CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	209410
Link to EDR	\\CDSESUB1\evsprod\NDA209410\0000
Submission Date	March 31, 2017
Submission Type	Original NDA (505(b)(2))
Brand Name	OSMOLEX® ER
Generic Name	Amantadine hydrochloride
Dosage Form and Strength	Extended Release Oral Tablets 160 mg, 240 mg and 320 mg amantadine HCl
Route of Administration	Oral
Proposed Indication	Treatment of Parkinson's Disease
Applicant	Osmotica Pharmaceuticals US LLC
OCP Review Team	Bilal AbuAsal, PhD; Kevin Krudys, PhD; Sreedharan Sabarinath, PhD

Table of Contents

1. EXECUTIVE SUMMARY

Osmotica Pharmaceuticals US LLC has submitted a New Drug Application (NDA) for OSMOLEX™ ER (Amantadine Hydrochloride Extended Release Tablets) for once daily oral administration for the treatment of Parkinson's disease. This is a 505(b)(2) application and relies on FDA's previous findings of safety and effectiveness for SYMMETREL® Syrup (amantadine HCl 50 mg/5 mL, NDA 016023), the reference listed drug.

OSMOLEX™ ER is available in three dose strengths: 160 mg, 240 mg and 320 mg. It has an extended release core and an immediate release outer layer. Drug release from the extended release core is controlled by an osmotic pump system. The reference listed drug (RLD), SYMMETREL® Syrup, is approved with a twice daily regimen, whereas OSMOLEX™ ER is recommended as a once daily regimen.

Amantadine HCl is indicated for the treatment of Parkinson's disease and drug induced extrapyramidal reactions[1]. The approved usual dose for the RLD for the treatment of Parkinson's disease is 100 mg twice daily when used alone (i.e., 200 mg amantadine HCl per day). For patients with serious associated medical illnesses or who are receiving high doses of other anti-Parkinson drugs, the recommended initial dose is 100 mg daily. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary. The maximum recommended dose is 400 mg daily in divided doses.

The approved dose for drug-induced extrapyramidal reactions is 100 mg twice daily with options to increase the dose up to 300 mg daily given as divided doses.

A single-dose bioavailability/bioequivalence (BA/BE) study comparing the proposed ER product to the RLD provided the necessary PK bridging for this application. This study demonstrated that OSMOLEX™ ER tablets were bioequivalent to SYMMETREL® Syrup at 320 mg total daily dose level. This study was not conducted at the approved dose levels of the RLD (see above for the approved doses of RLD). The review team consider this PK bridging study between SYMMETREL® syrup and OSMOLEX ER to be acceptable to support this 505(b)(2) application for the following reasons:

- The pharmacokinetics of amantadine is dose proportional over the proposed dosing range. The exposure to amantadine from once daily dosing with the available dose strengths of OSMOLEX™ ER tablets (i.e., 240 mg and 320 mg of amantadine HCl) is bracketed by the exposures obtained from the approved usual dose (i.e., 200 mg daily) and the highest dose (i.e., 400 mg daily) of SYMMETREL® Syrup, the reference listed drug. A combination of 160 mg and 240 mg strengths of OSMOLEX™ ER can match exposures of the maximum daily dose of the RLD.

[1] SYMMETREL Syrup USPI:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s016lbl.pdf

- Amantadine is generally dosed using a titration strategy to optimal and tolerated dose levels for each patient. Therefore, 160 mg strength OSMOLEX™ ER, although not bioequivalent to the approved usual dose of the RLD (i.e., 200 mg daily), can be considered as the initial or starting dose.

However, there are some important limitations with OSMOLEX™ ER. It is not possible to use OSMOLEX™ ER tablets in patients who require only 100 mg daily dose of amantadine HCl. This is because the lowest available OSMOLEX™ ER tablet strength is 160 mg. Also, matching of all approved total daily doses/exposures for immediate release (IR) products of amantadine HCl and OSMOLEX™ ER tablets is not possible with the available tablet strengths. This limits interchangeability of OSMOLEX™ ER tablets with IR products.

1.1 Recommendations

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.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	A PK bridging study between the proposed ER product OSMOLEX™ ER tablet and the RLD, SYMMETREL® Syrup, forms the basis for this NDA application. OSMOLEX™ ER was found to be bioequivalent to the RLD at 320 mg (amantadine HCl) total daily dose level. The exposure to amantadine from OSMOLEX™ ER with once daily dosing of 240, 320 and 400 mg were bracketed or equivalent to exposures from the approved usual dose of 200 mg daily and the maximum dose of 400 mg daily of the RLD. The lowest strength of the ER tablet (160 mg), provided exposures lower than that from the approved usual dose of the RLD. Therefore, the 160 mg strength of OSMOLEX™ ER is considered as the starting dose for initiating therapy.
General dosing instructions	• OSMOLEX™ ER is not interchangeable/switchable with other immediate release amantadine HCl drug products. • Should be taken once a day in the morning and not at bed time. Can be administered with/without food. Should be swallowed whole and should not be crushed before dosing. • Cannot be used for patients who require a daily dose of 100 mg of amantadine HCl. <u>For the treatment of Parkinson's disease and for the treatment of drug-induced extrapyramidal reactions:</u>

<table>
<tr><td></td><td>Initial dose of OSMOLEX™ ER tablet is 160 mg (amantadine HCl) once daily in the morning. The dose can be increased to 240 mg once daily, in one to several weeks. Patients whose responses are not optimal with 240 mg once daily may benefit from an increase to 320 mg once daily or to the maximum dose of 400 mg once daily.</td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>

No dose adjustment is required for patients with hepatic impairment.
The dose of OSMOLEX™ ER tablets should be adjusted in patients with renal impairment as per the table below:

<table>
<tr><td>Renal Impairment Category</td><td>Creatinine Clearance (mL/min/1.73 m^2)</td><td>Recommended Initial Dose/Regimen</td></tr>
<tr><td>Normal</td><td>≥90</td><td>160 mg every 24 hours</td></tr>
<tr><td>Mild</td><td>60 to 89</td><td>160 mg every 24 hours</td></tr>
<tr><td>Moderate</td><td>30 to 59</td><td>160 mg every 48 hours</td></tr>
<tr><td>Severe</td><td>15 to 29</td><td>160 mg every 96 hours</td></tr>
<tr><td>ESRD</td><td><15</td><td>Contraindicated</td></tr>
</table>

Do not administer OSMOLEX™ ER tablets with alcohol
Can be administered with or without food

</td></tr>
<tr><td>PK Bridge between the to-be-marketed and clinical trial formulations</td><td>The formulation used in the PK bridging study is the same as the to-be marketed formulation.</td></tr>
</table>

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The following is a summary of the PK of amantadine from SYMMETREL® Syrup label and from the clinical pharmacology studies conducted by the applicant using OSMOLEX™ ER tablets.

Mechanism of Action

The mechanism of action of amantadine for the treatment of Parkinson's disease is not known. It is suggested that amantadine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and it is believed to act on the dopaminergic system.

Absorption

After oral administration of 320 mg OSMOLEX™ ER tablet once daily for 7 days, the mean ± SD C_{max} was 1.3 ± 0.03 mcg/mL. The median time to C_{max} (T_{max}) was about 7.5 hours (range: 5 to 12 hours). Presence of food did not affect the absorption of amantadine from OSMOLEX™ ER tablets.

Results from Study OS320-PKP05 demonstrated that PK of amantadine from OSMOLEX™ ER tablets are dose proportional. Plasma amantadine exposure (C_{max}, AUC_{inf}) after single oral doses (160 mg, 240 mg, 320 mg amantadine HCl) of OSMOLEX™ ER increased proportionally with increasing dose.

Distribution

Amantadine is 67 % bound to plasma proteins. The volume of distribution after intravenous administration was 3-8 L/Kg.

Elimination:

Amantadine is mainly eliminated renally and about 85 % of the administered dose is excreted unchanged in urine. After the oral administration of a single 160 mg OSMOLEX™ ER tablet, the apparent oral clearance was approximately 11 L/h . The elimination half-life was about 18 hrs.

Metabolism:

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

Excretion:

Amantadine is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion. The pH of the urine has been reported to influence the excretion rate of amantadine. Since the excretion rate of amantadine increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended initial dosage is one OSMOLEX™ ER 160 mg (amantadine HCl) tablet administered orally once daily in the morning, when used alone. The dose can be increased to 240 mg daily, in one to several weeks. Occasionally, patients whose responses are not optimal with 240 mg tablets once daily may benefit from an increase to 320 or 400 mg once daily, taken in the morning. The maximum recommended dose of OSMOLEX™ ER is 400 mg once daily. Such patients should be supervised closely by their physicians.

Patients taking 100 mg daily of amantadine should not be started on OSMOLEX™ ER.

OSMOLEX™ ER is not interchangeable with other amantadine HCl drug products.

The tablets should be swallowed in full and should not be crushed before dosing.

2.2.2 Therapeutic individualization

Hepatic Impairment

No dose adjustments are needed for patients with hepatic impairment. The impact of hepatic impairment on the exposures of plasma amantadine has not been assessed. Since renal clearance is the predominant elimination pathway for amantadine, no significant changes in amantadine exposures are expected with hepatic impairment.

Renal Impairment

Renal impairment can increase the exposure of amantadine. The applicant conducted a single dose PK study of orally administered OSMOLEX ER tablets in subjects with renal impairment and normal renal function (Study OS320-PKP07). As expected, amantadine exposure increased and the clearance decreased for subjects with renal impairment, as reflected by an in increase in C_{max} and AUC values. PK simulations were used for providing dosing recommendations presented in Section 1.1 for patients with renal impairment and the details are provided in Section 3.3.3. OSMOLEX ER is not recommended in patients with ESRD who are on dialysis or otherwise. Amantadine is not efficiently removed by hemodialysis.

Extrinsic Factors (Drug Interactions and Food Effect):

No dose adjustment or therapeutic individualization is needed based on extrinsic factors. OSMOLEX ER can be administered without regard to food.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical pharmacology recommends the following labelling concepts to be included in the final package insert. The dose levels mentioned below are for amantadine HCl.

- The approval of OSMOLEX ER is based on PK bridging to RLD, SYMMETREL® syrup. A 320 mg OSMOLEX ER single daily dose in comparison to 160 mg twice daily dose of SYMMETREL® Syrup was found to be bioequivalent. The proposed daily doses of OSMOLEX ER are not similar to the approved dosing regimen for the RLD. Thus, direct switching from IR dosing regimen to the proposed doses of OSMOLEX ER regimen is not feasible (i.e., no interchangeability).
- Use 160 mg as starting dose for initiating therapy with OSMOLEX ER. Dose titration based on tolerability will be required as is the case with the RLD.
- Include maximum daily dose as 400 mg for OSMOLEX ER, which can be achieved using a combination of 160 mg and 240 mg tablet strengths. This is the same as the highest approved daily dose of the RLD, SYMMETREL® Syrup.

- Patients taking 100 mg daily dose of amantadine HCl should not be started on OSMOLEX ER. This is because the lowest available strength of OSMOLEX ER tablet is 160 mg.
- For the treatment of both Parkinson's disease and drug-induced extrapyramidal symptoms, the recommended initial dosage is one OSMOLEX ER 160 mg tablet once daily in the morning. The dose can be increased to 240 mg daily and then 320 and eventually to a maximum daily dose of 400 mg (160+240 mg tablets), if the desired clinical effect is not achieved after several weeks.
- Dose reduction is required as described in Section 1.1 for patients with moderate and severe renal impairment. OSMOLEX ER is contraindicated in ESRD patients (CRCL<15 ml/min). Hemodialysis cannot efficiently remove amantadine from systemic circulation.
- OSMOLEX ER should be taken in the morning without regard to food.
- No dose adjustment is required for patients with hepatic function impairment.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The first NDA for amantadine hydrochloride in the US was approved over 40 years ago. The immediate-release dosage forms of amantadine hydrochloride are approved for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus, for the treatment of parkinsonism (PD) and for drug-induced extrapyramidal reactions.
The usual dose of amantadine hydrochloride for treatment of Parkinsonism is 100 mg twice daily. Occasionally, PD patients whose responses are not optimal at 200 mg daily (100 mg twice daily) may receive up to 400 mg daily in divided doses (200 mg twice daily) under close supervision by their physicians. Osmotica Pharmaceutical US LLC developed a new extended-release (ER) tablet dosage form for once daily oral administration. The approved IR products of amantadine has a twice daily regimen.
Initially, the applicant aimed to develop OSMOLEX ER for the treatment of levodopa-induced dyskinesia (LID). Two placebo-controlled, double-blind phase 3 studies were conducted to investigate the efficacy and safety of OSMOLEX ER for the treatment of LID. Efficacy and safety data from these studies were not considered during the review of this application. Please refer to clinical review for more details. This NDA used 505(b)(2) pathway based on PK bridging to the RLD (SYMMETREL® syrup).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The mechanism of action of amantadine in the treatment of Parkinson's disease is not known. It is suggested that amantadine, is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. It is believed to act on the dopamine system and exert

	dopaminergic-like side effects such as hallucinations and dizziness.
Active moieties	Only the parent compound is believed to be active. One metabolite, an N-acetylated compound accounted for 0-15 % in multiple studies.
QT Prolongation	The effect of QT prolongation was not studied in a dedicated thorough QT study.
General Information	
Bioanalysis	Quantitative bioanalysis of amantadine was conducted using a validated LC/MS/MS method. The analytical method and the assay validation were found to be acceptable. A summary of the analytical method is included as Appendix 4.1.
Drug exposure at steady state following the therapeutic dosing regimen	The mean (CV) of $AUC_{0\text{-}24,\ ss}$ (ng.h/ml) and C_{max} (ng/ml) based on Study OS320-PKP06 in healthy subjects after a daily dose of 320 mg at steady state were 9946.7 (33.6) and 536.1 (31.3) respectively.
Maximum dose or exposure	Approved maximum dose of amantadine HCl is 400 mg daily.
Dose proportionality	PK of amantadine from OSMOLEX ER was dose-proportional for 160 mg, 240 mg and 400 mg strengths.
Accumulation at steady state	The steady-state exposures ($AUC_{0\text{-}Tau}$) were 20-30 % higher than after single dosing (accumulation ratio ~1.2-1.3-fold).
Absorption	
Median T_{max} for plasma amantadine was around 7.5 hours from OSMOLEX ER. Time to reach steady-state is approximately four days after dose initiation in subjects with normal renal function. Food effect: Ingestion of high-fat, high-calorie meal did not affect the PK of amantadine. The steady-state exposures (C_{max}, $AUC_{0\text{-}24}$) were bioequivalent with the immediate release formulation on a milligram (mg) to mg basis (i.e., 320 mg OSMOLEX ER given once daily and 160 mg SYMMETREL Syrup given twice daily).	

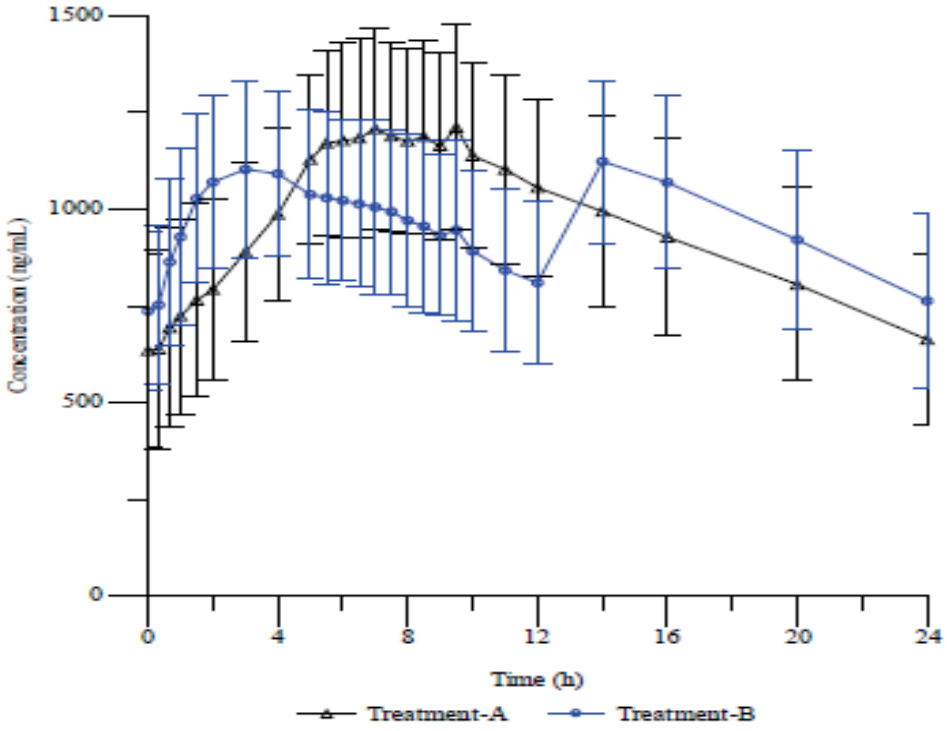
Distribution
The volume of distribution and plasma protein binding of amantadine are expected to be consistent with values indicated in SYMMETREL® label.
Elimination
• The primary elimination pathway of amantadine is renal, and the elimination half-life is about 16 hrs. • Amantadine is neither a substrate 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.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

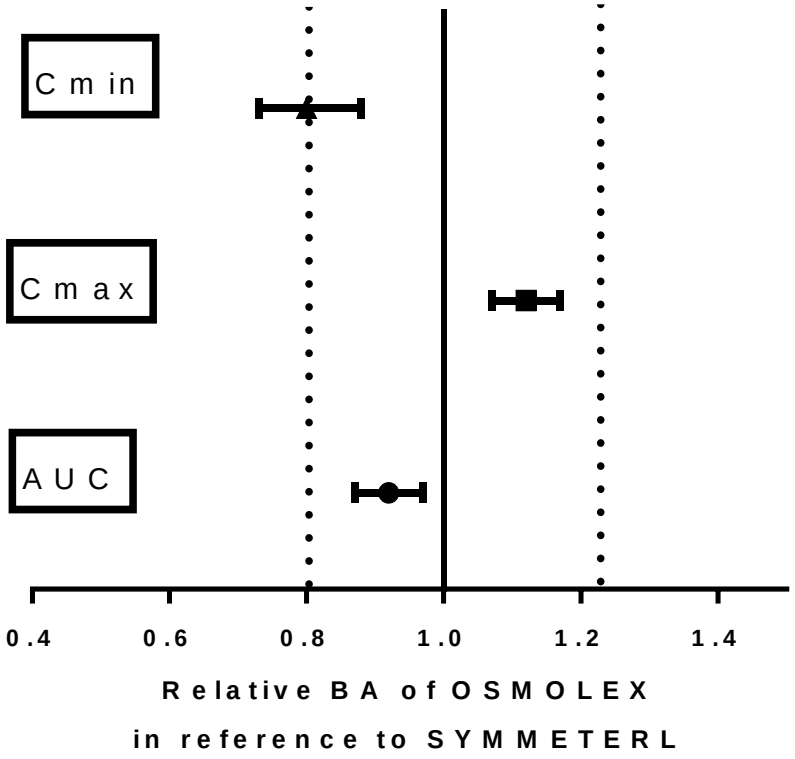
This is a 505(b)(2) NDA based on PK bridging of the proposed ER product to the approved immediate release drug product of amantadine hydrochloride (RLD, SYMMETREL® Syrup). The applicant conducted a relative bioavailability study (Study OS320-PKP06) to bridge the PK of OSMOLEX ER to the RLD. This was a single center, randomized, 2-treatment, 2-period, 2-sequence, multiple-dose, crossover study with a 2-day titration period. The relative bioavailability at steady state was compared after 7 consecutive days of dosing with 320 mg OSMOLEX ER in a once a day regimen and 320 mg SYMMETREL Syrup (50 mg/5mL) divided into two equal doses (i.e., 160 mg twice daily), in healthy subjects under fasting conditions. The results of this study are shown in Figure 1 and Figure 2 below. OSMOLEX ER was found to be bioequivalent to the RLD in terms of AUC_{inf} and C_{max} at steady state in this study.

Figure 1 Mean plasma concentration-time profiles following oral administration of 320-mg OSMOLEX ER tablets once daily (Treatment-A: 320 mg amantadine HCl ER tablets) or SYMMETREL syrup twice daily (Treatment-B: 160 mg x 2 amantadine HCl) for 7 days in healthy volunteers, Study OS320-PKP06



Source: Page 27 of 74. 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods. Link: \\cdsesub1\evsprod\nda209410\0000\m2\27-clin-sum\summary-biopharm-1.pdf

Figure 2. PK parameters of amantadine from Study OS320-PKP06 PK. The geometric mean ratios of AUC_{inf}, C_{max} and C_{min} of OSMOLEX ER and SYMMETREL Syrup at steady state and corresponding 90 % Confidence Intervals are shown.



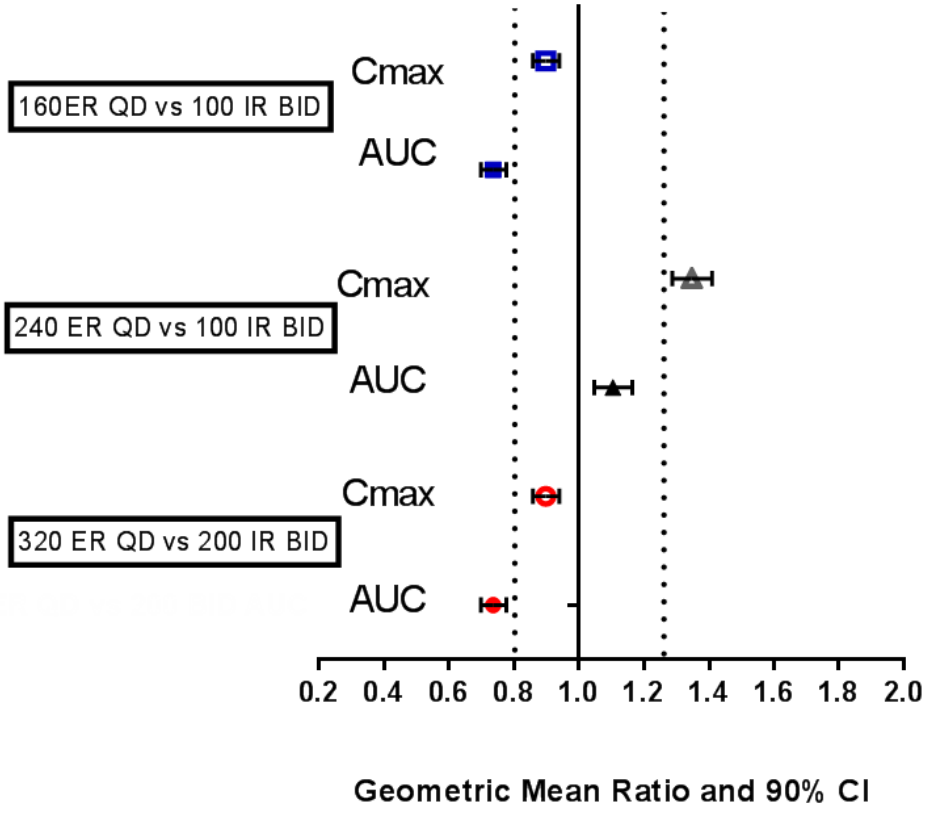
Source: Figure generated by FDA reviewer

The applicant also conducted a dose proportionality study to confirm PK linearity across the proposed dose strengths of 160, 240 and 320 mg OSMOLEX ER tablets (Study OS320-PKP05). Plasma amantadine exposure (C_{max}, AUC_{inf}) after single oral doses increased proportionally with increasing dose. Power model slope values of 0.9 and 1.0 for lnC_{max} and $lnAUC_{inf}$ indicate that amantadine exposure increased dose proportionally with OSMOLEX ER. The geometric LS mean ratio of the dose-normalized, natural log-transformed AUC_{inf} values ranged from 97.6 to 99.0 % for the comparison of each dose; the corresponding 90 % confidence intervals were between 92.0 and 105.0 %, further confirming the dose proportionality.
The exposure of amantadine from OSMOLEX ER was not highly variable. Based on the results from study OS320-PKP05, CV % for the C_{max} and AUC values across the different dose levels of OSMOLEX ER ranged from 18-21 % .

Even though OSMOLEX ER tablets administered once daily is shown to be bioequivalent to SYMMETREL syrup administered twice daily on a mg to mg basis, this study was not conducted at any of the approved dose levels of the RLD. Note that the approved 'usual dose' of the RLD is 200 mg per day and the maximum daily dose is 400 mg per day for the treatment of

Parkinson's disease. Therefore, the FDA reviewer conducted PK simulation studies and repeated the BE analysis at approved dose levels of the RLD. the results of this analysis are presented in . When the lowest dose strength of OSMOLEX ER (i.e., 160 mg) was compared with the closest total daily dose of the RLD (i.e., 200 mg per day as 100 mg twice daily) the geometric mean ratio for AUC was lower and out of the BE limit (i.e., less than 80 %). On the other hand, the C_{max} ratio for 240-mg dose of OSMOLEX ER, the next available dose strength, was higher and outside the BE limit (i.e., greater than 125 %) when compared with the 200-mg total daily dose of the RLD.

Figure 3 BE evaluation of OSMOLEX ER with the approved doses for SYMMETREL Syrup using PK simulations

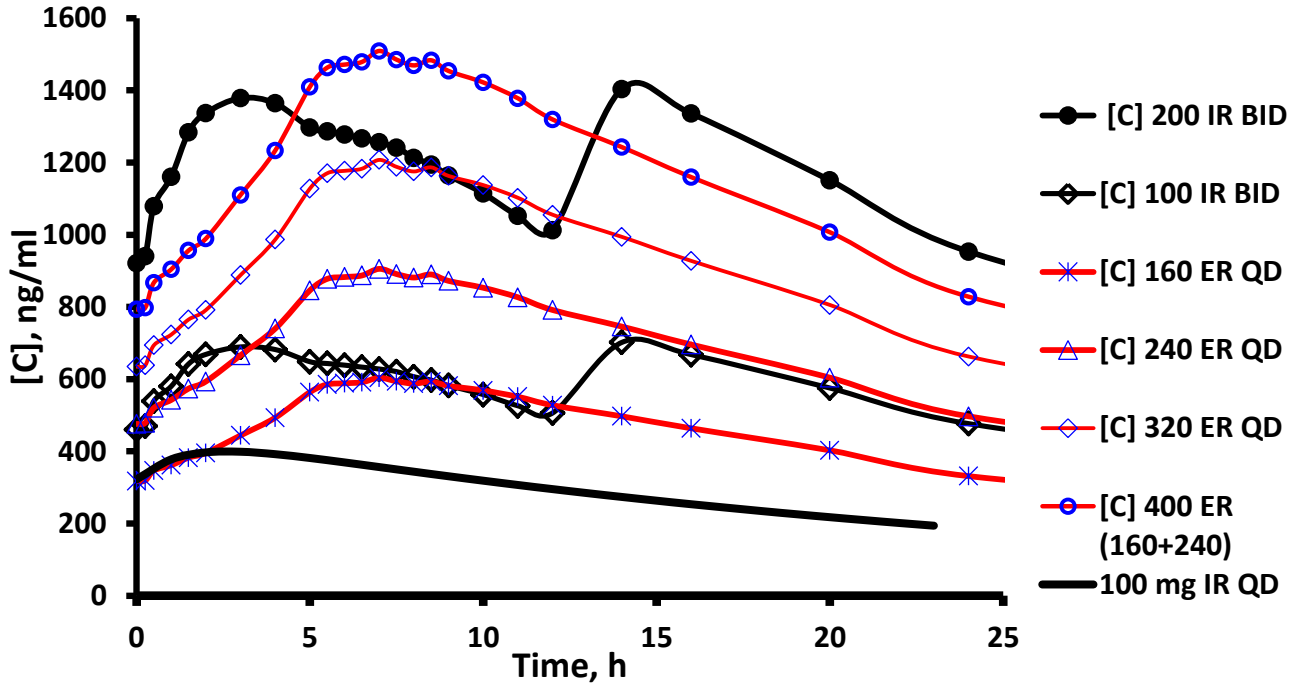


Source: Figure generated by FDA reviewer

The FDA reviewer also compared the PK profiles of different dose strengths of OSMOLEX ER with the lowest and highest dose of the approved daily dosing regimens of the RLD (See Figure 4). It was found that the PK profiles for all the doses of OSMOLEX ER, except for the 160 mg daily dose fall within the PK profiles for the highest (200 mg twice daily) and the usual dose (100 mg twice daily) of the RLD. Therefore, the 160 mg dose of OSMOLEX ER is considered as the starting dose to initiate therapy.

It should be noted that the 160 mg dose of OSMOLEX ER is higher than the lowest initial dose of the RLD recommended for some patients (i.e. 100 mg per day). This limits the use of OSMOLEX ER in such patients who may require a starting dose of 100 mg amantadine hydrochloride per day.
The maximum daily dose of the RLD can be achieved by using a combination of 160 mg and 240 mg tablets of OSMOLEX ER. This approach of combining two ER tablets to obtain a maximum daily dose of 400 mg was suggested to the applicant during the review and was accepted by the applicant.

Figure 4. Comparison of the steady state PK profiles of amantadine from the proposed OSMOLEX ER doses (160 mg, 240 mg, 320 mg and 160+240 mg) with the approved doses for the RLD, SYMMETREL Syrup. 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 the RLD. SYMMETREL Syrup is marked as 'IR' and OSMOLEX ER tablet is marked as 'ER' respectively.



Source: Figure generated by FDA reviewer (100, 160, 200, 240, 320 and 400 mg amantadine HCl are equivalent to 81, 129, 162, 193, 258 and 322 mg of amantadine free base respectively).

As observed in Figure 4, there are differences in the shape of the PK profiles of amantadine between OSMOLEX ER and the RLD. Following multiple-dose oral administration of 160-mg amantadine syrup twice daily, plasma concentrations increased rapidly with a median T_{max} value of 2 to 3hours post-dose and thereafter declined with a terminal half-life of 13.7 hours. In comparison, following multiple-dose oral administration of OSMOLEX ER 320-mg tablets once daily, amantadine plasma concentration increased slowly with a median T_{max} of 7.5 hours and declined with a similar terminal phase half-life of 13.3 hours. Longer T_{max} values confirmed slower rate of amantadine absorption from OSMOLEX ER tablets. Because of this delayed T_{max},

OSMOLEX ER tablets should be administered in the morning and not at bed time. If administered at bed time, amantadine levels will rise slowly and peak levels will be reached during the night. Because of the reported adverse event profile of amantadine, this is not considered desirable and administration of OSMOLEX ER at bed time is not preferred.

The review team considered the following, in addition to the steady state BE study conducted at 320 mg dose level for OSMOLEX ER, for evaluating the PK bridging strategy that supports this application.

- The pharmacokinetics of amantadine is dose proportional over the proposed dosing range.
- The exposure to amantadine from once daily dosing with the available dose strengths of OSMOLEX™ ER tablets (i.e., 240 mg and 320 mg of amantadine HCl) is bracketed by the exposures obtained from the approved usual dose (i.e., 200 mg daily) and the highest dose (i.e., 400 mg daily) of SYMMETREL® Syrup, the reference listed drug. A combination of 160 mg and 240 mg strengths of OSMOLEX™ ER can match exposures of the maximum daily dose of the RLD.
- Amantadine is generally dosed using a titration strategy to optimal and tolerated dose levels for each patient. Therefore, 160 mg strength OSMOLEX™ ER, although not bioequivalent to the approved usual dose of the RLD (i.e., 200 mg daily), can be considered as the initial or starting dose.
- Amantadine is a chronically administered drug and the reported onset of action as per the USPI of the RLD is usually within 48 hours for Parkinson's Disease. Therefore, the difference in time to peak plasma concentration between OSMOLEX ER and the RLD (7.5 hours vs. 2-3 hours) may not be clinically relevant.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The general dosing is based on titration to optimal tolerated dose of OSMOLEX ER. The proposed dosing scheme will provide plasma levels of amantadine that are within the levels obtained for the approved dosing regimen of the RLD (i.e., 200-400 mg of amantadine HCl daily).

The recommended initial dose for the treatment of Parkinson's Disease and extra pyramidal reactions is one OSMOLEX ER 160 mg tablet administered orally once daily in the morning, when used alone. The dose can be increased to 240 mg daily, in one to several weeks.

Occasionally, patients whose responses are not optimal with 240 mg once daily may benefit from an increase to 320 mg once daily, taken in the morning. The maximum recommended dose is 400 mg daily dose. The proposed titration strategy agrees with the clinical practice and the approved label of the RLD.

Although the approved maximum dose of amantadine hydrochloride for the treatment of extra pyramidal reaction is 300 mg daily for the RLD, the Clinical Division considers a 400 mg daily maximum recommended dose, similar to that recommended for Parkinson's Disease, also as acceptable. However, there are some important limitations with OSMOLEX™ ER. It is not possible to use OSMOLEX™ ER tablets in patients who require only 100 mg daily dose of amantadine HCl. This is because the lowest available OSMOLEX™ ER tablet strength is 160 mg. Matching of all approved total daily doses/exposures for IR products and OSMOLEX™ ER tablets are not possible with the available tablet strengths. This limits interchangeability of OSMOLEX™ ER tablets with IR products.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes. Amantadine is mainly eliminated renally and renal impairment increases the exposure of amantadine. The approved label for the RLD includes dose optimization for renal impairment. The applicant conducted a single dose study in subjects with renal impairment and normal renal function (Study OS320-PKP07) for OSMOLEX ER. As expected, exposure to amantadine increased and the clearance decreased for subjects with renal impairment. Dosing recommendation for patients with renal impairment were derived using PK simulations and are presented in Table 1 below (Section 4.2 provides more details).

It should be noted that the time required to reach PK steady state with OSMOLEX ER ranges from one week for patients with normal renal function and mild renal function impairment (CrCL >60 mL/min) to one month in patients with severe renal impairment (CrCL 15-29 mL/min).

Table 1. Dosing in Patients with Renal Impairment

Renal Function Category	eGFR (mL/min/1.73 m2)	OSMOLEX ER Dosing Regimen
Normal	≥ 90	Once every 24 hours
Mild	60 to 89	Once every 24 hours
Moderate	30 to 59	Once every 48 hours
Severe	15 to 29	Once every 96 hours
End Stage Renal Disease (ESRD)	< 15	Contraindicated

No dose adjustments are required for any other intrinsic factors such as hepatic impairment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. In a food-effect study (OS320-PKP04), ingestion of high-fat, high-calorie meal did not affect the plasma PK of amantadine from OSMOLEX ER. Therefore, the food-drug interaction is not considered clinically relevant and OSMOLEX ER can be taken with or without food.
No drug-drug interaction (DDI) studies were included in this NDA and the drug-drug interaction potential for OSMOLEX ER is same as that with the RLD.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

A validated HPLC method using MS/MS detection was employed for determining the concentrations of amantadine in human plasma. The sample analysis was conducted in accordance with FDA Guidance for the Industry, Bioanalytical Method Validation (May 2001) and EMA Guideline on Bioanalytical Method Validation.

Sample pre-treatment involved the protein precipitation extraction of amantadine from 0.81 mL of human plasma and amantadine-D6 was used as the internal standard. Summary of validation parameters is presented in Table 2.

Table 2 Validation Summary Table for Amantadine

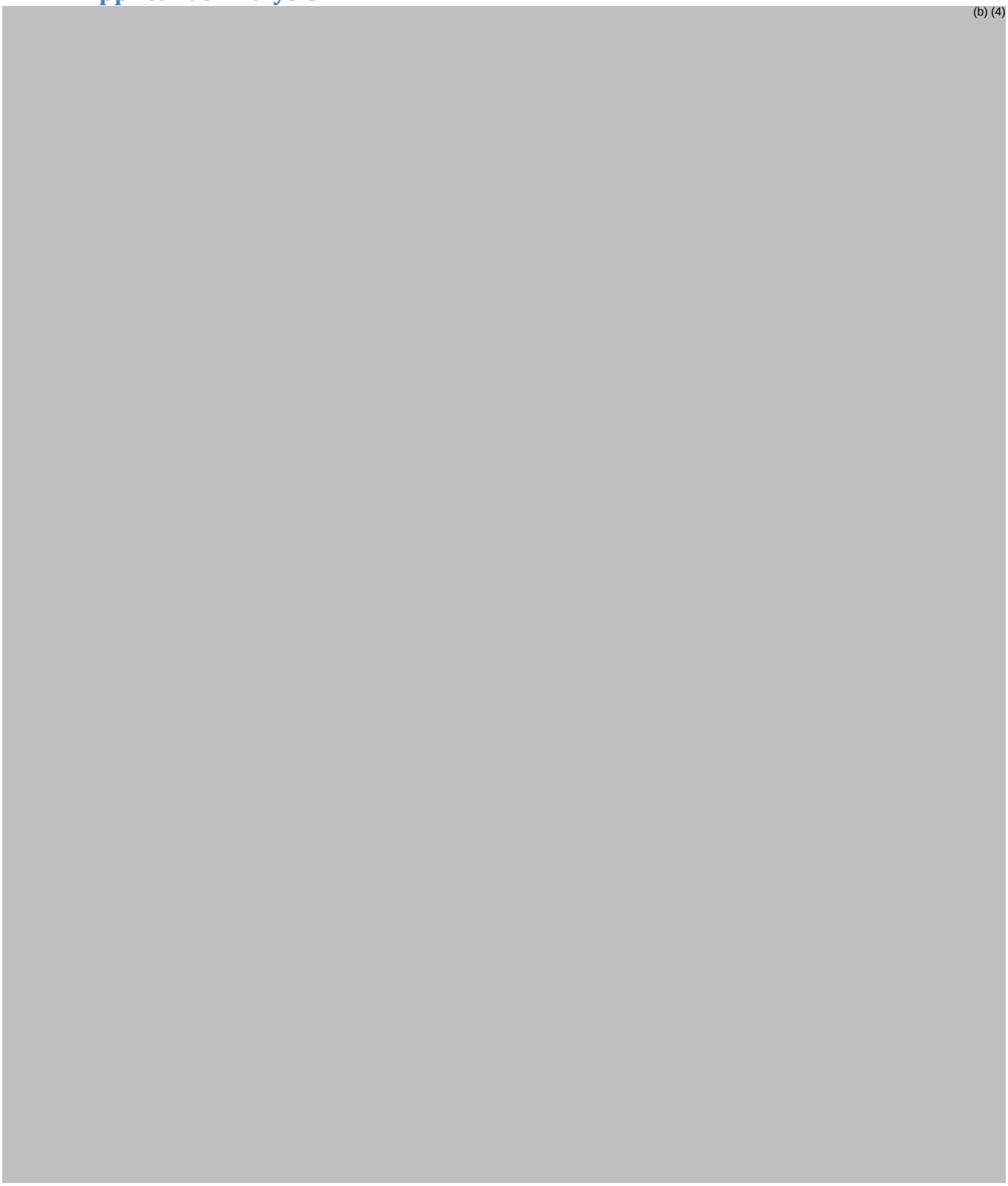
Analyte / Parameter	***Amantadine***
Range (ng/ml)	2-2000
Inter day Precision (%CV)	3.7%-7.9%
Inter day Accuracy (%Dev)	96%-104%
Intraday Precision (%CV)	1%-3%
Intraday Accuracy (%Dev)	95%-101%
Internal standard	1-Aminoadamantane-2,2,2',2',2",2"-d6 Lot # 3-WHH-131-3,
Reference standard	Amantadine hydrochloride Lot #103M4627V
Specificity	No interference in the blank matrix lots screened
Recovery (%)	103% -108%
Stability (% Mean Ratio):	
Freeze/Thaw Stability	3 cycles (100-102)
Human plasma (RT)	31 hrs (98-102)
Stock solution % deviation(-70C)	63 days (-1.5-3.4)
Auto sampler stability	164 hours (101%-108%)

Source: collected from the bioanalytical study report.
Link: \\cdsesub1\evsprod\nda209410\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\os320-3006\os320-3006-study-report-1.pdf

4.2 Dosing in Patients with Renal Impairment

4.2.1 Applicant's Analysis:

(b) (4)



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Dosing Recommendations for Subjects with Impaired Renal Function

(b) (4)

Table 5 Dosing regimens for patients with impaired renal function proposed by the Applicant

(b) (4)

Source: Page 8 of 24 model simulation report for dose adjustment in renal impairment.
Link: \\cdsesub1\evsprod\nda209410\0000\m2\27-clin-sum\summary-clin-pharm-2.pdf

Reviewer Comment:
The proposed dose adjustment strategy had the following limitations:

- The sponsor used (b) (4) for the calculation of the creatinine clearance instead of the baseline value (-1 day)
- The sponsor proposed (b) (4) . This was not necessary and is not consistent with dosing recommendations for approved drug products of amantadine (SYMMETREL®)

Reviewer Analysis:
Estimated eGFR values by MDRD equation at baseline were used as a covariate to parameterize the effect of degree of renal impairment on the elimination of amantadine. The reviewer used eGFR values with MDRD equation and repeated model parametrization using the same base model that the applicant developed.
The model was fit to the data from the renal impairment study and goodness of fit was evaluated using typical diagnostic plots. Final model parameters are presented in Table 6 Table 3

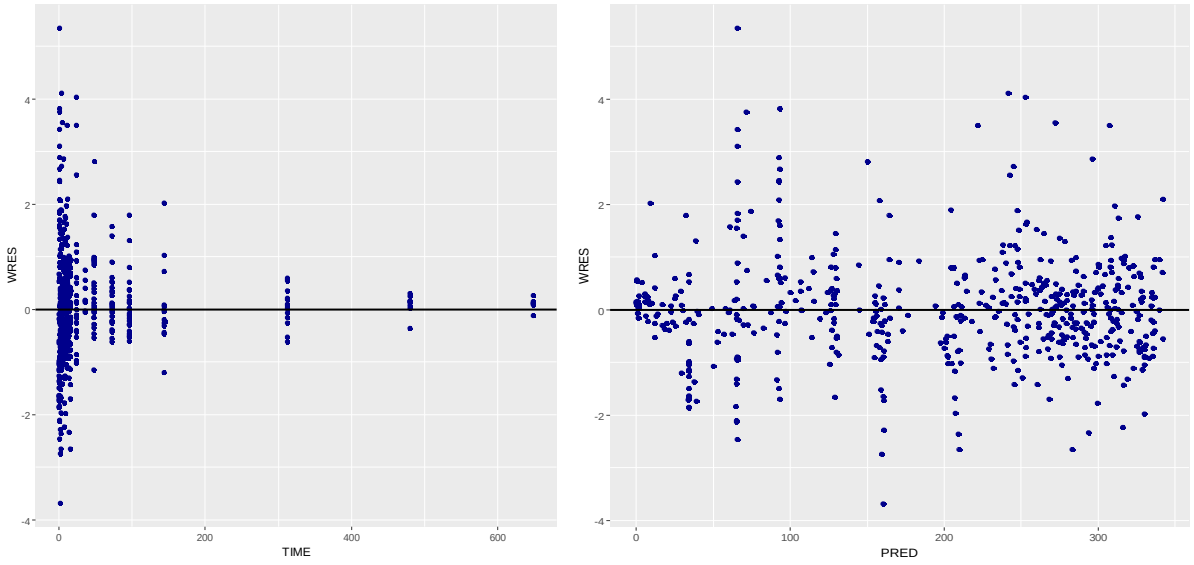
Table 6 FDA generated Population Pharmacokinetic Parameters

Model Parameter	Population Estimate (% SE)	Between subject Variability (% SE)
ka (h^{-1})	0.344 (13)	44 % (14)
Vc (mL)	437000 (5)	24 % (12)
k (h^{-1})	0.02 (10)	56 % (23)
D2 (h)	8.79 (6.0)	Not estimated
F1	0.799 (11)	Not estimated
Covariate model; k*eGFR/42 (42mL/min /1.7m2 is the median of MDRD)		

Source: Page 5 of 24 model simulation report for dose adjustment in renal impairment.
Link: \\cdsesub1\evsprod\nda209410\0000\m2\27-clin-sum\summary-clin-pharm-2.pdf

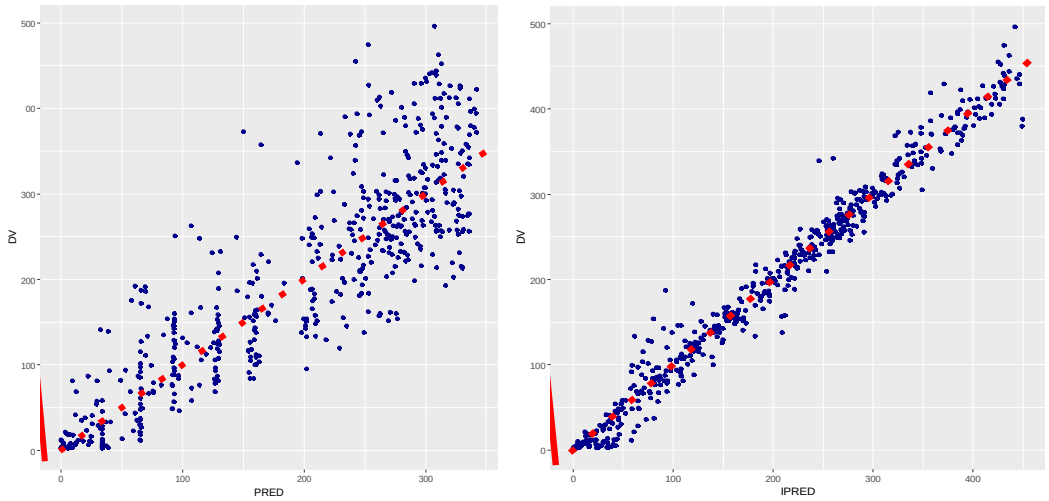
Graphical representations of goodness-of-fit of the base structural population PK model for amantadine are presented in Figure 5 and Figure 6. The observed (DV) vs individual predicted values of amantadine are presented in Figure 7.

Figure 5. Weighted residuals (WRES) vs. time (left) and (WRES) vs. model predictions (right) for the reviewer generated model



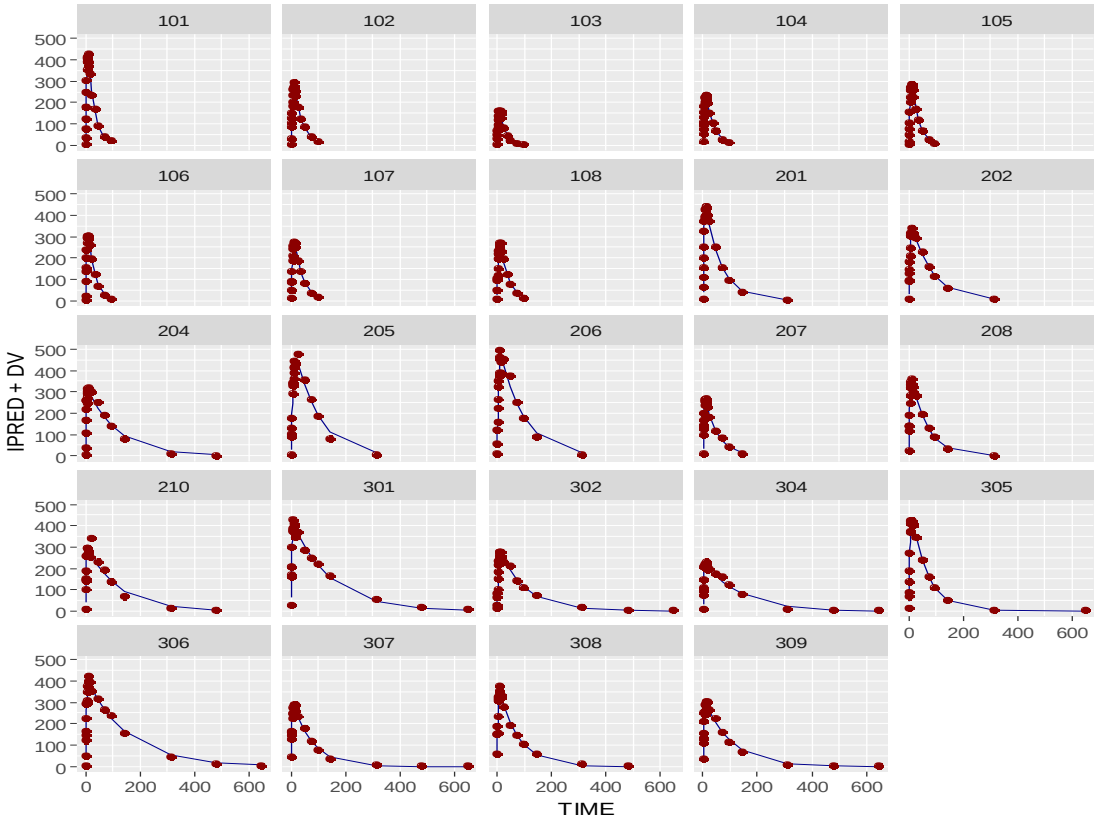
Source: Figure generated by FDA reviewer

Figure 6. Observed (DV) vs population predicted (Left) and individual predicted (Right) amantadine plasma concentrations



Source: Figure generated by FDA reviewer

Figure 7. Observed (DV), individual model predicted (IPRE) amantadine plasma concentrations vs time



Source: Figure generated by FDA reviewer

Identification of target exposure range

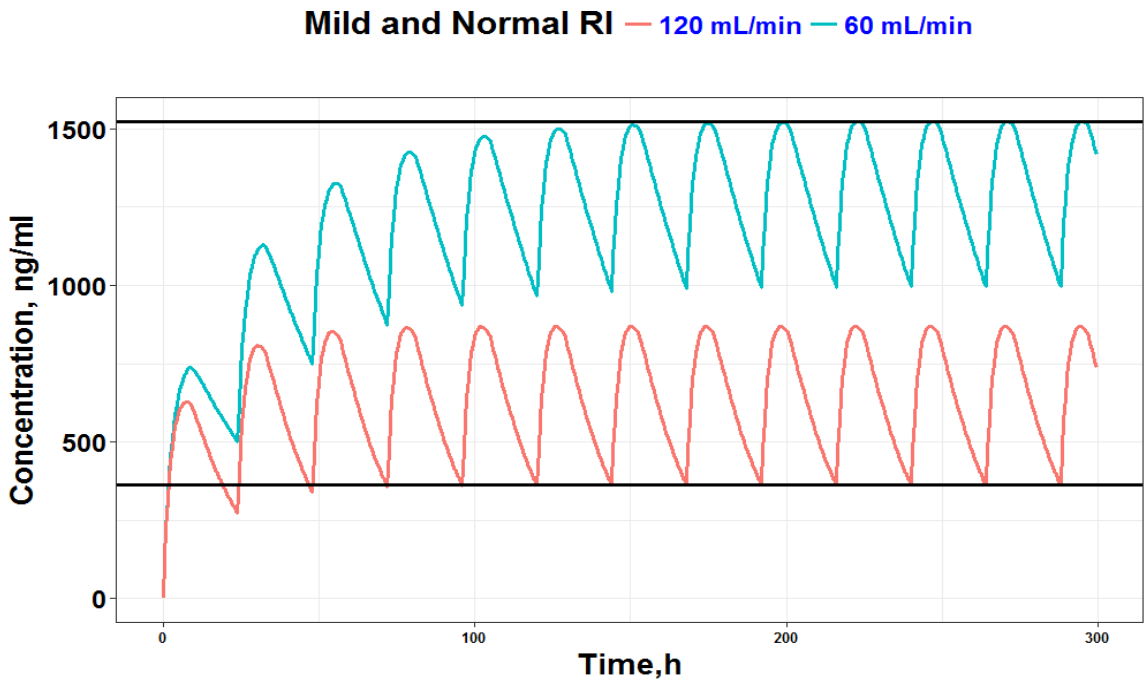
The target exposure range was identified from the groups with normal and mild renal function impairment, [redacted] (b) (4) This was based on the approved label for the RLD, SYMMETREL® syrup, in which the dosing regimen for patients with mild renal impairment and normal renal function is the same. From this, it was concluded that the changes in the exposures in patients with mild renal impairment are considered not clinically significant. Accordingly, the target exposure range was the concentration range bracketed between steady state C_{max} for patients with eGFR=60 ml/min/1.72 m^2 and the steady state C_{min} for patients with mean eGFR of 120 ml/min/1.72 m^2. The FDA reviewer conducted multiple dose PK simulations to predict steady state PK profiles for this group. Eventually, different dosing regimens were simulated to evaluate the optimal regimen for patients with different degrees of renal impairment.

Dosing regimens in the groups with impaired renal function that produced exposures within the target exposure range were considered appropriate.

Simulated steady state pharmacokinetic profiles for renal function groups with various dosing regimens of 400 mg dose strength are presented in Figure 8, Figure 9, and

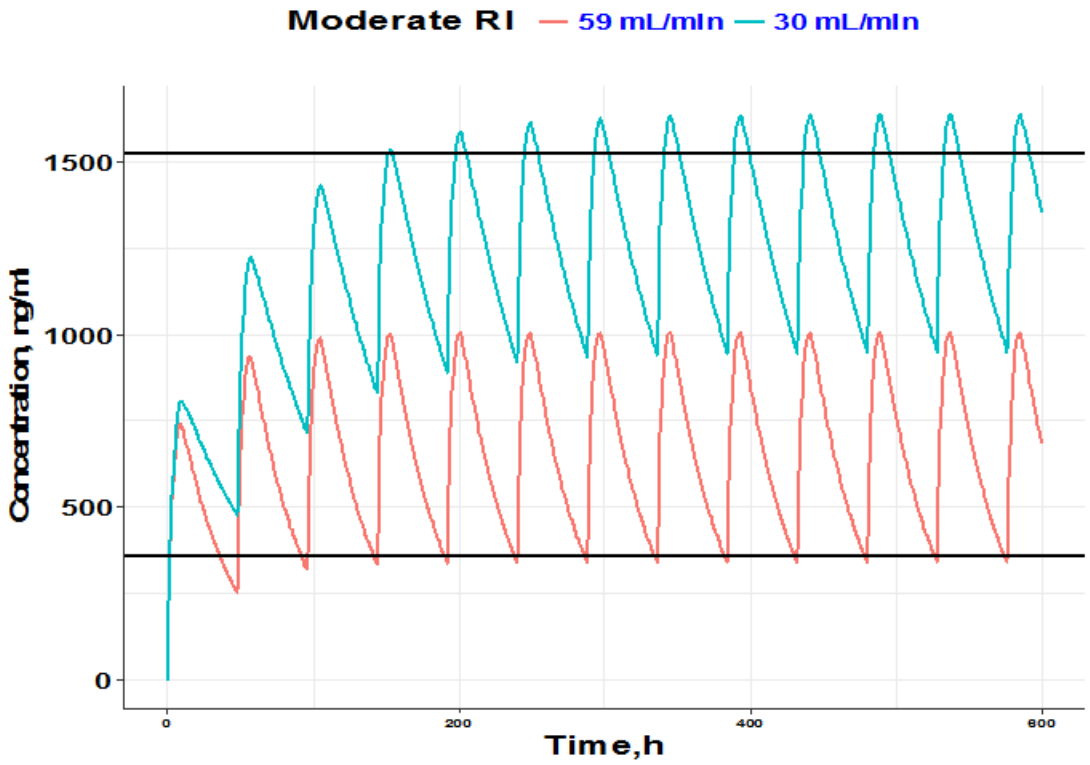
Figure 10. Note that these simulations were also repeated for the lowest dosing strength of 160 mg OSMOLEX ER and similar PK profile shapes and dosing recommendations were obtained.

Figure 8. Steady-state simulated PK profiles after multiple dose administration of 400 mg of OSMOLEX ER every 24 hrs in patients with mild renal impairment (blue line; CRCL=60 ml/min/1.72 m2) and normal (red line; CRCL=120 ml/min/1.72 m2) renal function. Black horizontal lines represent C_{trough} and C_{max} for subject with normal and mild impairment renal function



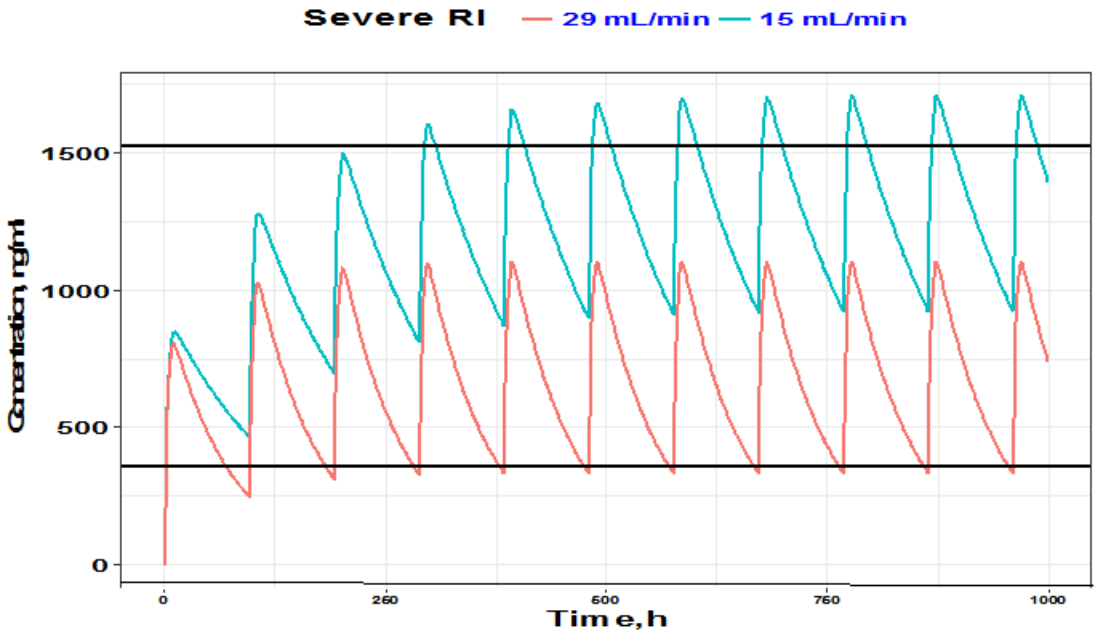
Source: Figure generated by FDA reviewer

Figure 9 Steady-state simulated PK profile after multiple dose administration of 400 mg of Amantadine every 48 hrs in patients with moderate renal function (CRCL=59 or 30 ml/min/1.72 m2). Black horizontal lines represent C_{trough} and C_{max} for subject with normal and mild impairment renal function



Source: Figure generated by FDA reviewer

Figure 10 Steady-state simulated PK profile after multiple dose administration of 400 mg of Amantadine every 96 hrs in patients with severe renal function (CRCL=29 or 15 ml/min/1.72 m2). Black horizontal lines represent C_{trough} and C_{max} for subject with normal and mild impairment renal function



Source: Figure generated by FDA reviewer

Based on the above analysis, the FDA reviewer proposed new dosing recommendations. The Table below provides the recommended regimens for the various renal function groups.

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

Estimated GFR (mL/min/1.73 m^2)		**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

4.3 Renal Impairment Study (OS320-PKP07)

Study report: OS320-PKP07	**Study period:** 2015/06/19-2015/10/09	EDR Link[2]

Title: An Open-Label, Adaptive Pharmacokinetic Single Dose Study of Orally Administered Amantadine HCl Extended-Release Tablets in Subjects with Severe Renal Impairment and Normal Renal Function

Objective:
The primary objective was to assess the PK of Amantadine ER tablet following administration of a single dose in subjects with renal impairment and matched control subjects with normal renal function.
The secondary objective was to evaluate the safety and tolerability of a single oral dose of Amantadine ER tablet in subjects with renal impairment.

Study Design

This was a phase 1, open-label, parallel-group, adaptive, single dose study conducted to evaluate pharmacokinetic, safety, and tolerability, of a single oral dose of 160 mg Amantadine ER tablet in patients with renal impairment and subjects with normal renal function under fasting conditions. This study planned for the enrollment of maximum 24 subjects using an adaptive design that allowed the inclusion of a maximum 2 groups of subjects with different degree of renal impairment and 1 group of healthy volunteers (controls).
There were 8 subjects in each of the following groups based on the renal function at screening:

- Group 1: Severe renal impairment (eGFR < 30 mL/min/1.73m^2 calculated using the modification of diet in renal disease [MDRD] equation) not receiving hemodialysis therapy
- Group 2: Healthy male and/or female with normal renal function (creatinine clearance [CLcr] > 89 mL/min calculated using the Cockcroft-Gault equation
- Group 3: Moderate renal impairment (eGFR 30-59 mL/min/1.73m^2 calculated using the MDRD equation)

A single dose of study drug (Amantadine ER, 160 mg) was administered orally in the morning on day 1, following a 10-hour fast. The subjects were confined in the clinical site until 24 hours following drug administration. Subjects returned to the clinical site on days 3, 4, 5, 7, 14, 21, and 28 days for collection of PK samples. The approximate study duration for subjects in the renal impairment group may have been upto 56 days, including screening.

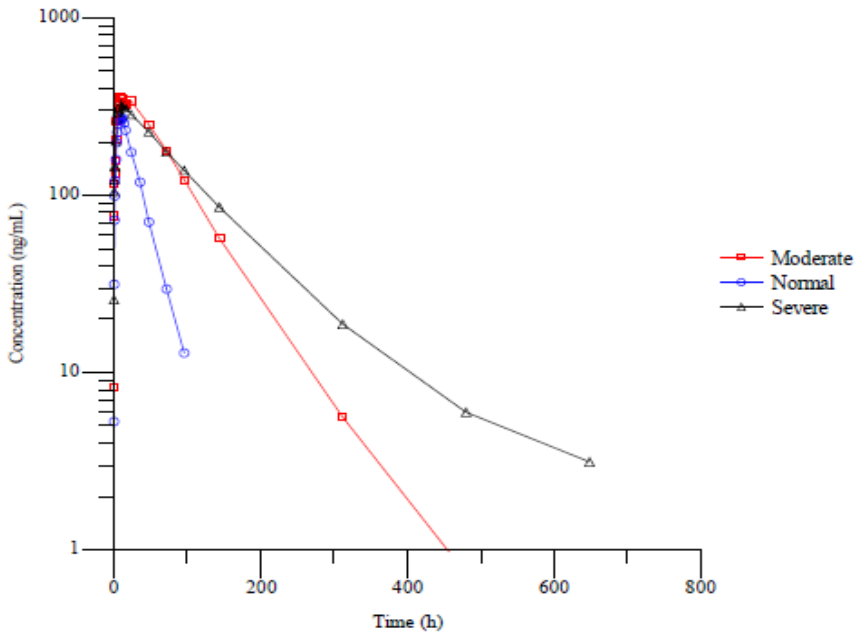
PK Sampling
Blood samples for pharmacokinetic measurements were collected prior to and up to 648 hours (serial sampling) after drug administration for the renal impairment groups, and up to 96 hours post-dose for the normal renal function group.
Statistical Method
Amantadine concentrations in plasma and urine were to be summarized by descriptive statistics, including N, mean, standard deviation, minimum, median, maximum, coefficient of variation (CV%), and geometric mean. Mean and individual plasma concentration-time profiles were to be presented graphically on linear and semi-logarithmic scales. The eGFR and Cockcroft-Gault estimate of the creatinine clearance at baseline were used as separate measures of renal function for a regression analysis to evaluate the relationships between estimated renal function and PK parameters.
Population
24 subjects (18 males/6 females) enrolled and completed the study. Subjects had a median (range) age of 60 (37-73) years, weight 83.2 (55.6-133) kg and BMI of 29.9 (22.3-41.8) Kg/m^2.
Results
Amantadine clearance decreased as the severity of renal impairment increased. Decreased amantadine clearance resulted in a 3 to 4 fold increase in amantadine exposure (AUC) in subjects with moderate to severe renal Impairment. It was concluded that the dosage regimen of Amantadine HCl ER tablet must be adjusted in patients with moderate to severely impaired renal function. Comparison of PK profiles and parameters across different renal function groups are presented in (**Figure 11**; Table 8). Regression analyses, using either eGFR or creatinine clearance with CG as the predictor variable, revealed that C_{max} and AUC values increased and that CLr, Ae(0-t), CL/F and λz values decreased as the severity of renal impairment increased (Figure 12). Arithmetic mean half-life values increased from 18.47 hours for subjects with normal renal function to 116 hours for severely impaired subjects.

Table 8. Summary of Pharmacokinetic Parameter Values of Amantadine following a Single Oral Dose of 160-mg Amantadine Extended-Release Tablets in Subjects with Moderate or Severe Renal Impairment and Normal Renal Function

	Severe eGFR <30 mL/min/1.73m2 n=8		Moderate eGFR 30-59 mL/min/1.73m2 n=8		Normal CLcr >89 mL/min n=8	
Parameter (Units)	**Mean**	**(C.V. %)**	**Mean**	**(C.V. %)**	**Mean**	**(C.V.%)**
C_{max} (ng/mL)	345	22.8	380	21.4	281	26.4
$AUC_{0-\infty}$ (ng·h/mL)	39031	39.9	33066	31.6	10109	26.9
CL/F (L/h)	4.564	29.9	5.475	45.2	17	40.3
λ_z ($hours^{-1}$)	0.0069	34.5	0.0161	34.2	0.0381	14.1
T_{half} (hours)	116	46.6	47	31.4	18	13.2

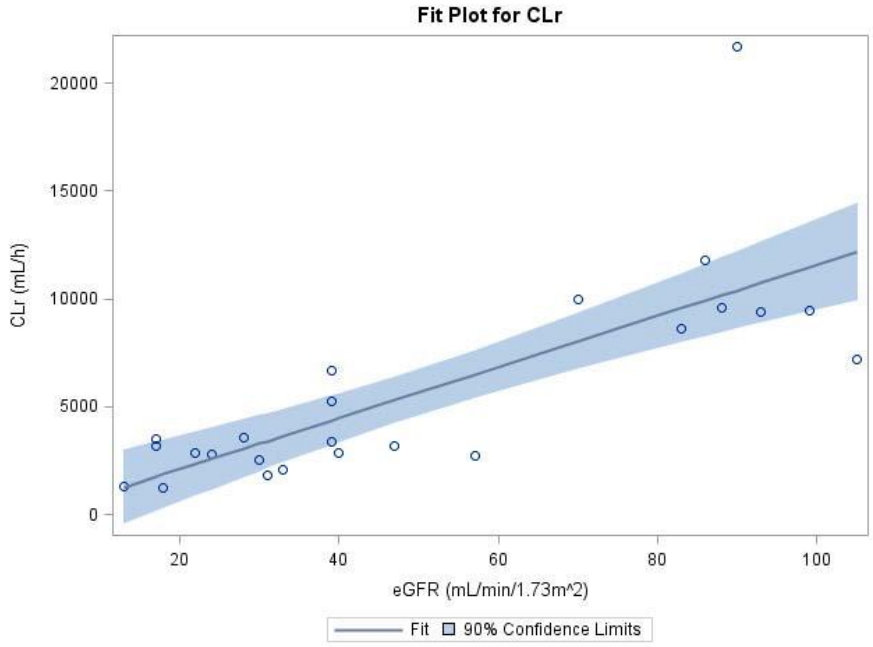
Source: Clinical study report OS320PK07(Table 7, Page 42).

Figure 11. Mean amantadine plasma concentration-time profiles following single dose oral administration of 160 mg ER tablet to fasted subjects with normal renal function and moderately or severely impaired renal function



Source: *Clinical Study Report.* study OS320-PKP07. Figure 2. Page 46

Figure 12. Relationship between amantadine renal clearance and eGFR following a Single Oral Dose of 160-mg Amantadine Extended-Release Tablets in Subjects with Moderate or Severe Renal Impairment and Normal Renal Function



Source: *Clinical Study Report.* study OS320-PKP07. Figure 8. Page 52

Bio-Analytical Assay

	Amantadine
Method	**HPLC-MS/MS**
LLOQ (ng/mL)	2 ng/ml
Range (ng/mL)	1500 ng/ml
Accuracy/Bias	Between run: 88.2 % to 92.5 % Within run: 88.7 % to 93.2 %
Precision	Between run: 1.4 % to 1.9% Within run: 0.6 % to 1.7 %

Reviewer Comment:
The analytical assay method is acceptable.

Safety

Six subjects (25 %) reported AEs (8). Most of these AEs were considered not related to the study drug (63 %). Only 1 subject (4 %) in the healthy group reported AEs that were considered drug-related. All the reported AEs were mild (5 AEs; 63 %) and moderate (3 AEs; 38%) in severity. None of the AEs reported by subjects with renal impairment were considered drug-related. No subject was withdrawn for safety reasons.

Summary
• Amantadine elimination decreased as the severity of renal impairment increased. Reduction in amantadine clearance resulted in a 3- to 4-fold increase in exposure (AUC) in subjects with moderate to severe renal impairment. • Amantadine HCl ER tablet dosage regimen should be adjusted in patients with moderately to severely impaired renal function. • Oral administration of one 160-mg Amantadine ER tablet was generally safe and well tolerated by healthy volunteers and subjects with moderate to severe renal impairment.

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/s/

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