CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-525

SUMMARY REVIEW

MEMORANDUM

DATE: June 13, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-525

SUBJECT: Action Memo for NDA 22-525, for the use of Namenda XR (memantine hydrochloride) extended release capsules

NDA 22-525, for the use of Namenda XR (memantine hydrochloride) extended release capsules, for the treatment of moderate to severe dementia of the Alzheimer's type (AD), was submitted by Forest Laboratories, Inc., on 8/20/09. Namenda (immediate release) tablets are currently approved for patients with moderate to severe AD at a maximum dose of 10 mg BID. The application contains the results of a single placebo controlled trial of the XR formulation in patients on stable doses of an acetylcholinesterase inhibitor (AChEI), that purports to demonstrate the effectiveness of a single daily dose of 28 mg, as well as safety data from this trial, from open-label trials in patients with AD, and from trials in non-AD patients of the immediate release Namenda at doses greater than 20 mg/day. The sponsor has also submitted the requisite CMC and pharmacokinetic data.

The application has been reviewed by Dr. Ranjit Mani, medical reviewer, Dr. Julia Luan, statistician, Dr. Sherita McLamore, chemist, Dr. Irene Chan, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Antoine El-Hage, Division of Scientific Investigations (DSI), Dr. Xikui Chen, DSI (Bioequivalence Branch), Drs. Huixia Zhang, and Hao Zhu, Office of Clinical Pharmacology. The team recommends that the application be approved.

I agree.

As described in detail by Drs. Mani and Luan, Study 50 randomized 677 patients, with 661 included in the primary intent-to-treat population, to receive either Namenda XR 28 mg, once a day, or placebo, for 24 weeks. The study was conducted at 83 centers in the US, Mexico, Argentina, and Chile. Patients were started on 7 mg/day for a week, and were titrated up by 7 mg/day each week, until the target dose of 28 mg given once a day. The primary outcomes were the mean change from baseline on the Severe Impairment Battery (SIB), the cognitive measure used in the trials supporting approval for immediate release Namenda, and the CIBIC-plus, also a standard measure in these trials. The comparisons between placebo were statistically significant for both outcomes (LS mean difference of 2.8, p=0.001 and mean difference of 0.3, p=0.008, for the contrasts on SIB and CIBIC-plus, respectively).

As Drs. Mani and Luan note, there was a difference in the estimate of the treatment effect on the SIB between countries.

Specifically, there were 38 (46% of the total) centers in the US, 23 in Argentina, and 11 each in Chile and Mexico. There were 170/661 (26% of the total) patients in the US. As Dr. Luan notes, the estimate of the treatment effect (the difference in mean change from baseline between drug and placebo) on the SIB by country were as follows:

US	0.8
Mexico	3.0
Chile	1.5
Argentina	3.3

The sponsor suggested analyses that included additional covariates to attempt to address (correct for) this "imbalance". Dr. Luan notes that the results of these analyses do not differ materially from the protocol-specified analyses.

Regarding safety, there were no unexpected adverse events noted, nor any unacceptable increased frequencies of any adverse events known to be associated with Namenda. It is worth noting that the 24 hour AUC of Namenda XR, given as 28 mg once a day is about 1.3 times that of immediate release Namenda, 10 mg BID, and the steady-state Cmax of the XR is about 1.5 times that of the immediate release tablet given as 10 mg BID.

The OCP review notes a moderate dose-dumping effect on all dose strengths of 20% v/v alcohol at 2 hours, and a pronounced effect at 40% v/v ethanol at 30 minutes.

Finally, the sponsor has performed a bioequivalence study to compare the clinically studied XR formulation to the to-be-marketed formulation. Dr. Chen of the Bioequivalence Branch of DSI noted that the inspection of that study revealed:

"The integrity and validity of all standard curves used in the analysis of study subject plasma samples in Study MEM-PK-17 cannot be confirmed as the source records related to the preparation of calibration standards were not maintained at Forest Research Institute and were not available for FDA audit (see discussion in 483 Item1)."

The sponsor responded to the deficiencies noted in the 483 with an explanation of how the plasma standard curves were prepared, and that all steps except the last step in their preparation were documented in the Sponsor's notebooks. Chromatograms for the standard curves were available. The OCP reviewers find this response acceptable.

There were no new toxicology studies submitted in this application. However, we had been aware of a report in the literature of a single dose study of the combination of memantine and donepezil that resulted in extensive "Olney"-type lesions. Though memantine, by itself, was known to have caused these lesions, the pathology in the combination study was more extensive than had occurred with memantine alone, and occurred at a lower dose of memantine when given alone. Because of this finding, we had asked the sponsor to perform a 28 day combination study. This study detected the lesion, but the pathology appeared to be considerably less severe and extensive than the results of the single dose combination study. For this reason, it was postulated that the lesion may, in fact, be more severe after a single dose than after repeated dosing. Because of this, Drs. Freed and Hawver have recommended that the sponsor repeat the single dose combination study (the first study had significant flaws), and this will be made a post-marketing requirement (PMR).

Comments

The sponsor has submitted a single controlled trial that they conclude provides substantial evidence of effectiveness for Namenda XR as a treatment for patients with moderate to severe AD. In addition, they have submitted safety experience in patients receiving Namenda XR 28 mg, given once a day, from this trial as well as from extended, open-label studies. Further, they have provided evidence of safety from studies with the immediate release Namenda at doses greater than the approved 20 mg/day (10 mg given BID). This data is presumed necessary because the Namenda XR 28 mg dose gives an AUC about 1.3 and a Cmax about 1.5 times greater than the 10 mg BID dose of the immediate release Namenda.

I agree that the data submitted establish the effectiveness of Namenda XR. I acknowledge, of course, the finding that the estimate of the treatment effect is smaller in the US than in other countries, but this poses no bar to approval in my view. As Dr. Mani notes, such disparate estimates of a treatment effect in different countries is not particularly unusual, and inspections of two sites in Argentina revealed no important irregularities.

The sponsor has proposed that Namenda XR be approved as a treatment for patients with moderate to severe AD. This would mirror the current indication for immediate release Namenda. However, immediate release Namenda was studied as monotherapy and adjunctive therapy with AChEIs; this supported the "global" claim it now has. Namenda XR has been studied only as adjunctive therapy.

Despite the fact that Namenda XR has been studied only as adjunctive therapy, I believe it is reasonable to grant it a "global" claim, as with the immediate release product. We come to the current application with the established fact that

memantine is an active moiety in the treatment of AD, both as mono- and adjunctive therapy. The purpose of requiring a controlled trial with Namenda XR is to establish that memantine remains effective with this new pattern of absorption provided by the XR formulation. We have concluded that this has been shown, for the reasons given above. Although it is true that we do not have information about the comparative effectiveness of these formulations (although, as has been also shown, the exposure with the XR formulation is greater than with the 10 mg BID dose of the IR formulation, suggesting that the XR should be at least as effective as the IR), and we do not have empirical evidence of the XR formulation's effectiveness when given as monotherapy, I believe it is perfectly reasonable to conclude that it will be effective as monotherapy, given the "proof of principle" of its effectiveness as a product, obtained in the adjunctive study.

I also agree that the safety of Namenda XR has been established. The data from the controlled trials at the proposed dose are quite re-assuring, despite the fact that the exposures are greater than that produced by the current approved dose of immediate release Namenda. The safety experience from controlled trials at higher doses than 10 mg BID of the immediate release Namenda, although admittedly obtained in populations less fragile than patients with AD, is also somewhat supportive of the safety of the proposed XR dose.

I am somewhat concerned about the dose-dumping effect of alcohol on Namenda XR, especially at higher concentrations of alcohol. However, both the OCP reviewer and Dr. Mani are reassured that the safety of Namenda XR is still assured if the entire dose was absorbed rapidly. Further, it is unlikely that the population for whom the product is intended will frequently ingest alcohol. For these reasons, the in vitro dose dumping effect should not preclude approval, nor need there be specific language in labeling warning against ingesting alcoholic beverages.

I also agree with the OCP reviewer that the conclusion reached by DSI about the bioequivalence study need not preclude approval; that is, I agree that the sponsor has adequately addressed DSI's concern.

Finally, Dr. Chan has numerous comments pertaining to requested changes in the carton and container labeling. These have been discussed with the sponsor and they have made the requested changes.

For the reasons described above, then, I will issue the attached Approval letter with agreed-upon product labeling.

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