DESVENLAFAXINE

▼Pristiq® in major depressive disorder in adults

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ABSTRACT

Desvenlafaxine is an active metabolite of venlafaxine.

In three placebo-controlled trials, the results on the reduction in HAM-D17 score were not consistent.

The most common adverse effects are of gastrointestinal origin or sleep disorders. There are no available long-term safety data.

In the only head-to-head trial carried out in post-menopause women, desvenlafaxine at high doses did not show superiority versus escitalopram.

The pharmaceutical company withdrew the application for marketing authorisation after an initial evaluation by the EMA´s CHMP that concluded that desvenlafaxine was less effective than venlafaxine and did not present any advantages with regard to safety.

Indications[1]

Treatment of major depressive disorder

Mechanism of action[1]

This is an active metabolite of venlafaxine, that inhibits the reuptake of serotonine and noradernaline. Its bioavailability reaches up to 80% while elimination occurs without alteration through the urine (45%) and metabolism by glucurono conjugation (19%).

Dosage and administration[1]

The recommended dose is 50 mg daily. The tablets are swallowed wholly, with liquid with or without food and at the same time. The increase in doses should be gradual and up to a maximum of 200 mg daily and at intervals of at least 7 days. In cases of severe renal failure or terminal renal disease the initial dose should be 50 mg on alternate days. Dose reductions should also be gradual, during at least one or two weeks, given the risk of withdrawal symptoms. For treatment lasting over 6 weeks, withdrawal should be carried out over at least a 2-week period. If symptoms appear after discontinuing treatment or dose reduction, then restoring the previous dose should be considered.

Clinical efficacy

There are no studies including reference comparators (SSRI, venlafaxine) in the general population. Only three randomised, double-blind, placebo-controlled, 8-week duration trials[6,7,8] employed the recommended dose. One of them included a branch with duloxetine (60 mg daily). The primary endpoint was change in the HAM-D17 score at week 8 compared to baseline (maximum score, 54 points; severe depression = 19-22 points). A 50% reduction in the HAM-D17 scale score was considered to be clinically relevant.[9] A total of 1,097 patients were included, and two thirds were women between 38 and 46 years of age. The average score at the onset of the study was similar: 24, 23 and 23, respectively (SD=3). The doses used were 50 and 100 mg daily (see table below).

It was only in the case of the Boyer et al study that statistically significant differences were found at both doses. The other two trials showed statistically significant differences, one with the daily 50 mg dose and the other at 100 mg daily dose, but in both cases the clinical relevance was only modest (1.9 and 1.8).

Studies with desvenlafaxine at higher doses (up to 400 mg daily) did not show any therapeutic advantage compared to lower doses whereas more patients dropped out treatment due to adverse effects.

In the study against escitalopram[4] flexible doses of desvenlafaxine were used (100 and 200 mg daily) in postmenopausal women. No advantage of desvenlafaxine over escitalopram was found.

There is only one long-term study[16] that evaluated relapse prevention. Patients responding after 8 weeks of treatment with desvenlafaxine 50 mg daily and with a stable response up to week 20 were randomized either to placebo or desvenlafaxine 50 mg daily for 6 months. The endpoint was time to relapse (defined as HAM-D17 score ≥16), treatment withdrawal due to unsatisfactory response, hospital admission due to depression, suicide attempt or suicide. Time to relapse was significantly lower in the case of placebo compared to desvenlafaxine ($p<0.001$). The estimated probability of relapse at the end of treatment was greater in placebo group (30.3%) compared to the desvenlafaxine group (14.3%).

Safety

Adverse reactions[1,17]

In general, these are mild or moderate, dose-dependent and more frequent in the first week.[1] A pooled analysis[17] of placebo-controlled studies showed that the most frequent adverse reactions were nausea, vomiting, constipation, loss of appetite, dry mouth, hyperhidrosis, headache, dizziness, insomnia, fatigue, erectile dysfunction, and tremor. Nausea was the most frequent adverse effect reported, 31.9% (desvenlafaxine) *vs* 10.5% (placebo).

Drop outs due to adverse effects were associated with the dose administered, 4.1% (100 mg daily) and 17.7% (400 mg daily). The proportion of drop outs in the placebo group was 3.9%.[17]

Other adverse effects included increase in blood pressure, heart rate, cholesterol and triglycerides, sexual function alterations and orthostatic hypotension (more frequent in patients > 65 years).[1]

Contraindications[1]

Hypersensitivity to the main substance, some of the excipients or to venlafaxine.

Warnings and precautions[1]

Use with precaution in patients with a history of mania or bipolar disorder; hypertension and heart disorders (which may also require blood pressure control); history of seizures; narrow angled glaucoma, acute glaucoma or elevated intraocular pressure; patients treated with anticoagulants or drugs affecting platelet function and patients with known bleeding diathesis.

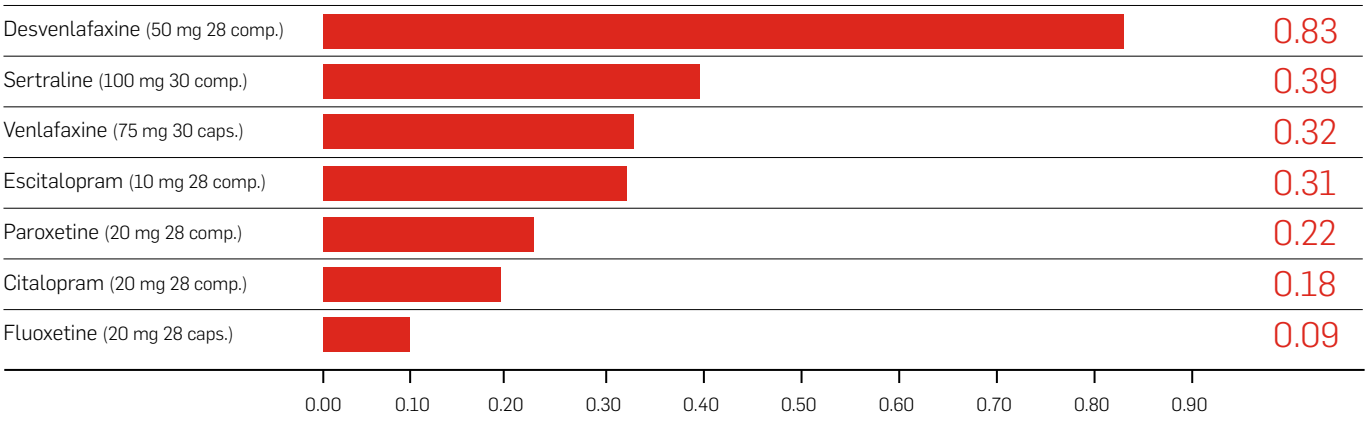
CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

	BOYER ET AL[6]			LIEBOWITZ ET AL[7]			TOURIAN ET AL[8]		
	DSV 50	DSV 100	PBO	DSV 50	DSV 100	PBO	DSV 50	DSV 100	PBO
Baseline HAM- D_{17}	24	24	24	23	23	23	23	23	24
Change HAM-D_{17}	-13.2	-13.7	-10.7	-11.5	-11.0	-9.53	-9.8	-10.5	-8.7
DSV / PBO	-2.5	-3.0	--	-1.9	-1.5	--	-1.1	-1.8	--
CI 95%	(-0.9 to -4.1)	(-1.4 to -4.7)	--	(-0.3 to -3.5)	(-0.1 to 3.1)	--	(-0.6 to 2.7)	(-0.2 to -3.4)	--
p value	0.002	<0.001	--	0.018	0.065	--	0.198	0.028	--

DAILY COST OF TREATMENT (€)



Withdrawal symptoms are frequent and self-limited on treatment interruption or after switching another antidepressant for desvenlafaxine (including switching venlafaxine to desvenlafaxine).

Some cases of suicidal ideation and behaviour have been reported during treatment or soon after withdrawal. It is necessary to monitor high-risk patients and physicians should be consulted when self destructive thoughts appear.

Use in especial situations[1]

Elderly patients: no dose adjustments are required. Dose increase should be made with precaution given the risk of orthostatic hypotension. **Pediatric patients:** not recommended in patients under 18 years of age. **Renal impairment:** a 50 mg daily dose is recommended on alternate days in cases of severe renal failure or terminal renal failure. **Liver impairment:** dose adjustment is not necessary. **Pregnancy:** do not prescribe unless absolutely necessary. **Breastfeeding:** it is excreted in breast milk. Either breastfeeding or drug treatment should be discontinued.

Interactions[1]

Interactions with food and medication.[1] Due to the risk of serotoninergic syndrome, it is recommended to not associate desvenlafaxine with MAO inhibitors. Do not use desvenlafaxine within the first 14 days after discontinuing MAO inhibitors treatment. Treatment with MAO inhibitors should be initiated at least 7 days after discontinuing treatment with desvenlafaxine. Precaution is advised when using concomitantly drugs such as SSRIs, triptans, other NSRIs, lithium, sibutramine, tramadol or St. John's wort (Hypericum perforatum) or any other drug affecting the serotonin metabolism (MAII, linezolid or tryptophan supplements).

Precaution should be taken in case of combining desvenlafaxine with drugs or substances with central action like alcohol or sedatives.

The concomitant use of desvenlafaxine with drugs metabolised via CYP2D6 can increase the plasma concentrations of these drugs and those drugs that are substrates of CYP3A4 can lead to a lower exposure to these drugs.

EMA Risk Management Plan[1]

Desvenlafaxine has been authorised through a national procedure (not centralised) and thus there is no existing EMA risk management plan.

Place in therapeutics

The goals of the management of major depressive disorder are to reach complete remission of symptoms, prevent recurrences and reduce the risk of committing suicide.[23]

In the case of mild depression, non-pharmacological measures are recommended. In moderate to severe major depression, the elective pharmacological treatment is SSRI drugs preferably combined with psychological interventions. The SNRIs are an adequate alternative in patients who do not respond to SSRIs. The reference comparators would be SSRIs (fluoxetine, paroxetine, citalopram and sertraline) and venlafaxine en case a change in therapeutic class is necessary.[23]

The majority of the available studies present methodological limitations such as short duration, use of unauthorised doses and exclusion of specific patients, which makes an assessment of its efficacy difficult.

The EMA carried out a preliminary assessment of desvenlafaxine and concluded that it was less effective than venlafaxine and also presented no safety advantages. The pharmaceutical company decided to withdraw the application for authorisation at the EMA and applied for authorisation at a national level in Spain.

Desvenlafaxine has not proven more effective than either the recommended SSRIs or venlafaxine in the general population and its long-term safety profile is still unknown. It is recommended to continue using those antidepressants with is greater experience and better efficacy and safety profile.

Presentations

Pristiq® (Pfizer): 50 mg 28 extended release tablets (23.17€) and 100 mg 28 extended release tablets (37.06€).

References

A complete report on desvenlafaxine can be found at: www.bit.navarra.es

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