

Desvenlafaxine (Pristiq) STEPS

Recommendation

Pristiq (desvenlafaxine) to be non-formulary. Clinical studies are against placebo and funded by the manufacturer. Head-to-head trials with venlafaxine or other antidepressants are lacking. Additionally, due to the upcoming availability of venlafaxine extended release generically it is not cost-effective nor is there convincing evidence to recommend this agent of venlafaxine or other agents. The package insert states that the recommended dose for Pristiq is 50mg once daily. Presently there are no published clinical studies that evaluate the 50mg dose in major depressive disorder.

Approved by the FDA February 29, 2008 (Wyeth)

Desvenlafaxine is an extended-release tablet for oral administration. It is a selective serotonin and nor epinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder. Desvenlafaxine is the major active metabolite of venlafaxine (Effexor® and Effexor XR®).

Indications

Pristiq (desvenlafaxine) is indicated for the treatment of major depressive disorder.

Safety — (new agent)

Sound-alike/Look-alike: None noted.

Drug Interactions:

Strong inhibitors of CYP3A4 (Biaxin, ketoconazole and others) could increase serum concentrations of desvenlafaxine and increase its toxicity. Desvenlafaxine inhibits CYP2D6, especially with higher doses and may increase serum concentrations of drugs metabolized by CYP2D6. It should not be taken with monoamine oxidase inhibitor (MAOI) or within 14 days of stopping one. Desvenlafaxine may increase the risk of serotonin syndrome if it is taken with other serotonergic drugs, such as sumatriptan (Imitrex, and others) or meperidine. Altered anticoagulation effects have been reported, patients should be monitored when desvenlafaxine is started or discontinued.

Contraindication:

Hypersensitivity to desvenlafaxine, venlafaxine or any component of the formulation; use of MAO inhibitors within 14 days; do not initiate MAO inhibitor within 7 days of discontinuing desvenlafaxine

Warnings/Precautions:

- Desvenlafaxine has a black box warning as with other antidepressants regarding risk of suicidal thinking and behavior.
- May increase blood pressure. Patients should have blood pressure monitoring.
- Patients should be monitored when discontinuing treatment.
- Monitor for **serotonin syndrome**, especially with concomitant use of other serotonergic drugs (including SSRIs, SNRIs, and triptans).
- Prescribe cautiously to patients with a seizure disorder or seizure history. Possible increase of bleeding events, narrow-angle glaucoma, activation of mania/hypomania.
- Use with caution in patients with cardiovascular, cerebrovascular, or lipid metabolism disorders.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including desvenlafaxine.

Renal:

$Cl_{cr} \geq 30$ mL/minute: No dosage adjustment required

$Cl_{cr} < 30$ mL/minute: 50 mg **every other day** (maximum)

Hemodialysis: 50 mg **every other day** (maximum). Supplemental doses not required after HD.

Hepatic:

Usual adult dose recommended; maximum dose: 100 mg/day

Children:

Safety and efficacy have not been established.

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Elderly:

Safety and efficacy not significantly different for patients 65 years and older. Serum concentrations of the drug are higher in the elderly. Possibility of reduced renal clearance should be taken into account.

Race/Gender:

Studies did not account for this effect.

Pregnancy:

Category Risk Factor C

Advise patients to notify their health provider if they become pregnant or intend to become pregnant during pregnancy.

Nursing Mothers: Desvenlafaxine is excreted in human milk. Only administer desvenlafaxine to breast-feeding women if the expected benefits outweigh any possible risk.

Tolerability =

As listed in the package insert below are common adverse events for desvenlafaxine 50mg occurring in $\geq 2\%$ of patients in the 8-week placebo-controlled, premarketing clinical studies. In men decreased libido was 4% and erectile dysfunction 3% versus $<1\%$ in placebo.

Adverse Event	Headache	Dizziness	Nausea	Insomnia	Sweating	Diarrhea	Dry Mouth	Constipation	Fatigue
Placebo N=636	23	23	10	6	4	9	9	4	4
Pristiq 50mg N=317	20	20	22	9	10	11	11	9	7
Effexor XR*		20	31	17	14		12	8	

*Adverse effects listed in Effexor XR package insert for short-term placebo-controlled trials in patients with major depressive disorder. This data is from separate studies, therefore not necessarily comparable.

Efficacy — (Long term efficacy should be evaluated)

Desvenlafaxine is an extended-release tablet for oral administration. It is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder. It is the major active metabolite of venlafaxine (Effexor® and Effexor XR®).

Pharmacokinetics:

Peak: 7 ½ hours (venlafaxine 5.5 hours)
t ½: 11 hours (mean) (venlafaxine 5 hours)

Metabolism/Excretion:

It is metabolized in the liver by conjugation and to a lesser extent by CYP 3A4 and it is excreted in the urine both unchanged and as metabolites.

Studies:

Four published studies (three for major depressive disorder and one for post-menopausal hot flashes). All studies are sponsored by the manufacturer. The only studies with the 50mg dose are the one for menopausal vasomotor symptoms or unpublished.

Liebowitz Design: Multicenter, randomized, double blind placebo controlled.
Dose: Desvenlafaxine **100mg to 200mg** or placebo for 56 days daily. These are not doses approved by the FDA in the labeling.
Conclusion: Desvenlafaxine was generally safe and well tolerated. In this study, it did not show significantly greater efficacy than placebo on the primary or key secondary efficacy endpoints, but it did demonstrate efficacy on an alternate depression scale and pain measure associated with MDD.

No statistically significant difference in HAM-D-17 scores between desvenlafaxine and placebo.

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DeMartinis	Design:	Multicenter, randomized, double-blind, placebo-controlled trial.
	Doses:	Desvenlafaxine 100mg (n=114), 200mg (n=116) or 400mg (n=121) daily and placebo (n=124) for 8 weeks. These are not doses approved by the FDA in the labeling.
	Conclusion:	Desvenlafaxine is effective and well-tolerated in the short-term treatment of MDD. 100mg and 400mg statistically significant in HAM-D-17 scores.
Septien-Velex	Design:	Multicenter, randomized, double-blind, placebo-controlled trial. Desvenlafaxine 200mg, 400mg or placebo for eight weeks. These are not doses approved by the FDA in the labeling.
		Patients receiving 200mg or 400mg of desvenlafaxine achieved a modest improvement in HAM-D-17 scores of -3.3 and -2.8 points respectively.
Speroff	Design:	Multicenter, randomized, double-blind, placebo-controlled trial.
	Dose:	Desvenlafaxine 50mg, 100mg, 150mg, 200mg or placebo daily for 52 weeks.
	Conclusion:	Desvenlafaxine is an effective non-hormonal treatment for vasomotor symptoms in postmenopausal women. Its tolerability profile is consistent with that of other serotonin-norepinephrine reuptake inhibitors.

Price = (vs. other SNRI)/ — (vs. other antidepressants)

Drug Store.com

Each/Monthly Cost

Pristiq 50mg	\$ 3.99/\$119.96 (50mg QD)
Pristiq 100mg	\$4.16/\$124.99 (100mg QD)

Effexor XR patent expired on June 13, 2008

Effexor XR 75mg	\$3.86/\$115.99 (QD)
Effexor XR 150mg	\$4.20/\$125.99 (QD)
Venlafaxine 75mg	\$1.99
Venlafaxine 100mg	\$6.37
Cymbalta 30mg	\$4.34/\$130.32
Cymbalta 60mg	\$4.37/\$131.99 (60mg QD)

Simplicity =

May be taken without regard to food. Available as extended release 50mg and 100mg tablets. Tablets should not be not divided, crushed, chewed, or dissolved. The starting dosage is 50mg once daily. Dosage increases above 50mg daily demonstrated no additional benefit.

References

Depression: Management of depression in primary and secondary care. National Clinical Practice Guideline Number 23. National Collaborating Centre for Mental Health, National Institute for Clinical Excellence. 2006. Available at: <http://guidance.nice.org.uk/CG23>. Accessed: July 2, 2008.

Product information for Pristiq. Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101. February 2008.

DeMartinis NA, Yeung PP, Entsuah R, et al, "A Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Desvenlafaxine Succinate in the Treatment of Major Depressive Disorder," *J Clin Psychiatry*, 2007, 68(5):677-88.

Liebowitz MR, Yeung PP, and Entsuah R, "A Randomized, Double-Blind, Placebo-Controlled Trial of Desvenlafaxine Succinate in Adult Outpatients With Major Depressive Disorder," *J Clin Psychiatry*, 2007, 68(11):1663-72.

Septien-Velez L, Pitrosky B, Padmanabhan SK, et al, "A Randomized, Double-Blind, Placebo-Controlled Trial of Desvenlafaxine Succinate in The Treatment of Major Depressive Disorder," *Int Clin Psychopharmacol*, 2007, 22(6):338-47.

Speroff L, Gass M, Constantine G, Olivier S; Study 315 Investigators. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol*. 2008 Jan; 11(1):77-87.