CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-627

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Memantine HCl
NDA:	21-627
PRODUCT (Brand Name):	NAMENDA oral solution
DOSAGE FORM:	Oral Solution
DOSAGE STRENGTHS:	2 mg/ml and 4 mg/ml
INDICATION:	Moderate to severe dementia of Alzheimer's type
NDA TYPE:	3S
SUBMISSION DATES:	5/1/03, 8/28/03
SPONSOR:	Forest Laboratories Inc
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

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1.0 EXECUTIVE SUMMARY

Forest Laboratories Inc. seeks approval for NDA 21-627 (memantine HCl) oral solution in the strengths of 2mg/ml and 4 mg/ml for the treatment of moderate to severe dementia of the Alzheimer's type (DAT). No new clinical pharmacology or clinical studies have been conducted with the oral solution formulation. The dosing and administration is the same as that approved for the memantine tablets (NAMENDA™). The recommended starting dose of memantine is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week. Memantine can be taken without regard to food.

The sponsor seeks waiver for conducting in vivo bioequivalence studies between the immediate release tablet and oral solution formulation of memantine based on the BCS classification of memantine.

Memantine was designated a BCS Class I drug based on its properties of being highly soluble, highly permeable and rapidly dissolving drug product (tablet). In addition to these characteristics the sponsor has demonstrated that the formulation ingredients of memantine oral solution are not likely to affect the bioavailability of memantine from the oral solution.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-I) grants a waiver for conducting in vivo bioequivalence studies between the immediate release and oral solution formulation of memantine based on BCS I classification of memantine. This submission is acceptable from OCPB point of view to support approval of memantine oral solution.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D._____

OCPB Briefing held on 2/6/04
Attendees:Mehta, Sahajwalla, Yu, Kwon, Selen, Powell, Mani, Uppoor, Vaidianathan, Ramachandani, Men, Tandon
In Absentia (provided comments): Lesko, Huang, Malinowski

2.0 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor has not submitted any new information in this application with regards to Clinical Pharmacology and Biopharmaceutics as well as efficacy or safety. The information on pharmacokinetics of memantine is based on the NDA 21-487 for memantine immediate release tablets, which was approved on October 19th 2003. For details on the general clinical pharmacology and biopharmaceutics findings please refer to the Clinical Pharmacology and Biopharmaceutics Review dated October 2nd 2003.

In this current application for memantine oral solution, the sponsor has requested a waiver of evidence of in vivo bioequivalence between memantine immediate release tablets and oral solution formulation based on the aqueous solubility, dissolution and in vitro permeability data. Based on this information, memantine was designated to be a BCS Class I drug (highly permeable, highly soluble and rapid dissolving). Details of this information can be found in the Clinical Pharmacology and Biopharmaceutics review of NDA 21-487 and excerpts attached in Appendix I (repeated from review of N 21-487).

Since the formulation of the memantine oral solution contains excipients that are different from the tablet formulation, the sponsor was asked to justify that the excipients in the oral solution formulation would not affect the rate and extent of absorption.
The excipients used in Memantine HCl Oral Solution are commonly used USP/NF materials. Since memantine is highly soluble at physiological pH range, no surfactants were used. An extensive literature research was done by the sponsor for the excipients used in the Memantine HCl Oral Solution. No decreasing effects on the bioavailability of drug compounds by these excipients could be found except for sorbitol (5 grams), which was reported to decrease the intestinal residence time and decrease the bioavailability (Cmax and AUC) of low permeability drugs such as ranitidine (Hussain et.al. 2001 FDA Science Forum).

In another FDA study with metoprolol a total of 5 grams of sorbitol in oral solution of metoprolol [redacted] did not affect the bioavailability (small effect on Cmax) of metoprolol, a high permeability drug(*Hussain et. al.* AAPS Annual Meeting, 2001)

In another study about 10 grams of sorbitol had no (minimal) effect on bioavailability of theophylline, a highly permeable drug (Fassihi et. al. Int. J. Pharm. 72: 175-178, 1991)

The highest dose of sorbitol in the oral solution of memantine is 1 gram (300 mg/ml [redacted] to obtain a 10 mg dose given a 2 mg/mL strength), which is less than the 5 or 10 grams used in the other studies and moreover memantine is also a highly permeable drug. Therefore, it seems unlikely that sorbitol will have any effect on the bioavailability of memantine from this oral solution.

Other supportive information can be obtained from prior experience with memantine that indicates Merz's tablet and oral solution formulations were bioequivalent (Study MRZ 90001-9201, NDA 21-487). Study MRZ 90001-9201 was a 3-way crossover study in which 12 healthy subjects received 2 x 10 mg memantine tablets, 20 mg of memantine drops (10 mg/mL) and 1 x 20 mg memantine controlled release tablet in a crossover fashion with a 2-week washout period between treatments.

This study has not been reviewed entirely as these formulations are not US formulations, nevertheless, based on the results no differences were observed in the rate or extent of absorption of memantine between the tablet and the oral solution formulations (see Table below). The oral solution formulation contained [redacted] of sorbitol (total dose of [redacted] sorbitol), which indicates that this component of the formulation does not affect the bioavailability of memantine. This information should only be used as supportive information.

Parameter	2 x 10 mg Merz Memantine Tablets (n = 12)	20 mg Merz Memantine Drops (n=12)	90 % Confidence Interval
C_{max} (ng/mL)	26.00 ± 4.07	26.00 ± 4.22	0.93 – 1.07
T_{max} (h)	3.25 ± 1.74	3.33 ± 1.93	-
$AUC_{0-\infty}$ (ng ·h/mL)	1870 ± 352	2230 ± 312	0.99 – 1.21

The sponsor's request for a waiver for conducting bioequivalence study between the approved immediate release tablets and oral solution can be granted because:

- memantine HCl met all the criteria for BCS I classification according to the FDA guidance and
- the formulation ingredients including sorbitol are not likely to affect the bioavailability of memantine from the oral solution formulation.

3.0 QUESTION BASED REVIEW

3.1 GENERAL ATTRIBUTES

3.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: 2 mg/ml and 4 mg/ml oral solution

Indication: Treatment of moderate to severe dementia of Alzheimer's type

Dosage and administration (Sponsor Proposed):

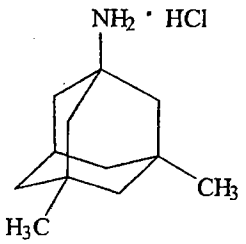
The dosage of memantine hydrochloride shown to be effective in controlled clinical trials is 10-20 mg/day.

The recommended starting dose of memantine is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.

Memantine can be taken with or without food.

Pharmacologic Class: Memantine HCl is a moderate affinity uncompetitive (open channel) NMDA receptor antagonist that binds preferentially to the NMDA receptor-operated cation channels in a use dependent and voltage dependent manner with rapid blocking/unblocking kinetics.

Chemical Name: 1-amino-3,5,-dimethyladamantane hydrochloride with the following structural formula



The molecular formula is $C_{12}H_{21}N.HCl$ and the molecular weight is 215.77.

Physical Characteristics: Memantine HCl occurs as a fine white to off-white powder and

is highly soluble in water,

Mechanism of action: In vitro electrophysiological studies suggest that memantine inhibits NMDA receptor-mediated currents in a use-dependent [i.e., it blocks the receptor channel in the presence of an agonist, e.g., glutamate] and voltage-dependent manner, with rapid receptor-unblocking kinetics. Because of these attributes, memantine can selectively antagonize pathological activation of NMDA receptors without affecting the physiological functioning of the receptor. Physiological activation of NMDA receptors is known to play a critical role in synaptic plasticity processes such as cognition.

In several in vitro and in vivo studies, memantine has been shown to protect neurons from cell death due to excitotoxicity. In addition, memantine attenuates β-amyloid (Aβ)-induced hippocampal cell death (apoptosis) in rats in vivo, and protects cholinergic neurons of the rat nucleus basalis magnocellularis from NMDA-induced neurotoxicity.

Memantine has also been shown to improve learning and memory in animal studies.

Formulation:

Components	*2 mg/ml*		*4 mg/ml*	
	mg/ml	*%w/v*	*mg/ml*	*%w/v*
MEMANTINE HCL	2.00	0.20	4.00	0.40
Sorbitol solution, USP 70%				
Methyl Paraben, NF				
Propyl Paraben, NF				
Propylene Glycol, USP				
Glycerin, USP				
Natural Pepermint flavor				
Citric Acid, USP, Anhydrous				
Sodium Citrate, USP, Dihydrate				
Purified Water, USP				

3.2 GENERAL CLINICAL PHARMACOLOGY

Based on N21-487 for memantine tablets. No new information submitted for N21-627.

3.3 INTRINSIC FACTORS

Based on N21-487 for memantine tablets. No new information submitted for N21-627.

3.4 EXTRINSIC FACTORS

Based on N21-487 for memantine tablets. No new information submitted for N21-627.

3.5 GENERAL BIOPHARMACEUTICS

Based on N21-487 for memantine tablets. The only new information submitted was the rationale that the excipients in the oral formulation would not alter the bioavailability of memantine from the oral solution formulation.

Based on the BCS principles, is memantine a BCS Class I drug? What solubility, permeability and dissolution data support this classification?

The following response is taken from the original N21-487 review:

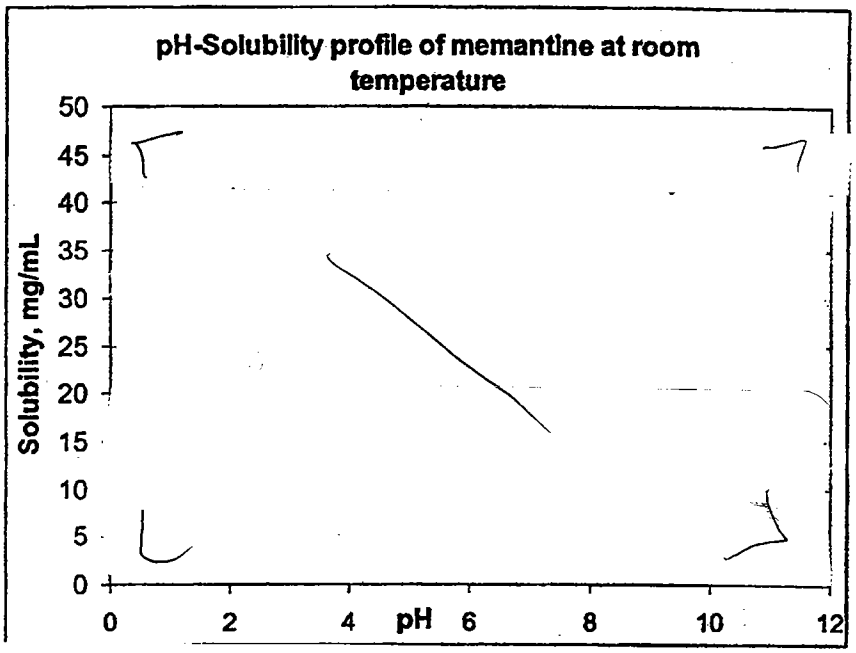
Memantine is highly soluble, highly permeable and rapidly dissolving drug and can be classified as a BCS Class I drug. The following information supports its classification:

Solubility:

The following Table lists the solubility values of memantine HCl at pH's 1.2, 4.5 and 7.0 at 37°C

pH	Solubility (mg/mL)
1.20	31.2 ± 2.6
4.50	36.7 ± 0.7
6.99	38.6 ± 0.1

The pH solubility profile in the entire pH range is shown in the following figure:



Over the pH range 2-9, the solubility of memantine HCl was observed to be about 40-45 mg/mL. At pH's lower than 2 and higher than 9.5, the solubility tended to decrease. The solubilities in the three buffers were similar to that observed in the pH-solubility profile.

According to the BCS, a drug substance is classified as highly soluble, if the highest strength is soluble in less than ——— of aqueous media over the pH range 1-7.5. The highest strength of memantine tablet formulation is 20 mg. If this dissolves in ———, it means that the resultant drug concentration would be ———. The solubility values of memantine HCl were significantly higher than this concentration in the pH range of 1-7.5.
Therefore, memantine can be classified as a highly soluble drug.

Permeability:
Although an absolute bioavailability study was conducted with memantine, the results were not realistic, showing absolute bioavailability of ——— with the 10, 20 and 40 mg tablets of memantine. Hence, in vitro permeability studies were conducted to show high permeability of memantine.

The following Table shows that the permeability of memantine HCl was generally ——— for all the concentrations (expressed as free base). The permeability was not concentration dependent or direction dependent (i.e., AP-BL vs. BL-AP), indicating passive permeability. There was no indication of involvement of any ——— system. In all the cases, the permeability of memantine HCl was greater than the permeability of

metoprolol (a marker for highly permeable compound), indicating memantine HCl to be highly permeable.

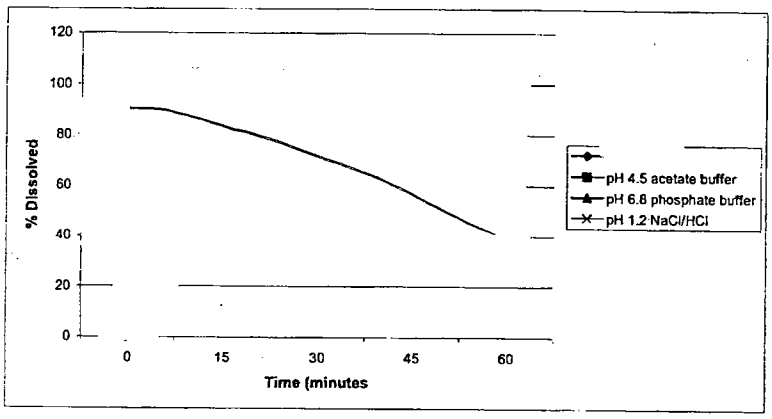
Memantine donor concentration	Memantine AP-BL Permeability x 10^6 (cm/sec)	Metoprolol AP-BL Permeability x 10^6 (cm/sec)	Memantine BL-AP Permeability x 10^6 (cm/sec)	Metoprolol BL-AP Permeability x 10^6 (cm/sec)

The permeability data was also reviewed and conclusions confirmed by Dr. Donna Volpe at the Division of Product Quality and Research (reviewed attached in Appendix I)

The results indicate that memantine could be classified as a "highly permeable" drug according to the Biopharmaceutics Classification System guidance.

Dissolution:

More than — is dissolved by 15 minutes, as shown in the following figure at various pHs.



Hence, memantine tablets can be considered as "rapidly dissolving".

Do excipients in memantine oral solution affect permeability?

The excipients used in Memantine HCl Oral Solution are commonly used USP/NF materials. Since memantine is highly soluble at physiological pH range, no surfactants were used. An extensive literature research was doné by the sponsor for the excipients used in the Memantine HCl Oral Solution.

The excipients in the oral solution formulation not likely to have effect on permeability were:

- Preservatives like methyl [redacted] and propyl paraben [redacted]
- Flavor like natural pepermint [redacted]
- Buffers like citric acid [redacted] and sodium citrate [redacted]
- In addition to these propylene glycol [redacted] and glycerine [redacted] as solubilizers are also not know to effect permeability at the concentrations used.

The following excipient that is likely (reported in literature) to affect permeability was:

- Sorbitol [redacted] present in larger quantity in the oral solution formulation.

In a study sorbitol (5 grams) was reported to decrease the intestinal residence time and decrease the bioavailability (Cmax and AUC) of low permeability drugs such as ranitidine (Hussain et.al. 2001 FDA Science Forum).

In another FDA study with metoprolol a total of 5 grams of sorbitol in oral solution of metoprolol [redacted] did not affect the bioavailability (small effect on Cmax) of metoprolol, a high permeability drug *(Hussain et. al.* AAPS Annual Meeting, 2001)

In another study about 10 grams of sorbitol had no (minimal) effect on bioavailability of theophylline, a highly permeable drug (Fassihi et. al. Int. J. Pharm. 72: 175-178, 1991)

The highest dose of sorbitol in the oral solution of memantine is [redacted] *70%*5 mL to obtain a 10 mg dose given a 2 mg/mL strength), which is less than the 5 or 10 grams used in the other studies and moreover memantine is also a highly permeable drug. Therefore, it seems unlikely that sorbitol will have any effect on the bioavailability of memantine from this oral solution.

Other supportive information can be obtained from prior experience with memantine that indicates Merz's tablet and oral solution formulations were bioequivalent (Study MRZ 90001-9201, NDA 21-487). Study MRZ 90001-9201 was a 3-way crossover study in which 12 healthy subjects received 2 x 10 mg memantine tablets, 20 mg of memantine drops (10 mg/mL) and 1 x 20 mg memantine controlled release tablet in a crossover fashion with a 2-week washout period between treatments.

This study has not been reviewed entirely as these formulations are not US formulations, nevertheless, based on the results no differences were observed in the rate or extent of

absorption of memantine between the tablet and the oral solution formulations (see Table below). The oral solution formulation contained ——— of sorbitol (total dose of —— —— sorbitol), which indicates that this component of the formulation does not affect the bioavailability of memantine. This information should only be used as supportive information.

Parameter	2 x 10 mg Merz Memantine Tablets (n = 12)	20 mg Merz Memantine Drops (n=12)	90 % Confidence Interval
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T_{max} (h)	3.25 ± 1.74	3.33 ± 1.93	-
$AUC_{0-\infty}$ (ng·h/mL)	1870 ± 352	2230 ± 312	0.99 – 1.21

Is it appropriate to grant waiver for oral solution (not pharmaceutically equivalent)?

The regulatory application of BCS Guidance to NDA/INDs applies to:

- Solid Oral dosage forms
- To formulations that are pharmaceutical equivalents

Memantine oral solution is not pharmaceutically equivalent to the approved tablet dosage form due to the difference in dosage form and is also not a solid dosage form. Therefore, extending the BCS application towards a biowaiver is a deviation from the regulatory guidance. However, memantine is a BCS Class I drug and dissolution will not be a rate limiting step in this case as the drug is in the solution dosage form. The gastric transit time is unlikely to be delayed due to a solution dosage from that contains excipients at levels that are not known to affect the bioavailability of highly permeable drugs. Therefore, scientifically, if the excipients are not likely to affect the permeability of the drug, it seems rational to extend the application of BCS class I to the oral solution dosage form.

Overall, is a biowaiver acceptable?

The sponsor's request for a waiver for conducting bioequivalence study between the approved immediate release tablets and oral solution can be granted because:

- memantine HCl met all the criteria for BCS I classification according to the FDA guidance and
- the formulation ingredients including sorbitol are not likely to affect the bioavailability of memantine from the oral solution formulation.

3.6 ANALYTICAL

Based on N21-487 for memantine tablets. No new information submitted for N21-627.

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4.0 DETAILED LABELING RECOMMENDATION

Label same as that approved for Namenda Tablets. No changes in the Clinical Pharmacology section required.

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On Original

10 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

APPENDIX II

FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N21-627	Brand Name	NURVIDA
OCPB Division (I, II, III)	I	Generic Name	Memantine HCl
Medical Division	120	Drug Class	NMDA receptor antagonist
OCPB Reviewer	Veneeta Tandon	Indication(s)	Moderate to severe dementia of Alzheimer's Type
OCPB Team Leader	Ramana Uppoor	Dosage Form	Oral Solution 2 mg/mL and 4 mg/mL
		Dosing Regimen	Target dose 20 mg/day Starting dose 5 mg QD, then 10 mg/day (5 mg b.i.d), then 15 mg/day (5 and 10 mg as separate doses), and finally 20 mg/day (10 mg b.i.d.) Dose should be increased at 5 mg increments
Date of Submission	5/1/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	1/1/04	Sponsor	Forest Laboratories
PDUFA Due Date	3/1/03	Priority Classification	1S
I. Division Due Date			

Background:

Memantine is an NMDA receptor antagonist and was first approved in Germany in 1978. Memantine tablets have been submitted for approval under the tradename ——— (NDA 21-487 under review). The current NDA is for a new dosage form, oral solution.

The sponsor claims that memantine is a BCS Class I drug and hence, is requesting for a biowaiver with the solution formulation. No new information has been submitted as part of this NDA, reference has been made to NDA 21-487.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
AIDS patients				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS	X			Solubility, permeability, and dissolution data provided. Absolute bioavailability is ———
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments				
II.	"X" if yes	Comments		
III. Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
IV. Comments sent to firm ? V.		Comments have been sent to firm (or attachment included). FDA letter date if applicable. • **The pH 4.5 buffer used for solubility determination mentioned in the summary volume is acetate buffer, where as the pH 4.5 buffer mentioned in the study report (volume 88) of N 21-487 is phthalate, please clarify.** • **Suitability of permeability method using 20 model drugs has not been addressed in the study report. If previously studied, please provide the reports.** • **The formulation contains certain excipients that can affect the rate and extent of absorption. The sponsor should provide information that justifies that the excipients used in this product will not have an impact on the bioavailability of memantine (as per the BCS guidance).** • **Please provide the expiration dates for tablets used in dissolution.**		
QBR questions (key Issues to be considered)	• **Is this a BCS Class I drug based on information provided?** • **Can a biowaiver be granted based on the information provided?**			
Other comments or information not included above	• **BCS waiver for Pharmaceutical Equivalents only per the guidance** • **Excipients like Sorbitol affect absorption of the drug.**			
Primary reviewer Signature and Date	**Veneeta Tandon, Ph.D**			
Secondary reviewer Signature and Date	**Ramana Uppoor, Ph.D**			

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

/s/

Veneeta Tandon
2/6/04 03:58:37 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
2/6/04 04:03:56 PM
BIOPHARMACEUTICS