 mg, 320-mg Amantadine HCl ER tablets in acidic (0.1 N HCl) or QC (water) media containing 0%, 5%, 20% and 40% ethanol

	160 mg		240 mg		360 mg	
Dissolution Media	$f2$ value	Amount dissolved (%LC)	$f2$ value	Amount dissolved (%LC)	$f2$ value	Amount dissolved (%LC)
0% EtOH /0.1 N HCl	NA	43%	NA	29%	NA	39%
5% EtOH /0.1 N HCl	90	44%	86	33%	82	42%
20% EtOH /0.1 N HCl	65	52%	59	42%	61	47%
40% EtOH /0.1 N HCl	46	63%	43	52%	49	52%
0% EtOH /water	NA	43%	NA	32%	NA	42%
5% EtOH /water	77	48%	78	37%	68	48%
20% EtOH /water	57	56%	56	46%	54	52%
40% EtOH /water	42	66%	42	55%	50	54%
	160 mg		240 mg		360 mg	
Dissolution Media	Amount dissolved (mg) in 2 hours		Amount dissolved (mg) in 2 hours		Amount dissolved (mg) in 2 hours	
0% EtOH /0.1 N HCl	69 mg		70 mg		125 mg	
5% EtOH /0.1 N HCl	70 mg		79 mg		134 mg	

20% EtOH /0.1 N HCl	83 mg	101 mg	150 mg
40% EtOH /0.1 N HCl	101 mg	125 mg	166 mg
0% EtOH /water	69 mg	70 mg	134 mg
5% EtOH /water	77 mg	89 mg	154 mg
20% EtOH /water	90 mg	110 mg	166 mg
40% EtOH /water	106 mg	132 mg	173 mg

The Applicant stated that the amount released over the 2-hour period in 40% ethanol increased only 39 to 41 mg (15% to 16% of the 260 mg amantadine HCl in the extended release tablet core of the 320-mg ER tablet). The Applicant also claimed that the profile maintained its pseudo-zero order characteristic: the release profile was linear from 30 minutes to 120 minutes and the Amantadine HCl ER 320-mg Tablets maintained their ER release properties.

Figure 18: Alcohol effect on the dissolution profiles of Amantadine HCl ER 160-mg, 240-mg, 360-mg Tablets (acidic media)

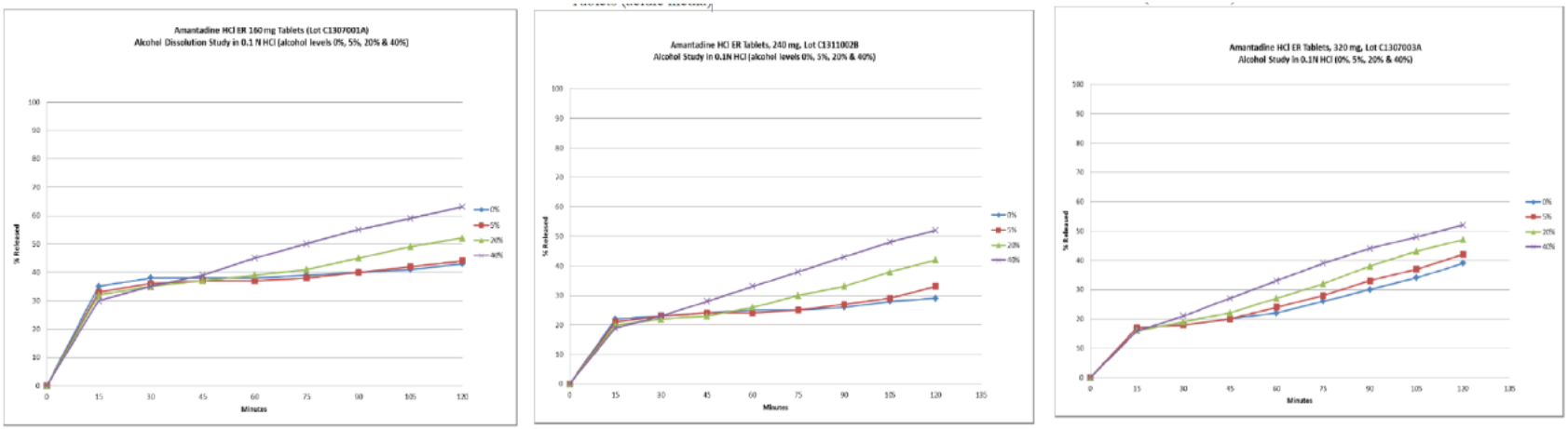
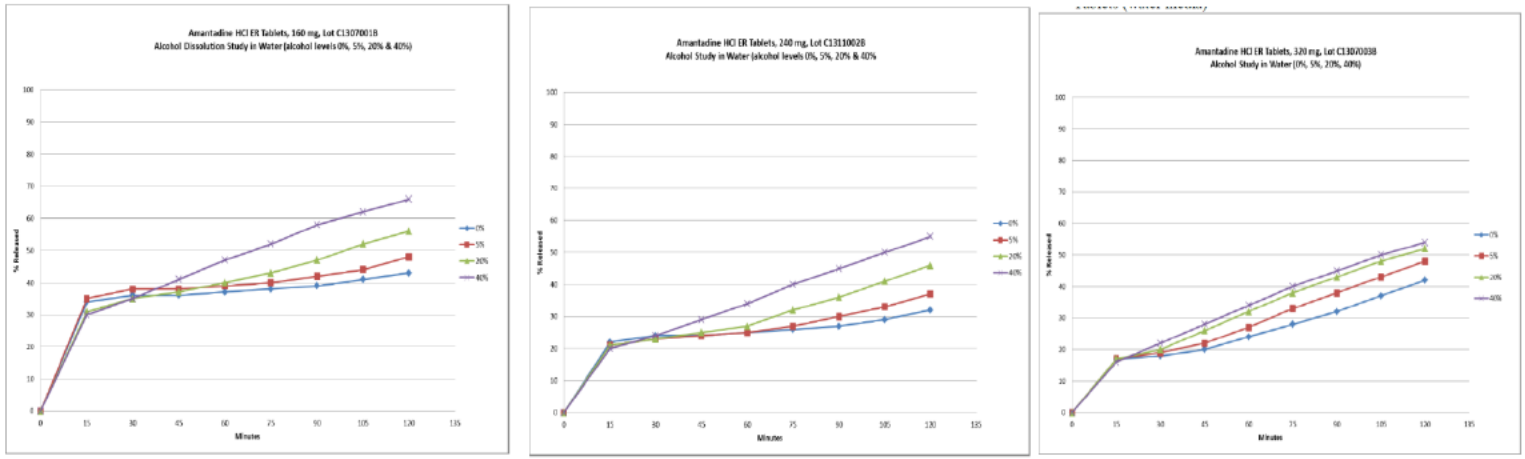
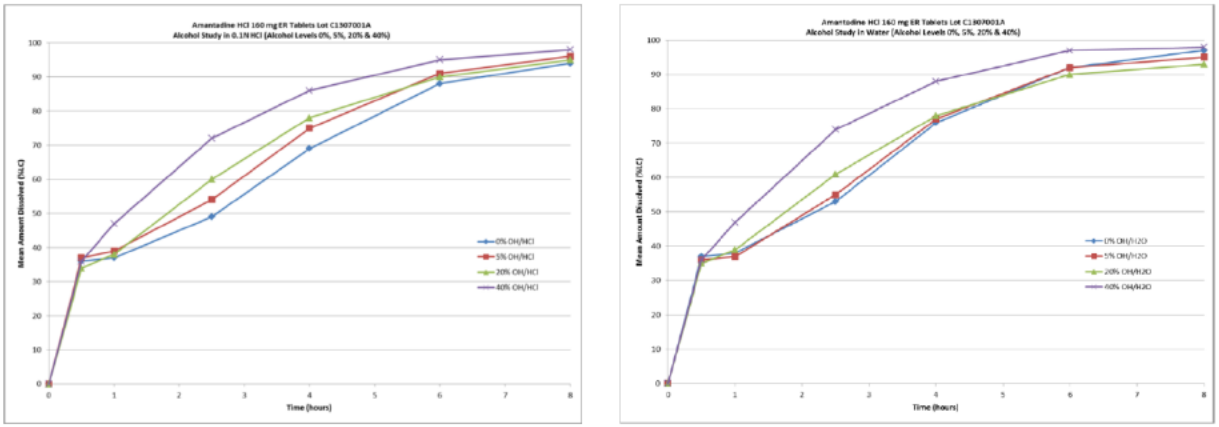


Figure 19: Alcohol effect on the dissolution profile of Amantadine HCl ER 160-mg, 240-mg, 360-mg Tablets (water media)



The impact of ethanol on the dissolution profile was examined further for the 160-mg Amantadine HCl ER Tablets as this strength was affected the most in the 2-hour studies. The 8-hour individual dissolution profile for the 160-mg Amantadine HCl ER Tablets in acidic (0.1N HCl) dissolution media and in water containing 0%, 5%, 20% and 40% ethanol are provided below in Figure 20.

Figure 20: Alcohol effect on the 8-hour dissolution profiles of Amantadine HCl ER 160-mg Tablets (0.1 N HCl) and water



The maximum amount released in 2 hours for the 160-mg, 240-mg and 320-mg ER Tablets was 53%, 66% and 87%, respectively, of the dose of a 200-mg immediate release amantadine HCl oral solution dose. Additional testing of amantadine HCl dissolution profiles for 160-mg Amantadine HCl ER Tablets in up to 40% ethanol for 8 hours confirmed the absence of dose dumping.

Reviewer's assessment: This Reviewer agrees that Amantadine HCl ER Tablets do not dose dump in ethanol solutions containing up to 20% ethanol ($f2$>50 for the dissolution profile comparison with 0% alcohol). Results presented in the figures and Table 10 above show that there is an approximately noticeable 20-25% increases in amantadine dissolution from Amantadine HCl ER Tablets at 2-2.5 hours in presence of 40% ethanol. The study finding was conveyed to the Clinical and OCP (Office of Clinical Pharmacology) review teams in the mid-cycle meeting and a labeling meeting.

10. Extended Release designation

Study OS320-PKP06 compared the steady-state bioavailability of amantadine from one Amantadine HCl ER 320-mg tablet (Treatment-A) administered orally once daily to 160 mg amantadine HCl syrup (Treatment-B), 50 mg/5 mL administered orally twice daily for 7 days. At steady-state, the 320-mg Amantadine HCl ER tablet is bioequivalent to 320 mg/day amantadine HCl syrup (160 mg twice daily). The geometric LS mean ratio of the natural log transformed Cmax and AUC0-24 was 108.69%, and 97.48%, respectively; the confidence limits were well within the 80.00 to 125.00% bioequivalence limits (Table 11 and Figure 21). Results demonstrate that the drug product's steady-state performance is equivalent to a currently marketed non extended-release drug product.

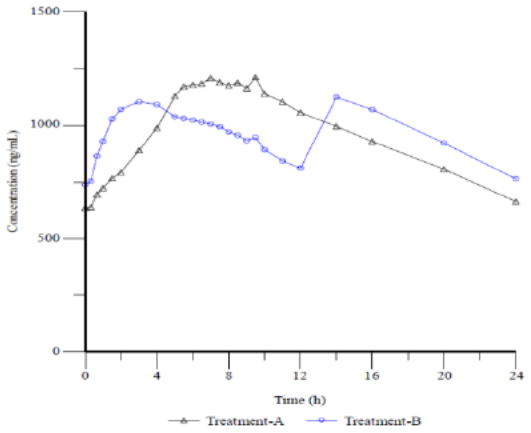
Table 11 Statistical results of amantadine following oral administration of one 320-mg Amantadine HCl ER tablet daily (Treatment-A) or 160 mg amantadine HCl oral syrup twice daily (Treatment-B) for 7 days to fasted healthy volunteers, Study OS320-PKP06

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-A ER tablet Test (n=23)	Treatment-B Syrup Reference (n=23)		LOWER	UPPER
C_{max}	9.3	1242.62	1143.30	108.69	103.66	113.96
AUC_{0-24}	8.9	22006.46	22576.18	97.48	93.20	101.95

* units are ng/mL for C_{max} and ng·h/mL for AUC_{0-24}

Source: section 14.2.1

Figure 21: Amantadine plasma concentration-time (mean) profile mean following oral administration of one 320-mg Amantadine HCL ER tablet daily (Treatment-A) or 160 mg of amantadine HCl oral syrup, 50 mg/5 mL twice daily (Treatment-B) for 7 days to fasted healthy volunteers, Study OS320-PKP06



It is noted that, as per the LD labels, the proposed Amantadine HCl ER tablet is recommended to be administered once a day based on its drug-release and pharmacokinetic properties, even at a much high dose level, compared to the adult dosage of Symmetrel given once or twice a day. As a supportive evidence, the proposed formulation or various strengths exhibit the extended release characteristics without dose-dumping under various pH conditions in vitro.

Based on the totality of the available information, this Reviewer determines that data submitted in the current submission meet the criteria cited in the 21 CFR 320.25 (f) and support the "Extended Release" claim for the proposed amantadine HCl drug product due to following reasons:

- 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. [Also refer to OCP review]
- Extended-release characteristics in humans to provide dosing benefit with respect to dosing frequency.

12. Overall review recommendations:

From the Biopharmaceutics perspective, NDA 209410 for Osmolex® ER (Amantadine Hydrochloride Extended Release) Tablets, 160 mg, 240 mg and 320 mg is recommended for **APPROVAL.**

Primary Biopharmaceutics Reviewer Name and Date:

Om Anand, Ph.D., 09/26/2017

Secondary Reviewer Name and Date:

Ta-Chen Wu, Ph.D., 11/10/2017

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Ta-Chen Wu

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