CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-992

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 20, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for desvenlafaxine sustained release (DVS-SR) tablets for major depressive disorder (MDD) (short-term efficacy only)

TO: File NDA 21-992
[Note: This overview should be filed with the 8-29-07 resubmission of the NDA in response to FDA's 1-22-07 approvable letter.]

1.0 BACKGROUND

DVS-SR is an extended release formulation of desvenlafaxine, an SNRI-type antidepressant. It is the major active metabolite of venlafaxine and has essentially the same pharmacological profile as venlafaxine XR which is approved for the treatment of MDD, GAD, Social Anxiety Disorder, and Panic Disorder. This NDA, as resubmitted, seeks a claim for the short-term [redacted] treatment of MDD, in a dose range of 50 to 200 mg/day.

We issued an approvable letter for DVS-SR on 1-22-07. The letter cited the following deficiencies:

-Several CMC issues needed to be addressed
-Needed agreement on dissolution method and specification
-Risk management plan: the letter posed a number of questions and made a number of requests regarding a risk management plan for possible overdose toxicity (related to concerns raised about the parent compound, venlafaxine)
-Post Marketing Commitments:
    -Longer-term efficacy studies
    -Pediatric studies
    -Further exploration of dose response for efficacy
    -Repeat embryo-fetal toxicity study
-The letter included draft labeling
-The letter included a number of carton and container label recommendations
-The letter asked for both regulatory and safety updates

The sponsor submitted a response to the approvable letter on 8-29-07. The response included:

-Efficacy results from 2 short-term MDD trials (332 and 333) involving a lower dose than had been previously studied (50 mg/day)
-Efficacy results from a randomized withdrawal study (study 302)
-A safety update
-Revised DVS-SR labeling in the PLR format
-A risk management plan
-A world literature update

2.0 CHEMISTRY

All CMC issues have now been addressed, and the CMC group has recommended an approval action.

3.0 PHARMACOLOGY

The only pharmacology/toxicology issue remaining to be resolved at the time we issued the approvable letter for this NDA is still pertinent, i.e., the need for a standard embryofetal toxicity study. The sponsor did not make an effective argument against the need for such a study, and we have asked them to commit to conducting such a study post-approval. They have agreed to conduct this study. Thus, there are no remaining pharmacology/toxicology issues.

4.0 BIOPHARMACEUTICS

OCP recommends approval of this NDA since agreement has been reached on dissolution specifications and labeling. They have no recommendations for phase 4 commitments.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

In the original NDA, the sponsor provided results for seven phase 3 double-blind, randomized, parallel-group, placebo-controlled, short-term (8-week) efficacy and safety trials. These studies evaluated DVS-SR doses in adult outpatients with MDD in a range of 100 to 400 mg/day. The primary endpoint was change from baseline to endpoint in HAMD-17 total score. Two of these studies (304 and 223) were clearly negative, and were not further reviewed. The 5 remaining studies were the focus of our review: 2 fixed dose studies (306 and 308) and 3 flexible-dose studies (309, 317, and 320). Two of these 5 studies (the 2 fixed-dose studies, 306 and 308) were

positive on the protocol-specified analysis (LOCF) for the primary endpoint. The 3 flexible-dose studies were not nominally positive, however, 2 (309 and 320) were positive on alternative analyses (OC, MMRM, and ETRANK) that seemed more appropriate given the dropout patterns in these trials. Thus, I agreed with the statistical reviewer that these 2 trials could be considered strongly supportive. Had a more rational SAP been in place from the beginning, these would have been 2 additional positive trials. As noted above, FDA's approvable letter requested that the sponsor further explore dose response at lower doses and provide the results of a maintenance study.

In response, the sponsor provided the results of 2 short-term (8-week) efficacy studies involving DVS-SR doses of 50 and 100 mg/day (studies 332 and 333) and the results of a randomized withdrawal study involving doses of 200 and 400 mg/day (study 302). This study had been designed and conducted before the sponsor discovered that much lower doses of DVS-SR were equally efficacious. Given that the doses used in the maintenance study were much higher than justified, based on the positive results from the 2 newer short-term trials at lower doses, we decided not to review the results from study 302.

Studies 332 and 333 were double-blind, randomized, parallel-group, placebo-controlled, short-term (8-week) efficacy and safety trials. These studies evaluated DVS-SR doses in adult outpatients with MDD at fixed doses of 50 and 100 mg/day. The rationale for including the 50 mg/day group was that, in the earlier studies, patients in the higher dose groups had higher dropout rates for adverse events. The primary endpoint was change from baseline to endpoint in HAMD-17 total score, and CGI-I was the designated key secondary endpoint. The primary analysis for the primary endpoint was ANCOVA (LOCF) with treatment and site as factors and baseline scores as the covariate. CMH was the primary analysis for the CGI-I data. Closed testing procedures were used to adjust for multiplicity in doses and endpoints. Study 332 was conducted in the US and study 333 was conducted in Europe and South Africa.

For study 333, the results on the primary endpoint in the primary analysis were positive for both the primary and secondary endpoints, with no apparent advantage for the higher dose compared to the lower dose. The results for this study were also positive for both doses in sensitivity analyses, i.e., OC analyses and MMRM analyses.

For study 332, the results on the primary endpoint in the primary analysis were positive for the 50 mg/day group, but just missed significance for the 100 mg/day group ($p=0.065$). However, the results for this study were positive for both doses in sensitivity analyses, i.e., OC analyses and MMRM analyses. This study was not positive, however, on the key secondary endpoint, i.e., CGI-I, for either the 50 or 100 mg/day group. Dr. Chen, the statistical reviewer, was somewhat critical of study 332 because of the fact that a small percentage of patients (about 8%) had assessments at weeks 5 and 7, i.e., these were not scheduled visits. The sponsor explained that these were essentially late visits, i.e., patients had missed scheduled appointments by a few days. When Dr. Chen excluded these patients from the analysis, the p-values were just beyond the nominal level for declaring the study positive, at least in the primary analysis. It was still positive on the 2 sensitivity analyses.

Comment: I disagree with Dr. Chen's exclusion of these patients for having visits that were late by several days. There isn't any imaginable way this could be considered a bias. Furthermore, I am inclined to rely less on the primary analysis than on the sensitivity analyses, for the same reasons we relied on the sensitivity analyses for studies 309 and 320. The dropout pattern for study 332 was similar to that in those studies, i.e., the dropout rate for adverse events for the 100 mg/day group was higher than for the 50 mg/day group and the placebo group, so the LOCF analysis would bias the results against the higher dose group. The MMRM analysis is less likely to do that and, therefore, is a preferable approach, in my view. Thus, I consider study 332 positive for both the 50 and 100 mg/day doses, and a replication of the finding from study 333, at least for the primary endpoint. But, as was true for study 333, there was no apparent advantage for the 100 mg/day group compared to the 50 mg/day group.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

DVS-SR has now been evaluated for efficacy in a dose range of 50 to 400 mg/day. It appears to be an effective antidepressant at 50 mg/day, and there appears to be no indication of an advantage of doses higher than 50 mg/day. The sponsor is recommending a target dose of 50 mg/day, [redacted] I don't object to permitting dosing up to 100 mg/day if, in the judgment of the clinician, such a dose is needed. However, I am not inclined to accept 200 mg/day as the maximum recommended dose, especially given the clear dose dependence for adverse events, including increases in blood pressure. However, labeling will need to be clear that no advantage of doses higher than 50 mg/day was demonstrated, while adverse events worsen as the dose is increased. The sponsor should be asked to commit to a fixed dose study at the lower end of the dose response curve to better establish efficacy at the lower end, i.e., they should look at least down to 25 mg/day.

Secondary Efficacy Variables

CGI-I was the designated key secondary endpoint for these new studies. For 3 of the 4 relevant studies, the results favored the CGI-I for both the 50 mg/day doses and the higher doses in those studies. I feel these results are sufficient to support inclusion of findings for this key secondary endpoint in labeling.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive depression trials.

Duration of Treatment

As noted, we have decided not to review the results of the randomized withdrawal study (302) because the doses used (200 and 400 mg/day) are not relevant to the much lower doses now found to be relevant for treating MDD. We will request that they agree to conduct a maintenance study at appropriate doses as a phase 4 commitment.

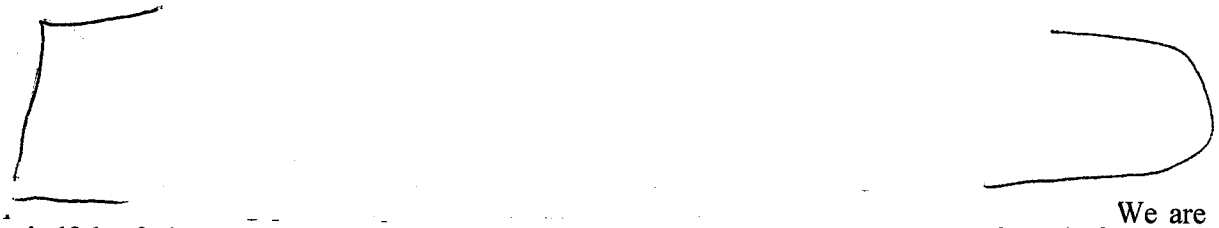
5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of efficacy of DVS-SR in the treatment of MDD.

5.2 Safety Data

5.2.1 Expanded Database

The expanded safety database for this resubmission of the NDA included safety data for a total of n=3,292 subjects exposed to DVS-SR. This included data from the 2 new studies (332 and 333), as well as studies 302 and 303. In addition, the sponsor provided integrated safety presentations for the entire expanded database. Overall, Dr. Levin's review of these data did not reveal any new or unexpected findings. Furthermore, as expected, the new data for the 50 mg/day dose suggested that this dose is better tolerated than the higher doses.



We are mindful of the modest hypertensive effect of this drug (at higher doses) and the modest hyperlipidemic risk, however, we felt those risks could be handled in labeling (both can be treated, or even better, managed with lower doses). Thus, we are not requiring any longer-term safety data.

The sponsor submitted a risk management plan in response to the approvable letter, and this was reviewed by OSE. However, their review with recommendations was not completed until 2-19-08. In essence, they have no comments on the risk plan, but instead, they repeat earlier recommendations for much stronger labeling regarding a theoretical risk of overdose toxicity. Their recommendations include a black box warning regarding overdose toxicity and second line status for DVS-SR. These are similar to earlier recommendations made by OSE for venlafaxine, and unanimously rejected by DPP staff, including myself. The finding of a possibly greater risk of overdose toxicity with venlafaxine compared to SSRIs is based on an observational study in the UK, however, other data suggest that venlafaxine-treated patients have a higher pre-existing risk of suicide than other depressed patients, i.e., there is already differential prescribing. Thus,

there is not a sufficient basis for the kinds of labeling changes suggested by OSE, in the view of DPP staff. The venlafaxine findings are described in the Overdosage section of DVS-SR labeling, and we feel this sufficiently addresses this issue.

5.2.2 Conclusions Regarding Safety of DVS-SR in the Treatment of MDD

I agree with Drs. Levin and Zornberg that the adverse event profile for DVS-SR is quite similar to that seen for venlafaxine XR, and can be adequately characterized in labeling.

5.3 Clinical Sections of Labeling

We made a number of modifications to the sponsor's proposed labeling, and have now reached agreement on final labeling.

6.0 WORLD LITERATURE

The sponsor provided updated literature references that were reviewed by Dr. Levin. He has indicated that they provide no new information that would change his conclusions about the safety of DVS-SR that would impact on its approvability or on labeling.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, DVS-SR is not approved anywhere at this time for the treatment of MDD.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This application was not referred to the PDAC for review for the following reasons: The efficacy endpoints were clear and easily measured. The evaluation of safety did not reveal any concerning safety signals that were not already known for the parent drug, venlafaxine, which has been approved and marketed for a number of years, and the design and results of the efficacy trials did not pose particular concerns. Thus, this application did not have any controversial issues which would have benefited from advisory committee discussion.

9.0 DSI INSPECTIONS

No additional inspections were requested for the additional studies submitted in response to the approvable letter.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling

As noted, we have reached agreement with the sponsor on final labeling.

10.2 Foreign Labeling

DVS-SR is not approved anywhere at this time for the treatment of MDD.

10.3 Approval Letter

The approvable letter includes our proposed labeling and requests for phase 4 commitments. These include a lower dose efficacy study, a maintenance study at appropriate doses, additional studies with specific assessments for sexual dysfunction, pediatric studies, and an embryofetal toxicity study.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Wyeth has submitted sufficient data to support the conclusion that DVS-SR is effective and acceptably safe in the treatment of MDD. As noted, we have reached agreement on final labeling and on phase 4 commitments. Thus, I recommend that we issue the attached approval letter along with the agreed upon final labeling.

cc:
Orig NDA 21-992
ODE-I/RTemple
HFD-130
HFD-130/TLaughren/MMathis/GZornberg/RLevin/RGrewal

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

/s/

Thomas Laughren
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MEDICAL OFFICER