

# Desvenlafaxine (Pristiq) for major depressive disorder

(des-VEN-la-FAX-een)

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## Summary

- Desvenlafaxine is the active metabolite of venlafaxine.
- There is no evidence that desvenlafaxine is more effective, safer or better tolerated than venlafaxine or other antidepressants.
- Doses above 50 mg/day are unlikely to provide further clinical benefit and are associated with a higher incidence of adverse effects.
- Common adverse effects include nausea, headache, dizziness, dry mouth and diarrhoea.
- Desvenlafaxine should not be used in children and adolescents.
- Reduce the dose slowly to avoid discontinuation symptoms.

## PBS listing

### Restricted benefit

Desvenlafaxine (Pristiq) 50 mg and 100 mg tablets can be prescribed on the Pharmaceutical Benefits Scheme (PBS) for people with major depressive disorder.<sup>1</sup>

The 50 mg and 100 mg tablets are listed as a month's supply with 5 repeats.

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended desvenlafaxine for listing on a cost-minimisation basis — that is, similar efficacy and cost — compared with its parent drug, venlafaxine, for the treatment of major depressive disorder.<sup>1,2</sup> This decision was based upon an indirect comparison in which randomised trials of desvenlafaxine and randomised trials of venlafaxine were compared using placebo as the common comparator.<sup>2</sup>

### Place in therapy

Desvenlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI). The other SNRIs are venlafaxine and duloxetine.

Desvenlafaxine does not have a novel mechanism of action; it is the active metabolite of venlafaxine. It has been formulated as a prolonged-release tablet. There is no evidence that it is more effective than any other

antidepressant or has any particular advantage over venlafaxine.

### Desvenlafaxine is the major active metabolite of venlafaxine

O-desmethylvenlafaxine (desvenlafaxine) is the major active metabolite of venlafaxine and has similar pharmacological activity to that of venlafaxine. Both venlafaxine and desvenlafaxine contribute to the pharmacological effect of venlafaxine.<sup>3</sup>

Venlafaxine is metabolised to desvenlafaxine by cytochrome P450 2D6 (CYP2D6). Desvenlafaxine is not metabolised by CYP2D6 and is excreted unchanged or after conjugation.

Using desvenlafaxine rather than venlafaxine avoids CYP2D6 metabolism. Theoretically, desvenlafaxine has lower potential than venlafaxine for drug interactions with substrates and inhibitors of CYP2D6. However, this does not appear to confer any particular advantage to desvenlafaxine — the product information for venlafaxine notes that dose adjustment is not required when venlafaxine is used with drugs that inhibit or are metabolised by CYP2D6.<sup>3</sup>

### No evidence that desvenlafaxine is more effective than venlafaxine or other antidepressants

No studies have been powered to directly compare the efficacy of desvenlafaxine with venlafaxine or any other antidepressant. An indirect comparison was made

**Table 1: Mean changes in HAM-D<sub>17</sub> scores in studies of 50 or 100 mg/day desvenlafaxine**

	Mean change from baseline		
	Placebo	50mg	100mg
Leibowitz <sup>4</sup>	-9.5	-11.5*	-11.0
Boyer <sup>5</sup>	-10.7	-13.2*	-13.7*
DeMartinis <sup>6</sup>	-7.65	—	-10.6*

\* Significant improvement over placebo

in the PBAC submission, comparing randomised trials of desvenlafaxine against randomised trials of venlafaxine, using placebo as the common comparator (see Reason for listing).<sup>2</sup>

### Desvenlafaxine improves depression scores

At doses of 50 or 100 mg/day, desvenlafaxine improves scores on the Hamilton Rating Scale for Depression (HAM-D<sub>17</sub>). In most studies the 50 mg and the 100 mg doses improved HAM-D<sub>17</sub> scores significantly more — by 1.5 to 3 points — than placebo (Table 1).

### Doses above 50 mg day are unlikely to provide further clinical benefit

The recommended dose of desvenlafaxine is 50 mg/day. Higher doses do not appear to improve clinical efficacy.<sup>6,7</sup> However, adverse effects are more common at higher doses (see Safety issues). There is no evidence as to whether an individual patient who does not respond at the 50 mg dose will respond at a higher dose and no studies have been designed to evaluate this.

The lowest effective dose of desvenlafaxine is still being investigated. A US Food and Drug Administration analysis did not find any advantage to increasing the dose above 50 mg/day and suggested the efficacy of a dose of 25 mg/day should be investigated.<sup>8</sup> This trial is currently underway.<sup>9</sup>

## Safety issues

Desvenlafaxine's adverse-effect profile appears to be similar to that of venlafaxine.<sup>3,10</sup> However, information on its full adverse-effect profile will only be established after more widespread and long-term use in a broader patient population.

Increasing the dose of desvenlafaxine increases the incidence of adverse effects without improving clinical efficacy.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online ([www.ebs.tga.gov.au](http://www.ebs.tga.gov.au)) [then click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website ([www.tga.gov.au](http://www.tga.gov.au)).

### Adverse effects increase with dose

Common adverse effects at the 50 mg dose include nausea (22%), headache (20%), dizziness (13%), dry mouth (11%) and diarrhoea (11%).<sup>10</sup> Other potential adverse effects include insomnia, increased blood pressure, sexual dysfunction and increases in blood pressure, heart rate, cholesterol and triglycerides.<sup>7,10</sup> Nausea is less commonly reported after the first week of therapy.<sup>4,6</sup>

The incidence of adverse effects increase with dose. Based on pooled trial data, nausea was reported in 22% of trial participants using 50 mg/day but rose to 26% in those using 100 mg/day and 36% in those using 200 mg/day.<sup>10</sup>

### Desvenlafaxine may increase blood pressure and cholesterol

Statistically significant increases in blood pressure and total cholesterol concentration were observed in a small number of trial participants using 50 mg or 100 mg desvenlafaxine.<sup>4,5</sup> In trials using 50 mg/day the maximum increase in mean systolic and diastolic blood pressure was 3.3 mmHg and 2.1 mmHg, respectively.<sup>11</sup> Consider whether more frequent monitoring of blood pressure is needed.

### Desvenlafaxine precautions are similar to those of other antidepressants

As with other SNRIs:

- Monitor all people prescribed desvenlafaxine for clinical worsening and suicidality during the early stages of treatment and during dosage adjustment.<sup>7,12</sup>
- Do not use desvenlafaxine in children and adolescents, as its safety and efficacy has not been established and it is not approved for use in these groups.<sup>7</sup> See the *NPS RADAR* review *Selective serotonin re-uptake inhibitors in child and adolescent depression* (available at [www.nps.org.au](http://www.nps.org.au)).
- Desvenlafaxine should be avoided in combination with other drugs that can increase serotonin levels. These include SSRIs, venlafaxine, duloxetine, tricyclic

antidepressants, monoamine oxidase inhibitor (MAOI) antidepressants (including moclobemide), triptans, tramadol, pethidine, fentanyl, St John's wort and the illicit drugs MDMA ('ecstasy'), cocaine and LSD.<sup>7,13</sup>

## Dosing issues

The recommended dose is 50 mg once daily.<sup>7,12</sup> Doses above 50 mg per day are unlikely to provide further clinical benefit.<sup>7</sup>

No dose adjustment is required in hepatic impairment.

For people with renal impairment the dose may need to be adjusted according to the level of impairment. See the Pristiq product information for further information.

## Reduce the dose slowly to avoid discontinuation symptoms

When stopping desvenlafaxine, gradually taper the dose (by asking the patient to take it less frequently — i.e. every other day) over at least 1–2 weeks to avoid discontinuation symptoms.<sup>10,12</sup> These include dizziness, sensory disturbances including paraesthesia, anxiety and agitation, sleep disturbances, tremor, sweating

and confusion. Slower dose tapering may be needed for patients who experience these symptoms.

## Information for patients

Advise patients that the benefits of using desvenlafaxine may take a few weeks to manifest and they should continue with treatment even when they feel better.

Advise patients:

- to take desvenlafaxine at the same time each day and to swallow the tablet whole and not to break, chew or crush it
- that the tablet casing may be visible in the faeces
- that side effects such as nausea, headache and dizziness are common. Nausea is less common after the first week of therapy.
- to check with their doctor or pharmacist before using any prescription medicines (e.g. tramadol), over-the-counter medicines or herbal medicines (e.g. St John's wort), as interactions may occur.

Discuss the Pristiq consumer medicine information (CMI) leaflet with the patient (this is available on the NPS website).

## References

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