CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-487

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Memantine HCl
NDA:	21-487
PRODUCT (Brand Name):	NAMENDA
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	5, 10, 15 and 20 mg
INDICATION:	Moderate to severe dementia of Alzheimer's type
NDA TYPE:	1S
SUBMISSION DATES:	12/19/02, 4/11/03, 3/5/03, 3/24/03, 8/8/03, 8/13/03, 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

1.0 EXECUTIVE SUMMARY

Forest Laboratories Inc. seeks approval for NDA 21-487 (memantine HCl) tablets in the strengths of 5, 10, 15 and 20 mg for the treatment of moderate to severe dementia of the Alzheimer's type (DAT). Memantine HCl is a moderate affinity uncompetitive NMDA receptor antagonist unlike other drugs for the treatment of DAT that are mainly acetylcholine esterase inhibitors. 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 has submitted 23 in vivo pharmacokinetic studies to support the pharmacokinetics of memantine, out of which 19 studies have been reviewed. Out of these studies only 5 had adequate assay validation reports as per the FDA guidelines on Bioanalytical Validation (these include bioequivalence evaluation, food effect, two drug-drug interaction studies and general pharmacokinetics after a single dose). All other studies had some aspect of the assay validation that was not done as per the current standards. The pharmacokinetic studies conducted earlier in the drug development used — methodology where as the more recent studies utilized — method for the analysis of plasma and urine samples. The sponsor states that some of the assay validation was not per the FDA guidelines on Bioanalytical Validation, but were based on the ICH guidelines at that time. A few studies lacked the quality control runs but had the calibration curves. Some of these studies (not considered pivotal) with less stringent analytical validation reports were accepted based on the following reasons: (a) no drift in the data from assays that had adequate quality control data and used the same methodology, (b) pharmacokinetic parameters across studies at the same dose level had similar parameter values using the same — methodology, (c) parameter values obtained for studies at same doses using the — method were very similar to those obtained using — method.

Some review issues have been identified that impact the quality of the data submitted for review. Key limitations from some studies are:

- One well conducted study and two other pilot studies suggest that the absolute bioavailability of memantine is greater than 100%. The reason for this is not clear.
- The study conducted in the mild and moderately impaired renal patients did not have adequate quality control data to assess the adequacy of the study. Three out of six subjects in the control group had CLr values that were greater than the CLt. Subjects with moderate renal impairment showed a 39% increase in exposure as compared to the normal subjects. Due to the inadequacy of the study, the results from this study cannot be used to propose dosage reduction in subjects with moderate renal impairment. —
- Adequate characterization of the extent of renal elimination of memantine has not been elucidated due to conflicting results from 3 studies. A lack of study in hepatic impaired subjects is not justified based on the data provided.
- There is inadequate representaion of the elderly population in the traditional pharmacokinetic studies. There were only 6 subjects that were ≥ 65 years across all pharmacokinetic studies with the highest age of 71 years. The mean age of Alzheimer's patients is >75 years. However, there is reasonable pharmacokinetic data in this age group in Phase 3 clinical trials.
- A good estimation of accumulation cannot be obtained from the multiple dose studies as plasma samples were not taken on Day 1 of the Study. Assuming linear pharmacokinetics the accumulation factor after multiple doses has been predicted. A multiple dose study with the proposed dosing regimen (titrated regimen with a

starting dose of 5 mg/day and escalated on weekly basis up to 20 mg/day) has not been conducted. Multiple dose study has been conducted with BID dosing of 1x10 mg memantine for 18 days (20 mg/day)

Dosing adjustments may be needed for the following populations/situations:

(a) Subjects with renal impairment may show an increase in exposure as compared to the normal subjects. Dose reduction may be necessary, although adequate data is not available at this time

(b) Diet, drugs or disease states (such as renal tubular acidosis or severe infection of the urinary tract) that alter the urine pH to make it alkaline can reduce the clearance of the drug. Caution should be exercized in these situations.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-I) has reviewed NDA 21-487. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided that the sponsor addresses the comments and Phase IV recommendations and agrees with the Agency's label recommendations. The labeling changes have been made to reflect the accuracy of the results obtained or to delete information from studies that were not conducted adequately.

The Phase IV Commitment recommendations on page 4 and labeling comments outlined in the Detailed Labeling Recommendation section of the review on page 46 should be conveyed to the sponsor.

The following comments should also be conveyed to the sponsor:

- For future NDA applications, the sponsor should have adequate assay validation reports as per the FDA guidance on Bioanalytical Method Validation submitted along with each study report. Any deviations from the validated method, should be clarified within the study report. All studies should have their own standard curves and quality control data for the analytical runs.
- CYP 450 inhibition studies with memantine have been conducted with liver from only one donor. In future such studies should be conducted with more than one donor as there can be large variability in CYP enzymes in livers from different donors and one donor may not represent this. Further all CYP isoenzymes may not be expressed in one donor. No information has been provided on the induction potential of memantine.
- When the dosing recommendations for the memantine tablets is to give them in divided doses with a maximum of 20 mg/day (as 10 mg BID), it is not clear why the sponsor would propose to market the 15 and 20 mg tablet strengths. Please justify the marketing of these two strengths.

1.2 PHASE IV COMMITMENTS

- The ongoing renal impairment study should be submitted within 1 year from the date of approval and the label should be modified based on the results of the study.
- About 57-82% of memantine is eliminated intact in the urine. This shows that about 18-43% of memantine is eliminated through the metabolic route. The extent of renal elimination of intact memantine is not clear at this time due to conflicting results from the studies, the sponsor should conduct a study in subjects with moderate hepatic impairment compared to normal subjects. This aspect could be addressed if there are adequate number of hepatic impaired subjects in the clinical trials.
- The sponsor should evaluate the induction potential of memantine.

/S/ 10/2/03

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