PUBLIC SUMMARY DOCUMENT
Product: Desvenlafaxine succinate, tablet, (extended release), 50 mg and 100 mg (base), Pristiq®
Sponsor: Wyeth Australia Pty Limited
Date of PBAC Consideration: November 2008

1. Purpose of Application
To request a restricted benefit listing for treatment of major depressive disorders (MDD).

2. Background
This was the first time desvenlafaxine had been considered by the PBAC. Desvenlafaxine is the major active metabolite of venlafaxine.

3. Registration Status
Desvenlafaxine was TGA registered on 18 August 2008 for the treatment of major depressive disorder (MDD) including prevention of relapse.

4. Listing Requested and PBAC's View
Restricted Benefit
Major depressive disorders

The PBAC had no objections to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy
Desvenlafaxine provides an alternative Serotonin-Noradrenaline Reuptake Inhibitor (SNRIs) for the treatment of major depressive disorder.

6. Comparator
The submission nominated venlafaxine, the parent compound of desvenlafaxine, as the main comparator. The PBAC considered venlafaxine a reasonable comparator.

7. Clinical Trials
The submission presented six placebo-controlled desvenlafaxine fixed dose trials and one flexible dose trial, five venlafaxine fixed dose trials and 15 flexible dose trials (three flexible dose trials Ven 217, 341 and 346 are safety only). The submission presented an indirect meta-analysis of desvenlafaxine vs. venlafaxine via placebo using Last Observation Carried Forward (LOCF) and Mixed Model Repeated Measures (MMRM) to deal with missing data, and a Bayesian analysis of the LOCF and MMRM results.

Trials and associated reports published at the time of the submission are listed in the table below.

Trial ID	Protocol title/Publication title	Publication citation
Desvenlafaxine trials		
Des 304	A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder.	Liebowitz MR, Yeung PP, Entsuah R. J Clin Psychiatry 2007; 68: 1663-1672.

Des 306	A Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Desvenlafaxine Succinate in the Treatment of Major Depressive Disorder.	DeMartinis NA, Yeung P P, Entsuah R, Manley A L. J Clin Psychiatry 2007; 68: pp 677-688.
Des 308	A Randomized, Double-Blind, Placebo-Controlled Trial of Desvenlafaxine Succinate in the Treatment of Major Depressive Disorder.	Septien-Velez L, Pitrosky B, Padmanabhan S K, Germain J M, Tourian K A. Int Clin Psychopharmacol 2007; 22: pp 338-347.
Venlafaxine trials		
Khan 1991	Venlafaxine in Depressed Outpatients.	Khan A, Fabre L F and Rudolph R. Psychopharmacol Bull 1991; 27: pp 141-144.
Ven 014	A Double-Blind, Placebo-Controlled Comparison of Venlafaxine and Fluoxetine Treatment in Depressed Outpatients.	Nemeroff CB, Thase M E. J Psychiatr Res 2007; 41: pp 351-359.
Ven 015	A Double-Blind, Placebo-Controlled Study of Venlafaxine and Fluoxetine in Geriatric Outpatients With Major Depression.	Schatzberg A, Roose S. Am J Geriatr 2006; Psychiatry 14: pp 361-370.
Ven 203	A Randomized, Placebo-Controlled, Dose-Response Trial of Venlafaxine Hydrochloride in the Treatment of Major Depression.	Rudolph RL, Fabre L F, Feighner J P, Rickels K, Entsuah R, Derivan A T. J Clin Psychiatry 1998; 59: pp 116-122.
Ven 208	Once-Daily Venlafaxine Extended Release (XR) and Venlafaxine Immediate Release (IR) in Outpatients With Major Depression.	Cunningham LA. Ann Clin Psychiatry 1997; 9: pp 157-164.
Ven 209	Efficacy and Tolerability of Once-Daily Venlafaxine Extended Release (XR) in Outpatients With Major Depression.	Thase ME. J Clin Psychiatry 1997; 58: pp 393-398.
Ven 211	A Double-Blind, Randomized, Placebo-Controlled Trial of Once-Daily Venlafaxine Extended Release (XR) and Fluoxetine for the Treatment of Depression.	Rudolph RL, Feiger A D. J Affective Disord 1999; 56: pp 171-181.
Ven 301	Comparison of Venlafaxine and Imipramine in the Acute Treatment of Major Depression in Outpatients.	Schweizer E, Feighner J, Mandos L A, Rickels K. J Clin Psychiatry 1994; 55: pp 104-108.
Ven 302	A Comparison of Venlafaxine, Trazodone, and Placebo in Major Depression.	Cunningham LA, Borison R L, Carman J S, Chouinard G, Crowder J E, Diamond B I et. al. J Clin Psychopharmacol 1994;14: pp 99-106.
Ven 313	Efficacy and Safety of B.i.d. Doses of Venlafaxine in a Dose-Response Study.	Mendels J, Johnston R, Mattes J, Riesenberg R. Psychopharmacol Bull 1993; 29: pp 169-174.
Ven 342	The Use of Venlafaxine in the Treatment of Major Depression and Major Depression Associated With Anxiety: A Dose-Response Study.	Khan A, Upton G V, Rudolph R L, Entsuah R and Leventer S M. J Clin Psychopharmacol 1998;18: pp 19-25.
Ven 346	Efficacy of Venlafaxine in Depressive Illness in General Practice.	Lecrubier Y, Bourin M, Moon C A L, Schifano F, Blanchard C, Danjou P et. al. Acta Psychiatr Scand 1997; 95: pp 485-493.

Ven 360	Once-Daily Venlafaxine Extended Release (XR) Compared With Fluoxetine in Outpatients With Depression and Anxiety.	Silverstone PH, Ravindran A. J Clin Psychiatry 1999; 60: pp 22-28.
Ven 367	Once-Daily Venlafaxine XR Vs. Paroxetine in Outpatients With Major Depression.	Salinas E. 11th European College of Neuropsychopharmacology Congress Paris, France 31st October 4th November 1998.

8. Results of Trials

The submission presented an indirect comparison of desvenlafaxine vs. venlafaxine via placebo, by weighted mean difference in mean change from baseline 17 item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) with a specified minimum clinically important difference (MCID) of 1.5. Both ANCOVA LOCF and MMRM analyses were presented, with Bayesian analyses of both LOCF and MMRM results. In the venlafaxine vs. placebo trials where the $HAM\text{-}D_{21}$ was used, primary outcomes were recalculated to the $HAM\text{-}D_{17}$ standard for the submission. Data on remission and response were presented. No evidence was presented on prevention of relapse.

Using a Bayesian analysis and based on the MMRM data, the posterior probability that the difference in effect between desvenlafaxine and venlafaxine is less than 1.5 HAM-D points is 0.9998. The median indirect difference and 95% credibility interval is -0.27 (-1.17, 0.65). This supported the claim of non-inferiority.

The serious adverse event rate was approximately 4% for venlafaxine, which was statistically significantly higher than the 2% placebo rate (RR 1.45; 1.03, 2.05; p = 0.03). The serious adverse event rate was approximately 1% for desvenlafaxine, and was not statistically significantly different to the 1% placebo rate (RR 1.10; 0.54, 2.24; p = 0.78). There were seven reports of suicide ideation or attempted suicide and two reports of intentional overdose in the venlafaxine group. There were two reports of suicide ideation or attempted suicide and four reports of intentional overdose in the desvenlafaxine group.

Nausea, headache, dizziness and insomnia were the most frequently reported adverse events. There were no statistically significant differences between desvenlafaxine and venlafaxine for "any adverse event" (RR 1.01; 95% CI 0.96, 1.06; p=0.07); "nausea" (RR 0.97; 95% CI 0.77, 1.22; p=0.80) or "discontinuations due to adverse events" (RR 0.86; 95% CI 0.58, 1.29; p=0.48).

9. Clinical Claim

The submission claimed that desvenlafaxine is non-inferior to venlafaxine in treatment effect for the indication of MDD and non-inferior to venlafaxine in terms of safety.

The PBAC accepted that the data presented supported the claim of non-inferiority of desvenlafaxine to venlafaxine in the treatment of MDD and in terms of safety.

The Committee was concerned with the evidence presented showing no increase in clinical benefit of doses of desvenlafaxine above 100 mg per day.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The submission argued that desvenlafaxine 50 mg daily is equi-effective to venlafaxine 75 mg daily, and desvenlafaxine 100 mg daily is equi-effective to venlafaxine 150 mg daily. The Committee accepted these equi-effective doses.

For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed/year accounting for market share as necessary were estimated to be greater than 200,000 for both the 50 mg and 100 mg tablets in year 5 of listing. It was noted by the PBAC that the utilisation estimates for desvenlafaxine in the submission may be an underestimate. The financial savings/year to the PBS were estimated in the submission to be less than $10 million per year in Year 5, which may be an overestimate. An alternate sensitivity analysis conducted during the evaluation shows a revised reduced savings in year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of desvenlafaxine on the PBS for major depressive disorders on a cost minimisation basis with the parent drug venlafaxine. The equi-effective doses are desvenlafaxine 50 mg and venlafaxine 75 mg.

The PBAC considered that desvenlafaxine would provide a further treatment option for major depressive disorders, however, no evidence was presented to suggest that desvenlafaxine would offer an advantage for any particular patient group over the parent drug venlafaxine.

The PBAC agreed that the indirect comparison presented in the submission supported the claim of non-inferiority of desvenlafaxine to venlafaxine in the treatment of major depressive disorders. Using a Bayesian analysis and based on the MMRM data, the posterior probability that the difference in effect between desvenlafaxine and venlafaxine is less than 1.5 HAM-D points is 0.9998 and the median indirect difference and 95% credibility interval was -0.27 (-1.17, 0.65).

The PBAC also accepted that the data presented supported the claim of non-inferiority of desvenlafaxine to venlafaxine in terms of safety.

The Committee was concerned with the evidence presented showing no increase in clinical benefit of doses of desvenlafaxine above 100 mg per day. The PBAC therefore recommended that the Government pay no more than the price of 100 mg per day for doses above 100 mg per day of desvenlafaxine, reflecting the lack of any increased clinical benefit.

It was noted that the utilisation estimates for desvenlafaxine in the submission may be an underestimate and that potential financial savings were likely to be overestimated.

The PBAC requested that the National Prescribing Service (NPS) consider providing education for prescribers on the use of desvenlafaxine in the treatment of major depressive disorders, noting that desvenlafaxine is a metabolite of venlafaxine, and the lack of any clinical benefit of desvenlafaxine doses above 100 mg per day.

Recommendation
DESVENLAFAXINE, tablets, extended release, 50 mg, 100 mg

Restriction:	Restricted Benefit Major depressive disorders
Maximum quantity:	28
Number of repeats:	5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Wyeth Australia welcomes the PBAC's decision to recommend Pristiq for listing on the PBS for the treatment of major depressive disorder.