

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-992

OFFICE DIRECTOR MEMO

Memorandum

Date: February 29, 2008
From: Robert Temple, MD
Subject: Approval of desvenlafaxine sustained release (DVS-SR, Pristiq)

Desvenlafaxine is the principal active metabolite of venlafaxine, a long-marketed SNRI antidepressant. The product is an extended release tablet for once daily use. With respect to effectiveness and safety, I have little to add to Dr. Laughren's, Zornberg's and Levin's reviews. This application is, however, a striking example of inadequate initial dose-finding, now at least substantially repaired. A likely reason was an attempt to give doses similar to venlafaxine, recommended at 75 mg usually but going to 150-225 mg if "needed." There appears to be few data from fixed dose dose-response studies. The initial work up at 100-400 mg/day, which included some fixed dose D/R data showing no DR from 100 to 400 mg resulted in a substantial rate of dropouts and troublesome ADR's. In the higher dose studies, 15% of patients dropped out for ADR vs 4% on placebo, and there was a high rate of nausea, dry mouth, sweating, asthenia, ejaculation abnormality, tremor, (Levin 8/29/06 MOR). There is a small increase in BP (mean 3.5-4/2-2.5), similar to venlafaxine, that is somewhat dose-related, with 4% of 400 mg patients having BP ≥ 90 and ≥ 10 mmHg above baseline compared with about 1% on lower doses.

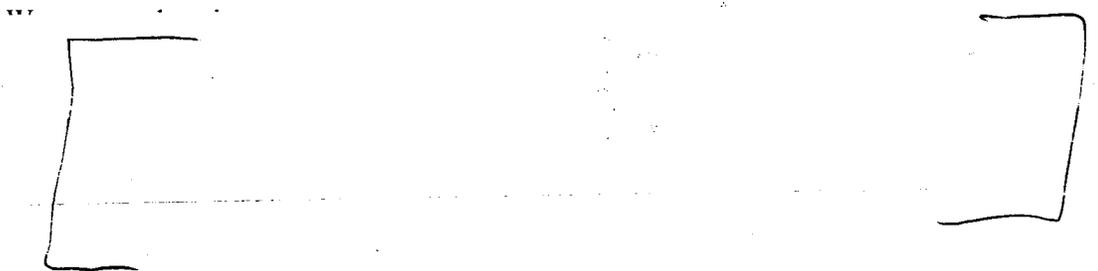
The new dose-response studies, 332 and 333 were good-sized (about 150 per group) 8 week comparisons of placebo, 50 mg, and 100 mg. There is no real hint of any effect until week 4 (Dr. Levin's 1/28/08 review, p 10) and the 100 mg dose does not work faster or better. There is no argument about which analysis shows an effect at 50 mg (all do) and I agree with Drs. Laughren, Zornberg, and others, that the LOCF with all patients (not dropping two with late visits; we'd certainly never let the sponsor do that) and the modeled (MMRM) analyses show persuasively that both doses were effective. The effect on the Ham-D was supported by the effect on CGI in study 333, but not in 332 where the Ham-D effect was smaller. The mean Ham-D effect in both trials was modestly greater than placebo, about 1.5-2.5 points and the full effect was not seen until weeks 6 and 8 (Dr. Levin's tables p 10 of 1/22/08 review). These effects are on the low side of usual, but there are no active control groups in these studies. The effect sizes at higher doses (these doses were not included in the recent trials), were not notably larger. For the two fixed dose D/R studies of adequate size.

- Study 306 showed effect sizes of 2.8, 1.9, and 2.8 for 100, 200, and 400 mg, respectively.
- Study 308 showed effect sizes of 3.3 and 2.8 for 200 and 400mg

In 4 flexible dose studies (100-200, 200-400) results were mostly NS on initial analysis (although 150-225 mg venlafaxine was effective in one study (317), with mean effect sizes in the studies of 0.7, 0.9, and 1.4 points, and we eventually concluded that some of the other analyses were persuasive.

Conclusion:

Desvenlafaxine is effective at 50 mg, with no added effect at 100 mg in the same studies, but a higher rate of several adverse effects, notably dry mouth, somnolence, and various male sexual dysfunctions. It is a good illustration of why initial studies should include a broad dose range, probably at least 10-fold for drugs that are tolerated at these doses. There are now data covering the range of 50-400 mg. We do not yet know the lowest effective dose, but it is clear that 50 and 100 cannot be distinguished. There is no apparent reason to use higher doses and the recommended dose should be 50 mg. We therefore considered not allowing marketing of the proposed 100 mg dose. There seems little doubt, however, that clinicians may want to go higher in non-responders, and will do so despite our labeling (and, of course, they could be correct for some patients), and it did not seem desirable to require that such patients be burdened with the extra cost of taking 2 tablets per day. Labeling will make it clear that there is no discernible effect of doses greater than 50 mg. The sponsor is committed to an examination of lower doses and further assessment of sexual effects when the lowest effective dose is found.



Desvenlafaxine appears to have effects similar to many other antidepressants with SSRI or SSRI pharmacology and no particular safety issues, except for a need to monitor BP, which, like venlafaxine, it raises. The long marketing history of venlafaxine, which yields the desvenlafaxine metabolite, is reassuring.

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/s/

Robert Temple
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