

# DESVENLAFAXINE - desvenlafaxine tablet, extended release

## Sun Pharmaceutical Industries, Inc.

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### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DESVENLAFAXINE safely and effectively. See full prescribing information for DESVENLAFAXINE.

DESVENLAFAXINE extended-release tablets, for oral use

Initial U.S. Approval: 2008

#### **WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

*See full prescribing information for complete boxed warning.*

- **Increased risk of suicidal thoughts and behaviors in children, adolescents and young adults taking antidepressants (5.1).**
- **Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)**
- **Desvenlafaxine is not approved for use in pediatric patients (8.4).**

#### **RECENT MAJOR CHANGES**

Warnings and Precautions (5.2, 5.4)

7/2023

#### **INDICATIONS AND USAGE**

Desvenlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of adults with major depressive disorder (MDD) (1). (1)

#### **DOSAGE AND ADMINISTRATION**

- Recommended dose: 50 mg once daily with or without food (2.1).
- There was no evidence that doses greater than 50 mg per day confer any additional benefit (2.1).
- Discontinuation: Reduce dose gradually whenever possible (2.1).
- Take tablets whole; do not divide, crush, chew, or dissolve (2.1).
- Moderate renal impairment: Maximum dose 50 mg per day (2.2).
- Severe renal impairment and end-stage renal disease: Maximum dose 50 mg every other day (2.2).
- Moderate to severe hepatic impairment: Maximum dose 100 mg per day (2.3).

#### **DOSAGE FORMS AND STRENGTHS**

Desvenlafaxine extended-release tablets are available as 50 and 100 mg tablets (3) (3)

#### **CONTRAINDICATIONS**

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the desvenlafaxine extended-release tablets formulation (4).
- *Serotonin Syndrome and MAOIs*: Do not use MAOIs intended to treat psychiatric disorders with desvenlafaxine or within 7 days of stopping treatment with desvenlafaxine. Do not use desvenlafaxine within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start desvenlafaxine in a patient who is being treated with linezolid or intravenous methylene blue (4).

#### **WARNINGS AND PRECAUTIONS**

- *Serotonin Syndrome*: Increased risk when co-administered with other serotonergic agents, but also when taken alone. If it occurs, discontinue desvenlafaxine and serotonergic agents and initiate supportive treatment (5.2).
- *Elevated Blood Pressure*: Control hypertension before initiating treatment. Monitor blood pressure regularly during treatment (5.3).
- *Increased Risk of Bleeding*: Concomitant use of aspirin, NSAIDs, other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk (5.4).
- *Angle Closure Glaucoma*: Avoid use of antidepressants, including desvenlafaxine, in patients with

untreated anatomically narrow angles treated (5.5).

- *Activation of Mania/Hypomania*: Use cautiously in patients with Bipolar Disorder. Caution patients about risk of activation of mania/hypomania (5.6).
- *Discontinuation Syndrome*: Taper dose when possible and monitor for discontinuation symptoms (5.7).
- *Seizure*: Can occur. Use cautiously in patients with seizure disorder (5.8).
- *Hyponatremia*: Can occur in association with SIADH (5.9).
- *Interstitial Lung Disease and Eosinophilic Pneumonia*: Can occur (5.10). (5)
- *Sexual Dysfunction*: Desvenlafaxine may cause symptoms of sexual dysfunction (5.11). (5)

#### -----ADVERSE REACTIONS-----

Most common adverse reactions (incidence  $\geq$ 5% and twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders (6.1). (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Alembic Pharmaceuticals Limited at 1-800-406-7984 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch) (6)**

#### -----USE IN SPECIFIC POPULATIONS-----

- *Pregnancy*: Third trimester use may result in neonatal discontinuation syndrome (8.1).
- *Geriatric Use*: There is an increased incidence of orthostatic hypotension in desvenlafaxine treated patients  $\geq$  65 years (6.1 and 8.5).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 8/2023**

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## **FULL PRESCRIBING INFORMATION**

## **WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

**Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [see Warnings and Precautions (5.1)].**

**In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Warnings and Precautions (5.1)].**

**Desvenlafaxine is not approved for use in pediatric patients [see Use in Specific Populations (8.4)].**

## **1 INDICATIONS AND USAGE**

Desvenlafaxine is indicated for the treatment of adults with major depressive disorder (MDD) [see Clinical Studies (14)].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 General Instructions for Use**

The recommended dose for desvenlafaxine is 50 mg once daily, with or without food. The 50 mg dose is both a starting dose and the therapeutic dose. Desvenlafaxine should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

In clinical studies, doses of 10 mg to 400 mg per day were studied. In clinical studies, doses of 50 mg to 400 mg per day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg per day and adverse reactions and discontinuations were more frequent at higher doses.

When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms [see Dosage and Administration (2.5) and Warnings and Precautions (5.7)].

## **2.2 Dosage Recommendations for Patients with Renal Impairment**

The maximum recommended dose in patients with moderate renal impairment (24-hr creatinine clearance [ $Cl_{Cr}$ ] = 30 to 50 mL/min, Cockcroft-Gault [C-G]) is 50 mg per day. The maximum recommended dose in patients with severe renal impairment ( $Cl_{Cr}$  15 to 29 mL/min, C-G) or end-stage renal disease (ESRD,  $Cl_{Cr}$  < 15 mL/min, C-G) is 25 mg every day or 50 mg every other day. Supplemental doses should not be given to patients after dialysis [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

## **2.3 Dosage Recommendations for Patients with Hepatic Impairment**

The recommended dose in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15) is 50 mg per day. Dose escalation above 100 mg per day is not recommended [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

## **2.4 Maintenance/Continuation/Extended Treatment**

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Longer-term efficacy of desvenlafaxine (50 to 400 mg) was established in two maintenance trials [see *Clinical Studies (14)*]. Patients should be periodically reassessed to determine the need for continued treatment.

## **2.5 Discontinuing Desvenlafaxine**

Adverse reactions may occur upon discontinuation of desvenlafaxine [see *Warnings and Precautions (5.7)*]. Gradually reduce the dosage rather than stopping desvenlafaxine abruptly whenever possible.

## **2.6 Switching Patients From Other Antidepressants to Desvenlafaxine**

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to desvenlafaxine. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

## **2.7 Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders**

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with desvenlafaxine. Conversely, at least 7 days should be allowed after stopping desvenlafaxine before starting an MAOI intended to treat psychiatric disorders [see *Contraindications (4)*].

## **2.8 Use of Desvenlafaxine with other MAOIs such as Linezolid or Methylene Blue**

Do not start desvenlafaxine in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered [see *Contraindications (4)*].

In some cases, a patient already receiving desvenlafaxine therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, desvenlafaxine should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 7 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first.

Therapy with desvenlafaxine may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue [see *Warnings and Precautions (5.2)*].

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with desvenlafaxine is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use [see *Warnings and Precautions (5.2)*].

## **3 DOSAGE FORMS AND STRENGTHS**

Desvenlafaxine extended-release tablets are available as 50 and 100 mg tablets.

- 50 mg, light pink colored, diamond shaped, biconvex tablets, debossed with 'L189' on one side and plain on other side.
- 100 mg, dark brown to red colored, diamond shaped, biconvex tablets, debossed with 'L190' on one side and plain on other side.

## **4 CONTRAINDICATIONS**

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the desvenlafaxine extended-release tablets formulation. Angioedema has been reported in patients treated with desvenlafaxine [see *Adverse Reactions (6.1)*].
- The use of MAOIs intended to treat psychiatric disorders with desvenlafaxine or within 7 days of stopping treatment with desvenlafaxine is contraindicated because of an increased risk of serotonin syndrome. The use of desvenlafaxine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated [see *Dosage and Administration (2.7)* and *Warnings and Precautions (5.2)*].
- Starting desvenlafaxine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome [see *Dosage and Administration (2.8)* and *Warnings and*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

Patients with major depressive disorder MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

**Table 1**

<b>Age Range</b>	<b>Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated</b>
	Increases Compared to Placebo
<18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult

studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see *Dosage and Administration (2.4)*, *Warnings and Precautions (5.7)*].

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for desvenlafaxine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

#### Screening patients for bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a



mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that desvenlafaxine is not approved for use in treating bipolar depression.

## 5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective-serotonin reuptake inhibitors (SSRIs), including desvenlafaxine, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidine, methadone, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs [see *Contraindications (4)*, *Drug Interactions (7.1)*]. Serotonin syndrome can also occur when these drugs are used alone.

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of desvenlafaxine with MAOIs is contraindicated. In addition, do not initiate desvenlafaxine in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking desvenlafaxine, discontinue desvenlafaxine before initiating treatment with the MAOI [see *Contraindications (4)*, *Drug Interactions (7.1)*].

Monitor all patients taking desvenlafaxine for the emergence of serotonin syndrome. Discontinue treatment with desvenlafaxine and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of desvenlafaxine with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

## 5.3 Elevated Blood Pressure

Patients receiving desvenlafaxine should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies [see *Adverse Reactions (6.1)*]. Pre-existing hypertension should be controlled before initiating treatment with desvenlafaxine. Caution should be exercised in treating patients with pre-existing hypertension, cardiovascular, or cerebrovascular conditions that might be

compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with desvenlafaxine.

Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving desvenlafaxine, either dose reduction or discontinuation should be considered [see *Adverse Reactions (6.1)*].

#### **5.4 Increased Risk of Bleeding**

Drugs that interfere with serotonin reuptake inhibition, including desvenlafaxine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Based on data from the published observational studies, exposure to SNRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage [see *Use in Specific Populations (8.1)*]. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of desvenlafaxine and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor coagulation indices when initiating, titrating, or discontinuing desvenlafaxine.

#### **5.5 Angle Closure Glaucoma**

The pupillary dilation that occurs following use of many antidepressant drugs including desvenlafaxine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including desvenlafaxine, in patients with untreated anatomically narrow angles.

#### **5.6 Activation of Mania/Hypomania**

During all MDD phase 2 and phase 3 studies, mania was reported for approximately 0.02% of patients treated with desvenlafaxine. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, desvenlafaxine should be used cautiously in patients with a history or family history of mania or hypomania.

#### **5.7 Discontinuation Syndrome**

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt

cessation is recommended whenever possible [*see Dosage and Administration (2.5), Adverse Reaction (6.1)*].

## **5.8 Seizure**

Cases of seizure have been reported in pre-marketing clinical studies with desvenlafaxine. Desvenlafaxine has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from pre-marketing clinical studies. Desvenlafaxine should be prescribed with caution in patients with a seizure disorder.

## **5.9 Hyponatremia**

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including desvenlafaxine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)*].

Discontinuation of desvenlafaxine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

## **5.10 Interstitial Lung Disease and Eosinophilic Pneumonia**

Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of desvenlafaxine) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with desvenlafaxine who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of desvenlafaxine should be considered.

## **5.11 Sexual Dysfunction**

Use of SNRIs, including desvenlafaxine, may cause symptoms of sexual dysfunction [*see Adverse Reactions (6.1)*]. In male patients, SNRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SNRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of desvenlafaxine and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of

symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity [*see Contraindications (4)*]
- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients [*see Warnings and Precautions (5.1)*]
- Serotonin Syndrome [*see Warnings and Precautions (5.2)*]
- Elevated Blood Pressure [*see Warnings and Precautions (5.3)*]
- Increased Risk of Bleeding [*see Warnings and Precautions (5.4)*]
- Angle Closure Glaucoma [*see Warnings and Precautions (5.5)*]
- Activation of Mania/Hypomania [*see Warnings and Precautions (5.6)*]
- Discontinuation Syndrome [*see Warnings and Precautions (5.7)*]
- Seizure [*see Warnings and Precautions (5.8)*]
- Hyponatremia [*see Warnings and Precautions (5.9)*]
- Interstitial Lung Disease and Eosinophilic Pneumonia [*see Warnings and Precautions (5.10)*]

### 6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

#### Patient exposure

Desvenlafaxine was evaluated for safety in 8,394 patients diagnosed with major depressive disorder who participated in multiple-dose pre-marketing studies, representing 2,784 patient-years of exposure. Of the total 8,394 patients exposed to at least one dose of desvenlafaxine; 2,116 were exposed to desvenlafaxine for 6 months, representing 1,658 patient-years of exposure, and 421 were exposed for one year, representing 416 patient-years of exposure.

#### Adverse reactions reported as reasons for discontinuation of treatment

In the pre-marketing pooled 8-week placebo-controlled studies in patients with MDD, 1,834 patients were exposed to desvenlafaxine (50 to 400 mg). Of the 1,834 patients, 12% discontinued treatment due to an adverse reaction, compared with 3% of the 1,116 placebo-treated patients. At the recommended dose of 50 mg, the discontinuation rate due to an adverse reaction for desvenlafaxine (4.1%) was similar to the rate for placebo (3.8%). For the 100 mg dose of desvenlafaxine the discontinuation rate due to an adverse reaction was 8.7%.

The most common adverse reactions leading to discontinuation in at least 2% and at a rate greater than placebo of the desvenlafaxine treated patients in the short-term studies, up to 8 weeks, were: nausea (4%); dizziness, headache and vomiting (2% each). In a longer-term study, up to 9 months, the most common was vomiting (2%).

## Common adverse reactions in placebo-controlled MDD studies

The most commonly observed adverse reactions in desvenlafaxine treated MDD patients in pre-marketing pooled 8-week, placebo-controlled, fixed-dose studies (incidence  $\geq 5\%$  and at least twice the rate of placebo in the 50 or 100 mg dose groups) were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders.

Table 2 shows the incidence of common adverse reactions that occurred in  $\geq 2\%$  of desvenlafaxine treated MDD patients and twice the rate of placebo at any dose in the pooled 8-week, placebo-controlled, fixed dose clinical studies.

**Table 2: Common Adverse Reactions ( $\geq 2\%$  in any Fixed-Dose Group and Twice the Rate of Placebo) in Pre-marketing Pooled MDD 8-Week Placebo-Controlled Studies**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction				
	Placebo (n=636)	Desvenlafaxine			
		50 mg (n=317)	100 mg (n=424)	200 mg (n=307)	400 mg (n=317)
<b>Cardiac disorders</b>					
Blood pressure increased	1	1	1	2	2
<b>Gastrointestinal disorders</b>					
Nausea	10	22	26	36	41
Dry mouth	9	11	17	21	25
Constipation	4	9	9	10	14
Vomiting	3	3	4	6	9
<b>General disorders and administration site conditions</b>					
Fatigue	4	7	7	10	11
Chills	1	1	<1	3	4
Feeling jittery	1	1	2	3	3
<b>Metabolism and nutrition disorders</b>					
Decreased appetite	2	5	8	10	10
<b>Nervous system disorders</b>					
Dizziness	5	13	10	15	16
Somnolence	4	4	9	12	12
Tremor	2	2	3	9	9
Disturbance in attention	<1	<1	1	2	1
<b>Psychiatric disorders</b>					
Insomnia	6	9	12	14	15
Anxiety	2	3	5	4	4
Nervousness	1	<1	1	2	2
Abnormal dreams	1	2	3	2	4
<b>Renal and urinary disorders</b>					

Urinary hesitation	0	<1	1	2	2
<b>Respiratory, thoracic and mediastinal disorders</b>					
Yawning	<1	1	1	4	3
<b>Skin and subcutaneous tissue disorders</b>					
Hyperhidrosis	4	10	11	18	21
<b>Special Senses</b>					
Vision blurred	1	3	4	4	4
Mydriasis	<1	2	2	6	6
Vertigo	1	2	1	5	3
Tinnitus	1	2	1	1	2
Dysgeusia	1	1	1	1	2
<b>Vascular disorders</b>					
Hot flush	<1	1	1	2	2

### Sexual function adverse reactions

Table 3 shows the incidence of sexual function adverse reactions that occurred in  $\geq 2\%$  of desvenlafaxine treated MDD patients in any fixed-dose group (pre-marketing pooled 8-week, placebo-controlled, fixed-dose, clinical studies).

**Table 3: Sexual Function Adverse Reactions ( $\geq 2\%$  in Men or Women in any Desvenlafaxine Group) During the On-Therapy Period**

	<b>Desvenlafaxine</b>				
	<b>Placebo</b> (n=239)	<b>50 mg</b> (n=108)	<b>100 mg</b> (n=157)	<b>200 mg</b> (n=131)	<b>400 mg</b> (n=154)
<b>Men only</b>					
Anorgasmia	0	0	3	5	8
Libido decreased	1	4	5	6	3
Orgasm abnormal	0	0	1	2	3
Ejaculation delayed	<1	1	5	7	6
Erectile dysfunction	1	3	6	8	11
Ejaculation disorder	0	0	1	2	5
Ejaculation failure	0	1	0	2	2
Sexual dysfunction	0	1	0	0	2
	<b>Desvenlafaxine</b>				
	<b>Placebo</b> (n=397)	<b>50 mg</b> (n=209)	<b>100 mg</b> (n=267)	<b>200 mg</b> (n=176)	<b>400 mg</b> (n=163)
<b>Women only</b>					
Anorgasmia	0	1	1	0	3

Other adverse reactions observed in premarketing and postmarketing clinical studies  
Other infrequent adverse reactions, not described elsewhere in the label, occurring at an incidence of  $< 2\%$  in MDD patients treated with desvenlafaxine were:

**Cardiac disorders** – tachycardia.

**General disorders and administration site conditions** – Asthenia.

**Investigations** – Weight increased, liver function test abnormal, blood prolactin increased.

**Musculoskeletal and connective tissue disorders** – Musculoskeletal stiffness.

**Nervous system disorders** –Syncope, convulsion, dystonia.

**Psychiatric disorders** – Depersonalization, bruxism.

**Renal and urinary disorders** – Urinary retention.

**Skin and subcutaneous tissue disorders** – Rash, alopecia, photosensitivity reaction, angioedema.

In clinical studies, there were uncommon reports of ischemic cardiac adverse reactions, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine treatment as compared to placebo.

#### **Laboratory, ECG and vital sign changes observed in MDD clinical studies**

The following changes were observed in pre-marketing placebo-controlled, short-term MDD studies with desvenlafaxine.

#### ***Lipids***

Elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant.

The percentage of patients who exceeded a predetermined threshold value is shown in Table 4.

**Table 4: Incidence (%) of Patients With Lipid Abnormalities of Potential Clinical Significance\***

	<b>Desvenlafaxine</b>				
	<b>Placebo</b>	<b>50 mg</b>	<b>100 mg</b>	<b>200 mg</b>	<b>400 mg</b>
Total Cholesterol	2	3	4	4	10
*(Increase of $\geq$ 50 mg/dl and an					

absolute value of $\geq 261$ mg/dl)					
LDL Cholesterol	0	1	0	1	2
*(Increase $\geq 50$ mg/dl and an absolute value of $\geq 190$ mg/dl)					
Triglycerides, fasting	3	2	1	4	6
*(Fasting: $\geq 327$ mg/dl)					

### ***Proteinuria***

Proteinuria, greater than or equal to trace, was observed in the pre-marketing fixed-dose controlled studies (see Table 5). This proteinuria was not associated with increases in BUN or creatinine and was generally transient.

**Table 5: Incidence (%) of Patients with Proteinuria in the Fixed-dose Clinical Studies**

	Placebo	Desvenlafaxine			
		50 mg	100 mg	200 mg	400 mg
Proteinuria	4	6	8	5	7

### ***Vital sign changes***

Table 6 summarizes the changes that were observed in placebo-controlled, short-term, pre-marketing studies with desvenlafaxine in patients with MDD (doses 50 to 400 mg).

**Table 6: Mean Changes in Vital Signs at Final on Therapy for All Short-term, Fixed-dose Controlled Studies**

	Placebo	Desvenlafaxine			
		50 mg	100 mg	200 mg	400 mg
<b>Blood pressure</b>					
Supine systolic bp (mm Hg)	-1.4	1.2	2	2.5	2.1
Supine diastolic bp (mm Hg)	-0.6	0.7	0.8	1.8	2.3
<b>Pulse rate</b>					
Supine pulse (bpm)	-0.3	1.3	1.3	0.9	4.1
<b>Weight (kg)</b>	0	-0.4	-0.6	-0.9	-1.1



Treatment with desvenlafaxine at all doses from 50 mg per day to 400 mg per day in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP)  $\geq 90$  mm Hg and  $\geq 10$  mm Hg above baseline for 3 consecutive on-therapy visits (see Table 7). Analyses of patients in desvenlafaxine pre-marketing short-term controlled studies who met criteria for sustained hypertension revealed a consistent increase in the proportion of patients who developed sustained hypertension. This was seen at all doses with a suggestion of a higher rate at 400 mg per day.

**Table 7: Proportion of Patients with Sustained Elevation of Supine Diastolic Blood Pressure**

<b>Treatment Group</b>	<b>Proportion of Patients with Sustained Hypertension</b>
Placebo	0.5%
Desvenlafaxine 50 mg per day	1.3%
Desvenlafaxine 100 mg per day	0.7%
Desvenlafaxine 200 mg per day	1.1%
Desvenlafaxine 400 mg per day	2.3%

### ***Orthostatic hypotension***

In the pre-marketing short-term, placebo-controlled clinical studies with doses of 50 to 400 mg, systolic orthostatic hypotension (decrease  $\geq 30$  mm Hg from supine to standing position) occurred more frequently in patients  $\geq 65$  years of age receiving desvenlafaxine (8%, 7/87) versus placebo (2.5%, 1/40), compared to patients  $< 65$  years of age receiving desvenlafaxine (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218).

## **6.2 Postmarketing Experience**

The following adverse reaction has been identified during post-approval use of desvenlafaxine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

***Respiratory, thoracic and mediastinal disorders*** - Anosmia, hyposmia

***Skin and subcutaneous tissue disorders*** - Stevens-Johnson syndrome

***Gastrointestinal system*** - Acute pancreatitis

***Cardiovascular system*** - Takotsubo cardiomyopathy

## **7 DRUG INTERACTIONS**

## 7.1 Drugs Having Clinically Important Interactions with Desvenlafaxine

**Table 8: Clinically Important Drug Interactions with Desvenlafaxine**

Monoamine Oxidase Inhibitors (MAOI)	
<i>Clinical Impact</i>	The concomitant use of SSRIs and SNRIs including desvenlafaxine with MAOIs increases the risk of serotonin syndrome.
<i>Intervention</i>	Concomitant use of desvenlafaxine is contraindicated: <ul style="list-style-type: none"> <li>•With an MAOI intended to treat psychiatric disorders or within 7 days of stopping treatment with desvenlafaxine.</li> <li>•Within 14 days of stopping an MAOI intended to treat psychiatric disorders.</li> <li>•In a patient who is being treated with linezolid or intravenous methylene blue.</li> </ul> <i>[see Dosage and Administration (2.7), Contraindications (4) and Warnings and Precautions (5.2)].</i>
<i>Examples</i>	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Other Serotonergic Drugs	
<i>Clinical Impact</i>	Concomitant use of desvenlafaxine with other serotonergic drugs increases the risk of serotonin syndrome.
<i>Intervention</i>	Monitor for symptoms of serotonin syndrome when desvenlafaxine is used concomitantly with other drugs that may affect the serotonergic neurotransmitter systems. If serotonin syndrome occurs, consider discontinuation of desvenlafaxine and/or concomitant serotonergic drugs <i>[see Warnings and Precautions (5.2)].</i>
<i>Examples</i>	Other SNRIs, SSRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort
Drugs that Interfere with Hemostasis	
<i>Clinical Impact</i>	Concomitant use of desvenlafaxine with an antiplatelet or anticoagulant drug may potentiate the risk of bleeding. This may be due to the effect of desvenlafaxine on the release of serotonin by platelets.
<i>Intervention</i>	Closely monitor for bleeding for patients receiving an antiplatelet or anticoagulant drug when desvenlafaxine is initiated or discontinued <i>[see Warnings and Precautions (5.4)].</i>
<i>Examples</i>	NSAIDs, aspirin, and warfarin
Drugs that are Primarily Metabolized by CYP2D6	
<i>Clinical Impact</i>	Concomitant use of desvenlafaxine increases C <sub>max</sub> and AUC of a drug primarily metabolized by CYP2D6 which may increase the risk of toxicity of the CYP2D6 substrate drug <i>[see Clinical Pharmacology (12.3)].</i>
<i>Intervention</i>	Original dose should be taken when co-administered with desvenlafaxine 100 mg or lower. Reduce the dose of these drugs by up to one-half if co-administered with 400 mg of desvenlafaxine.
<i>Examples</i>	desipramine, atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine

## 7.2 Drugs Having No Clinically Important Interactions with Desvenlafaxine

Based on pharmacokinetic studies, no dosage adjustment is required for drugs that are mainly metabolized by CYP3A4 (e.g., midazolam), or for drugs that are metabolized by both CYP2D6 and CYP3A4 (e.g., tamoxifen, aripiprazole), when administered concomitantly with desvenlafaxine [see *Clinical Pharmacology (12.3)*].

## 7.3 Alcohol

A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking desvenlafaxine.

## 7.4 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of desvenlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185.

### Risk summary

Based on data from published observational studies, exposure to SNRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage [see *Warnings and Precautions (5.4) and Clinical Considerations*].

There are no published studies on desvenlafaxine in pregnant women; however published epidemiologic studies of pregnant women exposed to venlafaxine, the parent compound, have not reported a clear association with adverse developmental outcomes (see *Data*). There are risks associated with untreated depression in pregnancy and with exposure to SNRIs and SSRIs, including desvenlafaxine, during pregnancy (see *Clinical Considerations*).

In reproductive developmental studies in rats and rabbits treated with desvenlafaxine succinate, there was no evidence of teratogenicity at a plasma exposure (AUC) that is up to 19-times (rats) and 0.5-times (rabbits) the exposure at an adult human dose of

100 mg per day. However, fetotoxicity and pup deaths were observed in rats at 4.5-times the AUC exposure observed with an adult human dose of 100 mg per day.

-

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

### Clinical Considerations

#### *Disease-associated maternal and/or embryo/fetal risk*

A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

#### *Maternal adverse reactions*

Exposure to desvenlafaxine in mid to late pregnancy may increase the risk for preeclampsia, and exposure to desvenlafaxine in the month before delivery may be associated with an increased risk of postpartum hemorrhage [see *Warnings and Precautions (5.4)*].

#### *Fetal/Neonatal adverse reactions*

Exposure to SNRIs or SSRIs in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding. Monitor neonates who were exposed to desvenlafaxine in the third trimester of pregnancy for drug discontinuation syndrome (see *Data*).

### Data

#### *Human Data*

Published epidemiological studies of pregnant women exposed to the parent compound venlafaxine have not reported a clear association with major birth defects or miscarriage. Methodological limitations of these observational studies include possible exposure and outcome misclassification, lack of adequate controls, adjustment for confounders, and confirmatory studies; therefore, these studies cannot establish or exclude any drug-associated risk during pregnancy.

Retrospective cohort studies based on claims data have shown an association between venlafaxine use and preeclampsia, compared to depressed women who did not take an antidepressant during pregnancy. One study that assessed venlafaxine exposure in the second trimester or first half of the third trimester and preeclampsia showed an increased risk compared to unexposed depressed women (adjusted (adj) RR 1.57, 95% CI 1.29 to 1.91). Preeclampsia was observed at venlafaxine doses equal to or greater than 75 mg/day and a duration of treatment >30 days. Another study that assessed

venlafaxine exposure in gestational weeks 10 to 20 and preeclampsia showed an increased risk at doses equal to or greater than 150 mg/day. Available data are limited by possible outcome misclassification and possible confounding due to depression severity and other confounders.

Retrospective cohort studies based on claims data have suggested an association between venlafaxine use near the time of delivery or through delivery and postpartum hemorrhage. One study showed an increased risk for postpartum hemorrhage when venlafaxine exposure occurred through delivery, compared to unexposed depressed women (adj RR 2.24, 95% CI 1.69 to 2.97). There was no increased risk in women who were exposed to venlafaxine earlier in pregnancy. Limitations of this study include possible confounding due to depression severity and other confounders. Another study showed an increased risk for postpartum hemorrhage when SNRI exposure occurred for at least 15 days in the last month of pregnancy or through delivery, compared to unexposed women (adj RR 1.64 to 1.76). The results of this study may be confounded by the effects of depression.

Neonates exposed to SNRIs or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions (5.2)*].

### *Animal Data*

When desvenlafaxine succinate was administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 300 mg/kg/day and 75 mg/kg/day, respectively, no teratogenic effects were observed. These doses were associated with a plasma exposure (AUC) 19 times (rats) and 0.5 times (rabbits) the AUC exposure at an adult human dose of 100 mg per day. However, fetal weights were decreased and skeletal ossification was delayed in rats in association with maternal toxicity at the highest dose, with an AUC exposure at the no-effect dose that is 4.5-times the AUC exposure at an adult human dose of 100 mg per day.

When desvenlafaxine succinate was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weights and an increase in pup deaths during the first four days of lactation at the highest dose of 300 mg/kg/day. The cause of these deaths is not known. The AUC exposure at the no-effect dose for rat pup mortality was 4.5-times the AUC exposure at an adult human dose of 100 mg per day. Post-weaning growth and reproductive performance of the progeny were not affected by maternal treatment with desvenlafaxine succinate at exposures 19 times the AUC exposure at an adult human dose of 100 mg per day.

## **8.2 Lactation**

## Risk Summary

Available limited data from published literature show low levels of desvenlafaxine in human milk, and have not shown adverse reactions in breastfed infants (see *Data*). There are no data on the effects of desvenlafaxine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for desvenlafaxine and any potential adverse effects on the breastfed child from desvenlafaxine or from the underlying maternal condition.

## Data

A lactation study was conducted in 10 breastfeeding women (at a mean of 4.3 months postpartum) who were being treated with a 50 to 150 mg daily dose of desvenlafaxine for postpartum depression. Sampling was performed at steady state (up to 8 samples) over a 24 hour dosing period, and included foremilk and hindmilk. The mean relative infant dose was calculated to be 6.8% (range of 5.5 to 8.1%). No adverse reactions were seen in the infants.

## **8.4 Pediatric Use**

The safety and effectiveness of desvenlafaxine have not been established in pediatric patients for the treatment of MDD.

Antidepressants, such as desvenlafaxine, increase the risk of suicidal thoughts and behaviors in pediatric patients [see the *Boxed Warning and Warnings and Precautions (5.1)*].

*Additional information describing clinical studies in which efficacy was not demonstrated in pediatric patients is approved for Wyeth Pharmaceuticals Inc. a subsidiary of Pfizer Inc.'s PRISTIQ® (desvenlafaxine) Extended-Release Tablets. However, due to Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.'s marketing exclusivity rights, this product is not labeled with that pediatric information.*

## Juvenile Animal Studies

In a juvenile animal study, male and female rats were treated with desvenlafaxine (75, 225 and 675 mg/kg/day) starting on postnatal day (PND) 22 through 112. Behavioral deficits (longer time immobile in a motor activity test, longer time swimming in a straight channel test, and lack of habituation in an acoustic startle test) were observed in males and females but were reversed after a recovery period. A No Adverse Effect Level (NOAEL) was not identified for these deficits. The Low Adverse Effect Level (LOAEL) was 75 mg/kg/day which was associated with plasma exposure (AUC) twice the levels measured with a pediatric dose of 100 mg/day.

In a second juvenile animal study, male and female rats were administered desvenlafaxine (75, 225 or 675 mg/kg/day) for 8 to 9 weeks starting on PND 22 and were mated with naïve counterparts. Delays in sexual maturation and decreased fertility, number of implantation sites and total live embryos were observed in treated females at all doses. The LOAEL for these findings is 75 mg/kg/day which was associated with an

AUC twice the levels measured with a pediatric dose of 100 mg/day. These findings were reversed at the end of a 4-week recovery period. The relevance of these findings to humans is not known.

## **8.5 Geriatric Use**

Of the 4,158 patients in pre-marketing clinical studies with desvenlafaxine, 6% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients  $\geq 65$  years of age compared to patients  $< 65$  years of age treated with desvenlafaxine [see *Adverse Reactions (6.1)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

SSRIs and SNRIs, including desvenlafaxine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions (5.9)*].

## **8.6 Renal Impairment**

Adjust the maximum recommended dosage in patients with moderate or severe renal impairment (CL<sub>cr</sub> 15 to 50 mL/min, C-G), or end-stage renal disease (CL<sub>cr</sub>  $< 15$  mL/min, C-G) [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

## **8.7 Hepatic Impairment**

Adjust the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15) [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

# **9 DRUG ABUSE AND DEPENDENCE**

## **9.1 Controlled Substance**

Desvenlafaxine is not a controlled substance.

# **10 OVERDOSAGE**

## **10.1 Human Experience with Overdosage**

There is limited clinical trial experience with desvenlafaxine succinate overdosage in humans. However, desvenlafaxine is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of desvenlafaxine) is presented below; the identical information can be found in the Overdosagesection of the venlafaxine package insert.

In postmarketing experience, overdose with venlafaxine (the parent drug of desvenlafaxine) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear.

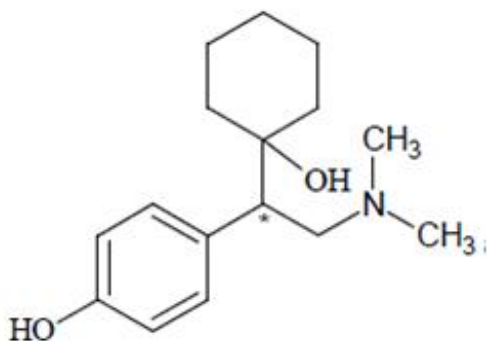
## 10.2 Management of Overdosage

No specific antidotes for desvenlafaxine are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

## 11 DESCRIPTION

Desvenlafaxine extended-release tablets for oral administration contains desvenlafaxine, USP, a structurally novel SNRI for the treatment of MDD. Desvenlafaxine (O-desmethylvenlafaxine), USP is the major active metabolite of the antidepressant venlafaxine, a medication used to treat major depressive disorder.

Desvenlafaxine, USP is designated *RS*-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol and has the empirical formula of  $C_{16}H_{25}NO_2$ . Desvenlafaxine, USP has a molecular weight of 263.38. The structural formula is shown below.





\* Chiral Centre

Desvenlafaxine, USP is a white to off-white crystalline powder that is sparingly soluble in dimethyl sulfoxide. The solubility of desvenlafaxine is pH dependent.

Desvenlafaxine, USP is formulated as an extended-release tablet for once-a-day oral administration.

Each 50 mg or 100 mg extended-release tablet contains 50 or 100 mg of desvenlafaxine, USP, respectively.

Inactive ingredients for the 50 mg tablet consist of alginic acid, citric acid monohydrate powder, hypromellose, microcrystalline cellulose, povidone, talc, magnesium stearate and film coating, which consist of hypromellose, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

Inactive ingredients for the 100 mg tablet consist of alginic acid, citric acid monohydrate powder, hypromellose, microcrystalline cellulose, povidone, talc, magnesium stearate and film coating, which consist of hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, and iron oxide black.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

The exact mechanism of the antidepressant action of desvenlafaxine is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of their reuptake. Non-clinical studies have shown that desvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI).

### **12.2 Pharmacodynamics**

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H<sub>1</sub>-histaminergic, or  $\alpha_1$ -adrenergic receptors in vitro. Desvenlafaxine also lacked monoamine oxidase (MAO) inhibitory activity.

#### ECG changes

Electrocardiograms were obtained from 1,492 desvenlafaxine treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between desvenlafaxine treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval.

### **12.3 Pharmacokinetics**

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 50 to 600 mg (1 to 12 times the recommended approved dosage) per day. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4 to 5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.

### Absorption

The absolute oral bioavailability of desvenlafaxine after oral administration is about 80%.

### *Effect of Food*

Ingestion of a high-fat meal (800 to 1000 calories) increased desvenlafaxine  $C_{max}$  about 16% and had no effect on AUC.

### Distribution

Steady-state volume of distribution of desvenlafaxine is 3.4 L/kg. Plasma protein binding of desvenlafaxine is 30% and is independent of drug concentration.

### Elimination

### *Metabolism*

Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 mediates the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved. The pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype.

### *Excretion*

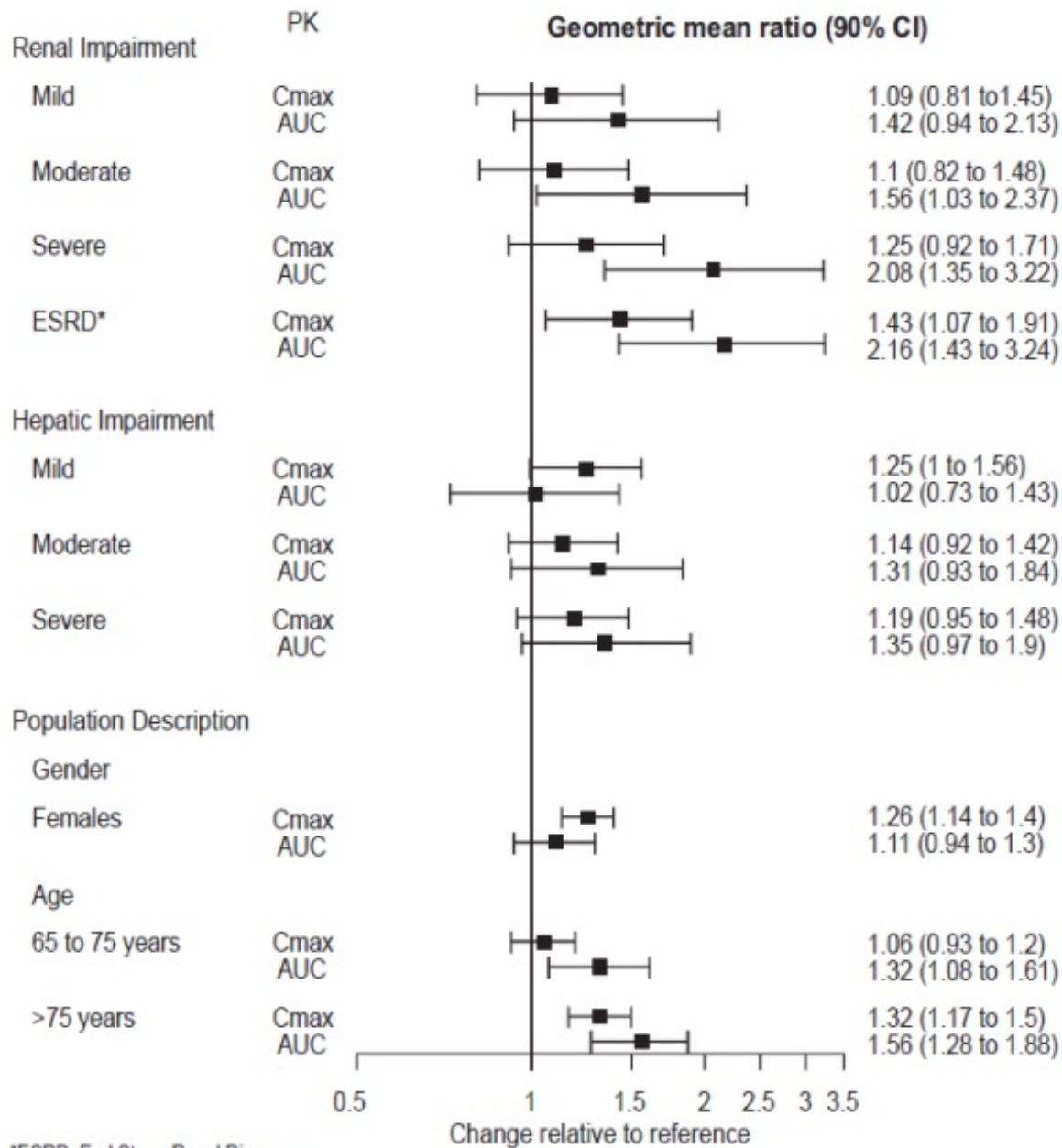
Approximately 45% of desvenlafaxine is excreted unchanged in urine at 72 hours after oral administration. Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

### Specific Populations

No clinically significant differences in the exposures of desvenlafaxine were observed based on ethnicity (White, Black, Hispanic).

The effect of intrinsic patient factors on the pharmacokinetics of desvenlafaxine is presented in Figure 1.

## **Figure 1. Impact of Intrinsic Factors (Renal, Hepatic Impairment and Population Description) on Desvenlafaxine Pharmacokinetics**



\*ESRD: End Stage Renal Disease

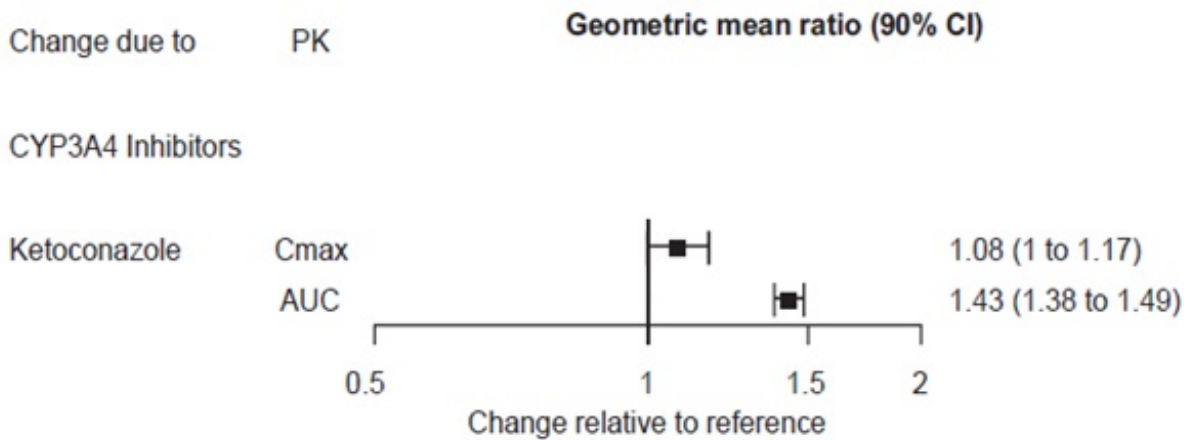
## Drug Interaction Studies

### *Clinical Studies*

#### *Other Drugs on Desvenlafaxine*

The effect of ketoconazole on the exposures of desvenlafaxine is summarized in Figure 2.

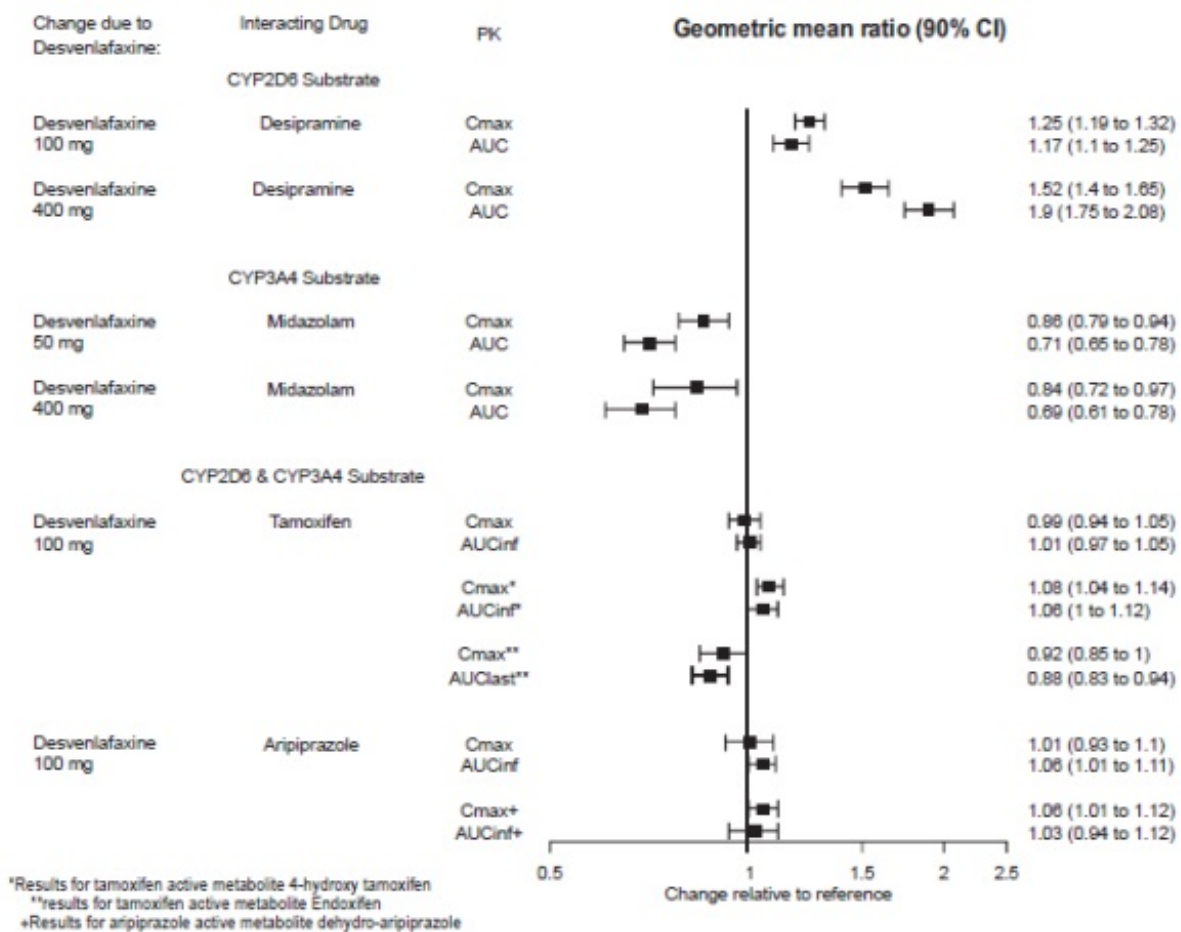
### **Figure 2. Effect of Other Drugs on Desvenlafaxine Pharmacokinetics**



### Desvenlafaxine on Other Drugs

The effects of desvenlafaxine on the exposures of other drugs are summarized in Figure 3.

**Figure 3. Effects of Desvenlafaxine on Pharmacokinetics of Other Drugs**



### In Vitro Studies

Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of desvenlafaxine.

Desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, 2C19, CYP2D6, or CYP3A4 isozymes. Desvenlafaxine does not induce CYP3A4 either.

Desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein (P-gp) transporter.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Desvenlafaxine succinate administered by oral gavage to mice and rats for 2 years did not increase the incidence of tumors in either study.

Mice received desvenlafaxine succinate at dosages up to 500/300 mg/kg/day (dosage lowered after 45 weeks of dosing). The AUC exposure at 300 mg/kg/day dose is estimated at 10 times the AUC exposure at an adult human dose of 100 mg per day.

Rats received desvenlafaxine succinate at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The AUC exposure at the highest dose is estimated at 11 (males) or 26 (females) times the AUC exposure at an adult human dose of 100 mg per day.

#### Mutagenesis

Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine was not genotoxic in the *in vitro* CHO mammalian cell forward mutation assay and was negative in the *in vitro* BALB/c-3T3 mouse embryo cell transformation assay.

#### Impairment of fertility

When desvenlafaxine succinate was administered orally to male and female rats, fertility was reduced at the high dose of 300 mg/kg/day, which is 10 (males) and 19 (females) times the AUC exposure at an adult human dose of 100 mg per day. There was no effect on fertility at 100 mg/kg/day, which is 3 (males) or 5 (females) times the AUC exposure at an adult human dose of 100 mg per day. These studies did not address reversibility of the effect on fertility. The relevance of these findings to humans is not known.

## **14 CLINICAL STUDIES**

### **Major Depressive Disorder**

The efficacy of desvenlafaxine as a treatment for depression was established in four 8-week, randomized, double-blind, placebo-controlled, fixed-dose studies (at doses of 50

mg per day to 400 mg per day) in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder. In the first study, patients received 100 mg (n = 114), 200 mg (n = 116), or 400 mg (n = 113) of desvenlafaxine once daily, or placebo (n = 118). In a second study, patients received either 200 mg (n = 121) or 400 mg (n = 124) of desvenlafaxine once daily, or placebo (n = 124). In two additional studies, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of desvenlafaxine once daily, or placebo (n = 150 and n = 161).

Desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D<sub>17</sub>) total score in four studies and overall improvement, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four studies. In studies directly comparing 50 mg per day and 100 mg per day there was no suggestion of a greater effect with the higher dose and adverse reactions and discontinuations were more frequent at higher doses [see Dosage and Administration (2.1)].

**Table 9: Primary Efficacy (HAM-D<sub>17</sub>) Results for Short-term Studies**

Study No.	Primary Endpoint: HAM-D <sub>17</sub>	Placebo	Desvenlafaxine			
			50 mg/day	100 mg/day	200 mg/day	400 mg/day
1	Baseline Score (SD <sup>a</sup> )	23.1 (2.5)		23.2 (2.5)	22.9 (2.4)	23 (2.2)
	Difference from Placebo (95% CI <sup>c</sup> )			-2.9 <sup>b</sup> (-5.1, -0.8)	-2	-3.1 <sup>b</sup> (-5.2, -0.9)
2	Baseline Score (SD <sup>a</sup> )	25.3 (3.3)			24.8 (2.9)	25.2 (3.2)
	Difference from Placebo (95% CI <sup>c</sup> )				-3.3 <sup>b</sup> (-5.3, -1.2)	-2.8 <sup>b</sup> (-4.8, -0.7)
3	Baseline Score (SD <sup>a</sup> )	23 (2.6)	23.4 (2.6)	23.4 (2.6)		
	Difference from Placebo (95% CI <sup>c</sup> )		-1.9 <sup>b</sup> (-3.5, -0.3)	-1.5		
4	Baseline Score (SD <sup>a</sup> )	24.3 (2.6)	24.3 (2.4)	24.4 (2.7)		
	Difference from Placebo (95% CI <sup>c</sup> )		-2.5 <sup>b</sup> (-4.1, -0.9)	-3 <sup>b</sup> (-4.7, -1.4)		

<sup>a</sup> Standard deviation;

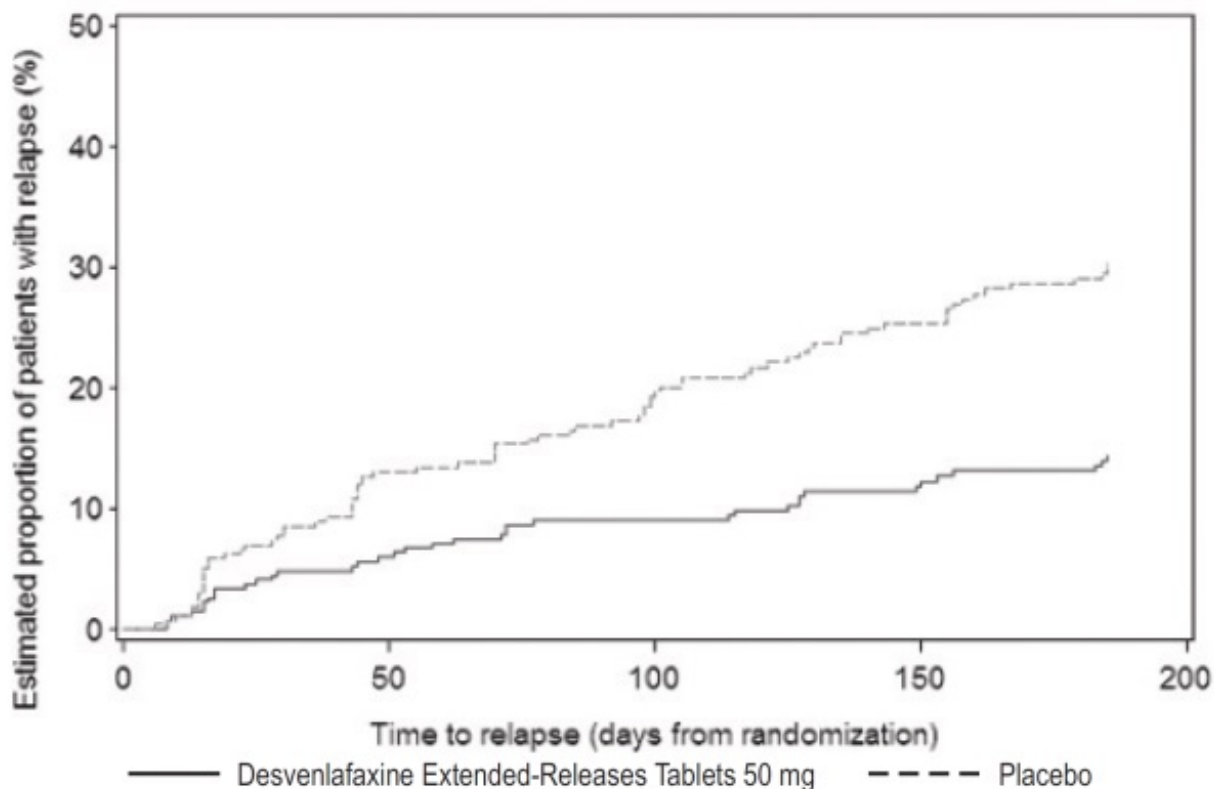
<sup>b</sup> Adjusted p-value < 0.05;

<sup>c</sup> Difference between least squares means at final evaluation, calculated as drug response minus placebo response; unadjusted 95% confidence intervals

Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics. There was insufficient information to determine the effect of race on outcome in these studies.

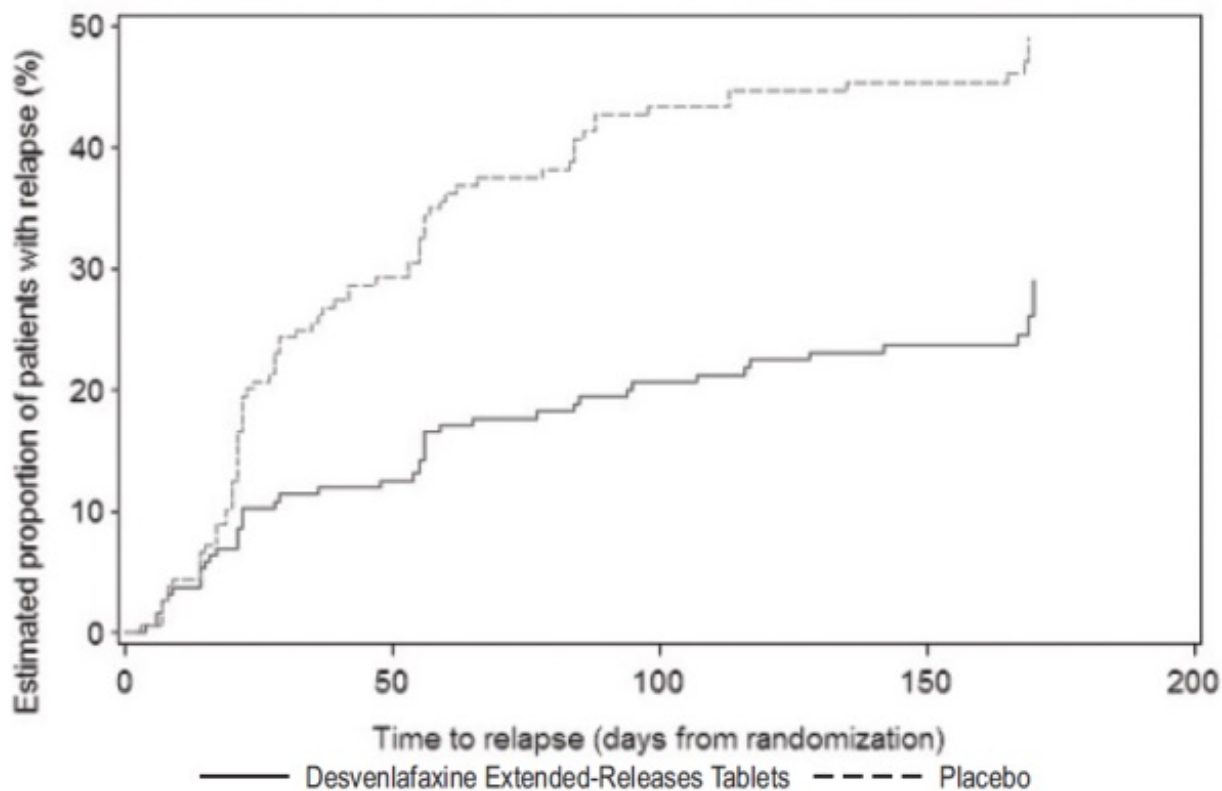
In a longer-term trial (Study 5), adult outpatients meeting DSM-IV criteria for major depressive disorder, who responded to 8 weeks of open-label acute treatment with 50 mg per day desvenlafaxine and subsequently remained stable for 12 weeks on desvenlafaxine, were assigned randomly in a double-blind manner to remain on active treatment or switch to placebo for up to 26 weeks of observation for relapse. Response during the open-label phase was defined as a HAM-D<sub>17</sub> total score of  $\leq 11$  and CGI-I  $\leq 2$  at the day 56 evaluation; stability was defined as HAM-D<sub>17</sub> total score of  $\leq 11$  and CGI-I  $\leq 2$  at week 20 and not having a HAM-D<sub>17</sub> total score of  $\geq 16$  or a CGI-I score  $\geq 4$  at any office visit. Relapse during the double-blind phase was defined as follows: (1) a HAM-D<sub>17</sub> total score of  $\geq 16$  at any office visit, (2) discontinuation for unsatisfactory efficacy response, (3) hospitalized for depression, (4) suicide attempt, or (5) suicide. Patients receiving continued desvenlafaxine treatment experienced statistically significantly longer time to relapse compared with placebo. At 26 weeks, the Kaplan-Meier estimated proportion of relapse was 14% with desvenlafaxine treatment versus 30% with placebo.

**Figure 4. Estimated Proportion of Relapses vs. Number of Days since Randomization (Study 5)**



In another longer-term trial (Study 6), adult outpatients meeting DSM-IV criteria for major depressive disorder and who responded to 12 weeks of acute treatment with desvenlafaxine were assigned randomly to the same dose (200 or 400 mg per day) they had received during acute treatment or to placebo for up to 26 weeks of observation for relapse. Response during the open-label phase was defined as a HAM-D<sub>17</sub> total score of  $\leq 11$  at the day 84 evaluation. Relapse during the double-blind phase was defined as follows: (1) a HAM-D<sub>17</sub> total score of  $\geq 16$  at any office visit, (2) a CGI-I score of  $\geq 6$  (versus day 84) at any office visit, or (3) discontinuation from the trial due to unsatisfactory response. Patients receiving continued desvenlafaxine treatment experienced statistically significantly longer time to relapse over the subsequent 26 weeks compared with those receiving placebo. At 26 weeks, the Kaplan-Meier estimated proportion of relapse was 29% with desvenlafaxine treatment versus 49% with placebo.

**Figure 5. Estimated Proportion of Relapses vs. Number of Days since Randomization (Study 6)**



In a postmarketing study, the efficacy of desvenlafaxine at a dose lower than 50 mg per day was evaluated in an 8-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study in adult outpatients with Major Depressive Disorder. The treatment arms were 25 mg (n=232), 50 mg (n=236), and placebo (n=231). The 50 mg dose was superior to placebo, as measured by the mean change from baseline on the HAM-D<sub>17</sub>. The 25 mg dose was not superior to placebo.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Desvenlafaxine extended-release tablets are available as follows:



50 mg, light pink colored, diamond shaped, biconvex tablets, debossed with 'L189' on one side and plain on other side.

NDC 63304-191-30, bottle of 30 tablets

NDC 63304-191-90, bottle of 90 tablets

100 mg, dark brown to red colored, diamond shaped, biconvex tablets, debossed with 'L190' on one side and plain on other side.

NDC 63304-192-30, bottle of 30 tablets

NDC 63304-192-90, bottle of 90 tablets

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Each 50 mg or 100 mg extended-release tablet contains 50 or 100 mg of desvenlafaxine, USP respectively.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down, and instruct them to report such symptoms to the healthcare provider [see *Boxed Warning and Warnings and Precautions (5.1)*].

### Concomitant Medication

Advise patients taking desvenlafaxine extended-release tablets not to use concomitantly other products containing desvenlafaxine or venlafaxine. Healthcare professionals should instruct patients not to take desvenlafaxine with an MAOI or within 14 days of stopping an MAOI and to allow 7 days after stopping desvenlafaxine before starting an MAOI [see *Contraindications (4)*].

### Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of desvenlafaxine with other serotonergic agents (including triptans, tricyclic antidepressants, opioids, lithium, tryptophan, buspirone, amphetamines, and St. John's Wort supplements)[see *Warnings and Precautions (5.2)*].

### Elevated Blood Pressure

Advise patients that they should have regular monitoring of blood pressure when taking desvenlafaxine [see *Warnings and Precautions (5.3)*].

### Sexual Dysfunction

Advise patients that use of desvenlafaxine extended-release tablets may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider [see *Warnings and Precautions (5.11)*].

### Increased Risk of Bleeding

Inform patients about the concomitant use of desvenlafaxine with NSAIDs, aspirin, other antiplatelet drugs, warfarin, or other coagulants because the combined use of has been associated with an increased risk of bleeding. Advise patients to inform their health care providers if they are taking or planning to take any prescription or over-the-counter medications that increase the risk of bleeding [see *Warnings and Precautions (5.4)*].

### Activation of Mania/Hypomania

Advise patients, their families, and caregivers to observe for signs of activation of mania/hypomania [see *Warnings and Precautions (5.6)*].

### Discontinuation

Advise patients not to abruptly stop taking desvenlafaxine without talking first with their healthcare professional. Patients should be aware that discontinuation effects may occur when stopping desvenlafaxine [see *Warnings and Precautions (5.7) and Adverse Reactions (6.1)*].

### Switching Patients From Other Antidepressants to Desvenlafaxine

Discontinuation symptoms have been reported when switching patients from other antidepressants, including venlafaxine, to desvenlafaxine. Tapering of the initial antidepressant may be necessary to minimize discontinuation symptoms.

### Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that desvenlafaxine therapy does not adversely affect their ability to engage in such activities.

### Alcohol

Advise patients to avoid alcohol while taking desvenlafaxine [see *Drug Interactions (7.3)*].

### Allergic Reactions

Advise patients to notify their physician if they develop allergic phenomena such as rash, hives, swelling, or difficulty breathing.

### Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become

pregnant during therapy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to desvenlafaxine during pregnancy [see *Use in Specific Populations (8.1)*].

#### Residual Inert Matrix Tablet

Patients receiving desvenlafaxine may notice an inert matrix tablet passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

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Manufactured by:  
Alembic Pharmaceuticals Limited  
(Formulation Division),  
Village Panelav, P. O. Tajpura, Near Baska,  
Taluka-Halol, Panchmahal, Gujarat, India.

Distributed by:  
Sun Pharmaceutical Industries, Inc.  
Cranbury, NJ 08512 USA

### **MEDICATION GUIDE** **Desvenlafaxine (des VEN la FAX een)** **extended-release tablets**

#### **What is the most important information I should know about desvenlafaxine?**

##### **Desvenlafaxine can cause serious side effects, including:**

o **Increased risk of suicidal thoughts or actions in some children, adolescents and young adults.** Desvenlafaxine and other antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger, **especially within the first few months of treatment or when the dose is changed. Desvenlafaxine is not for use in children.**

• **Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a higher risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness) or have a history of suicidal thoughts or actions.

##### **How can I watch for and try to prevent suicidal thoughts and actions?**

o Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings, or if you develop suicidal thought or actions. This is very important when an antidepressant medicine is started or when the dose is changed.

o Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.

o Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call your healthcare provider or get emergency help right away if you or a**

**family member have any of the following symptoms, especially if they are new, worse, or worry you:**

- o thoughts about suicide or dying
- o attempts to commit suicide
- o new or worse depression
- o new or worse anxiety
- o feeling very agitated or restless (mania)
- o panic attacks
- o mood
- o trouble sleeping (insomnia)
- o new or worse irritability
- o acting aggressive, being angry, or violent
- o acting on dangerous impulses
- o an extreme increase in activity and talking
- o other unusual changes in behavior or

### **What is desvenlafaxine?**

Desvenlafaxine is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder (MDD).

It is not known if desvenlafaxine is safe and effective for use in children.

### **Who should not take desvenlafaxine?**

#### **Do not take desvenlafaxine if you:**

- are allergic to desvenlafaxine succinate, venlafaxine hydrochloride, or any of the ingredients in desvenlafaxine extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in desvenlafaxine.
- take a Monoamine Oxidase Inhibitor (MAOI)
- have stopped taking an MAOI in the last 14 days
- are being treated with the antibiotic linezolid or intravenous methylene blue

Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI or one of these medicines, including intravenous methylene blue.

#### **Do not start taking an MAOI for at least 7 days after you stop treatment with desvenlafaxine.**

#### **Before taking desvenlafaxine, tell your healthcare provider about all your medical conditions, including if you:**

- have or have a family history of suicide, depression, bipolar disorder, mania or hypomania
- have high blood pressure
- have or had heart problems or stroke
- have or had bleeding problems
- have glaucoma (high pressure in the eye)
- have or had seizures (convulsions)
- have low sodium levels in your blood
- have lung or breathing problems
- have high cholesterol or high triglycerides
- have kidney or liver problems
- drink alcohol
- are pregnant or plan to become pregnant. Desvenlafaxine may harm your unborn baby. Taking desvenlafaxine during your pregnancy may cause an increased risk of bleeding after delivery and may cause harm to you or your baby. Talk to your healthcare provider about the risk to your unborn baby if you take desvenlafaxine during pregnancy.
  - o Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with desvenlafaxine.
  - o There is a pregnancy registry for females who are exposed to desvenlafaxine during pregnancy. The purpose of the registry is to collect information about the health of females exposed to desvenlafaxine and their baby. If you become pregnant during

treatment with desvenlafaxine, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants. You can register by calling 1-844-405-6185.

- are breastfeeding or plan to breastfeed. Desvenlafaxine can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with desvenlafaxine.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Desvenlafaxine and other medicines may affect each other causing possible serious side effects. Desvenlafaxine may affect the way other medicines work and other medicines may affect the way desvenlafaxine works.

**Especially tell your healthcare provider if you take:**

- other MAOIs
- medicines to treat migraine headaches known as triptans
- tricyclic antidepressants
- lithium
- tramadol, fentanyl, meperidine, methadone, or other opioids
- tryptophan
- buspirone
- amphetamines
- St. John's Wort
- medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and warfarin
- medicines used to treat mood, anxiety, psychotic or thought disorders, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

Ask your healthcare provider if you are not sure if you are taking any of these medicines. Your healthcare provider can tell you if it is safe to take desvenlafaxine with your other medicines.

Do not start or stop any other medicines during treatment with desvenlafaxine without talking to your healthcare provider first. Stopping desvenlafaxine suddenly may cause you to have serious side effects. See, **“What are the possible side effects of desvenlafaxine?”**

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

---

#### **How should I take desvenlafaxine?**

- Take desvenlafaxine exactly as your healthcare provider tells you to. Do not change your dose or stop taking desvenlafaxine without first talking to your healthcare provider.
- Your healthcare provider may change the dose of desvenlafaxine until it is the right dose for you.
- Take desvenlafaxine 1 time a day at about the same time each day.
- Take desvenlafaxine with or without food.
- Swallow desvenlafaxine tablets whole with fluid. Do not divide, crush, chew, or dissolve desvenlafaxine tablets.
- When you take desvenlafaxine, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.
- If over-exposure occurs, call your Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

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#### **What should I avoid while taking desvenlafaxine?**

- Do not drive a car, operate heavy machinery or do other dangerous activities until you know how desvenlafaxine affects you.
- Avoiding drinking alcohol during treatment with desvenlafaxine.

### **What are the possible side effects of desvenlafaxine?**

#### **Desvenlafaxine can cause serious side effects, including:**

- See, **“What is the most important information I should know about desvenlafaxine?”**

- **Serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when you take desvenlafaxine with certain other medicines. See, **“Who should not take desvenlafaxine?”** Stop taking desvenlafaxine and call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the following signs and symptoms of serotonin syndrome:

- |   |   |
|---|---|
| o agitation                                   | o seeing or hearing things that are not real (hallucinations) |
| o confusion                                   | o coma  |
| o fast heart beat                             | o blood pressure changes                                      |
| o dizziness                                   | o sweating  |
| o flushing (hyperthermia)                     | o high body temperature                                       |
| o tremors, stiff muscles, or muscle twitching | o loss of coordination  |
| o seizures                                    | o nausea, vomiting, diarrhea                                  |

- **High blood pressure (hypertension).** Your healthcare provider should check your blood pressure before you start and during treatment with desvenlafaxine. If you have high blood pressure, it should be controlled before you start treatment with desvenlafaxine.

- **Increased risk of bleeding.** Taking desvenlafaxine with aspirin, NSAIDs, warfarin or blood thinners may add to this risk. Tell your healthcare provider right away about any unusual bleeding or bruising.

- **Eye problems (angle closure glaucoma).** Many antidepressant medicines, including desvenlafaxine, may cause a certain type of eye problem called angle closure glaucoma. Call your healthcare provider if you have changes in your vision or eye pain.

- **Manic episodes.** Manic episodes may happen in people with bipolar disorder who take desvenlafaxine. Symptoms may include:

- |                                     |                                       |
|-------------------------------------|---------------------------------------|
| o greatly increased energy          | o severe trouble sleeping             |
| o racing thoughts                   | o reckless behavior                   |
| o unusually grand ideas             | o excessive happiness or irritability |
| o talking more or faster than usual |                                       |

- **Discontinuation syndrome.** Suddenly stopping desvenlafaxine may cause you to have serious side effects. Your healthcare provider may want to decrease your dose slowly. Symptoms may include:

- |                              |                                   |  |
|------------------------------|-----------------------------------|--|
| o nausea                     | o sweating                        | o changes in your mood                   |
| o irritability and agitation | o dizziness                       | o electric shock sensation (paresthesia) |
| o tremor                     | o anxiety                         | o confusion                              |
| o headache                   | o tiredness                       | o problems sleeping                      |
| o hypomania                  | o ringing in your ears (tinnitus) | o seizures                               |

- **Seizures (convulsions).**

• **Low sodium levels in your blood (hyponatremia).** Low sodium levels in your blood may be serious and may cause death. Elderly people may be at greater risk for this. Signs and Symptoms of low sodium levels in your blood may include:

- o headache
- o difficulty concentrating
- o memory changes
- o confusion
- o weakness and unsteadiness on your feet which can lead to falls

**In severe or more sudden cases, signs and symptoms include:**

- o seeing or hearing things that are not real (hallucinations)
- o fainting
- o seizures
- o coma
- o respiratory arrest
- o death

• **Lung problems.** Some people who have taken the medicine venlafaxine, which is the same kind of medicine as the medicine in desvenlafaxine, have had lung problems. Symptoms of lung problems include difficulty breathing, cough, or chest discomfort. Tell your healthcare provider right away if you have any of these symptoms.

• **Sexual problems (dysfunction).** Taking serotonin and norepinephrine reuptake inhibitors (SNRIs), including desvenlafaxine, may cause sexual problems.

Symptoms in males may include:

- o Delayed ejaculation or inability to have an ejaculation
- o Decreased sex drive
- o Problems getting or keeping an erection

Symptoms in females may include:

- o Decreased sex drive
- o Delayed orgasm or inability to have an orgasm

Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with desvenlafaxine. There may be treatments your healthcare provider can suggest.

**The most common side effects of desvenlafaxine include:**

- nausea
- problems sleeping
- constipation
- decreased appetite
- sexual function problems
- dizziness
- sweating
- feeling sleepy
- anxiety

These are not all the possible side effects of desvenlafaxine.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store desvenlafaxine?**

- Store desvenlafaxine at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep desvenlafaxine and all medicines out of the reach of children.**

**General Information about the safe and effective use of desvenlafaxine**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use desvenlafaxine for a condition for which it was not prescribed. Do not give desvenlafaxine to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about desvenlafaxine that is written for healthcare professionals.

**What are the ingredients in desvenlafaxine?**

**Active ingredient:** desvenlafaxine

**Inactive ingredients:**

**50 mg tablet:** alginic acid, citric acid monohydrate powder, hypromellose, microcrystalline cellulose, povidone, talc, magnesium stearate and film coating, which consist of hypromellose, titanium dioxide, polyethylene glycol, talc, and iron oxide red

**100 mg tablet:** alginic acid, citric acid monohydrate powder, hypromellose, microcrystalline cellulose, povidone, talc, magnesium stearate and film coating, which consist of hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, and iron oxide black

Manufactured by:

Alembic Pharmaceuticals Limited  
(Formulation Division),  
Village Panelav, P. O. Tajpura, Near Baska,  
Taluka-Halol, Panchmahal, Gujarat, India.

Distributed by:

Sun Pharmaceutical Industries, Inc.  
Cranbury, NJ 08512 USA

For more information, call 1-800-406-7984.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 08/2023

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL- 50 mg**

Desvenlafaxine Extended-Release Tablets 50 mg (30 Tablets in 1 Bottle)

Each tablet contains 50 mg desvenlafaxine, USP.

63304-191-30

SEAL FOR YOUR PROTECTION  
Each tablet contains 50 mg desvenlafaxine, USP.  
Usual Dosage: See package insert.  
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]  
Package intended to be dispensed as a unit.  
Manufactured by:  
Alembic Pharmaceuticals Limited  
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Cranbury, NJ 08512 USA

NDC 63304-191-30  
**DESVENLAFAXINE  
EXTENDED-RELEASE  
TABLETS**  
**50 mg**  
PHARMACIST: Dispense the accompanying  
Medication Guide to each patient.  
SUN  
PHARMA  
Rx only 30 Tablets

63304191301  
N 3 20037354  
11/2022  
GUJ/RUGS/G/859

Coding Area  
NOT TO BE  
PRINTED  
34 x 30 mm

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL- 100 mg**

Desvenlafaxine Extended-Release Tablets 100 mg (30 Tablets in 1 Bottle)

Each tablet contains 100 mg desvenlafaxine, USP.

63304-192-30



SEALED FOR YOUR PROTECTION  
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 Village Panelav, P.O. Tajpura, Near Baska,  
 Taluka-Halol, Panchmahal, Gujarat, India.  
 Distributed by:  
 Sun Pharmaceutical Industries, Inc.  
 Cranbury, NJ 08512 USA

NDC 63304-192-30  
**DESVENLAFAXINE  
 EXTENDED-RELEASE  
 TABLETS**

**100 mg**

**PHARMACIST: Dispense the accompanying  
 Medication Guide to each patient.**



**Rx only 30 Tablets**



**Coding Area  
 NOT TO BE  
 PRINTED**

**34 x 30 mm**

# DESVENLAFAXINE

desvenlafaxine tablet, extended release

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:63304-191
<b>Route of Administration</b>	ORAL		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>DESVENLAFAXINE</b> (UNII: NG99554ANW) (DESVENLAFAXINE - UNII:NG99554ANW)	DESVENLAFAXINE	50 mg

## Inactive Ingredients

Ingredient Name	Strength
<b>ALGINIC ACID</b> (UNII: 8C3Z4148WZ)	
<b>CITRIC ACID MONOHYDRATE</b> (UNII: 2968PHW8QP)	
<b>HYPROMELLOSES</b> (UNII: 3NXW29V3WO)	
<b>CELLULOSE, MICROCRYSTALLINE</b> (UNII: OP1R32D61U)	
<b>POVIDONE K30</b> (UNII: U725QWY32X)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>POLYETHYLENE GLYCOL 6000</b> (UNII: 30IQX730WE)	
<b>FERRIC OXIDE RED</b> (UNII: 1K09F3G675)	

## Product Characteristics

<b>Color</b>	PINK (Light Pink)	<b>Score</b>	no score
<b>Shape</b>	DIAMOND (Biconvex)	<b>Size</b>	12mm
<b>Flavor</b>		<b>Imprint Code</b>	L189
<b>Contains</b>			

## Packaging

		<b>Marketing Start</b>	<b>Marketing End</b>
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-191-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/05/2013	
2	NDC:63304-191-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/05/2013	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204150	03/05/2013	

## DESVENLAFAXINE

desvenlafaxine tablet, extended release

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:63304-192
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DESVENLAFAXINE (UNII: NG99554ANW) (DESVENLAFAXINE - UNII:NG99554ANW)	DESVENLAFAXINE	100 mg

### Inactive Ingredients

Ingredient Name	Strength
ALGINIC ACID (UNII: 8C3Z4148WZ)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE K30 (UNII: U725QWY32X)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	

### Product Characteristics

Color	BROWN (Dark Brown to Red)	Score	no score
Shape	DIAMOND (Biconvex)	Size	12mm
Flavor		Imprint Code	L190
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63304-192-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	03/05/2013	
2	NDC:63304-192-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	03/05/2013	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204150	03/05/2013	

**Labeler** - Sun Pharmaceutical Industries, Inc. (146974886)

## Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		650574671	MANUFACTURE(63304-191, 63304-192)

Revised: 8/2023

Sun Pharmaceutical Industries, Inc.