For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

NEWVEN OD

1. Generic Name

Desvenlafaxine Extended-Release Tablets 50 / 100 mg.

2. Qualitative and quantitative Composition:

NEWVEN OD 50

Each film coated extended-release tablet contains:

Desvenlafaxine Succinate Monohydrate U.S.P

equivalent to Desvenlafaxine……. 50 mg

Excipients ……..q.s.

Colours: Ferric Oxide Red USP-NF & Titanium Dioxide I.P.

The list of excipients used are Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyvinylpyrrolidone, Isopropyl alcohol, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Polyethylene glycol, Titanium dioxide, Red oxide of Iron, Dichloromethane.

NEWVEN OD 100

Each film coated extended-release tablet contains:

Desvenlafaxine Succinate Monohydrate U.S.P

equivalent to Desvenlafaxine…….100 mg

Excipients ……..q.s.

Colours: Lake of Quinoline Yellow & Titanium Dioxide I.P.

The list of excipients used are Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyvinylpyrrolidone, Isopropyl alcohol, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Polyethylene glycol, Titanium dioxide, Quinoline Yellow Lake Colour, Methylene Chloride

3. .Dosage form and strength

Dosage form: Extended release Tablet

Strength: 50 mg and 100 mg

4. Clinical particulars

4.1. Therapeutic indication

Desvenlafaxine used for the treatment of major depressive disorder (MDD)

4.2. Posology and method of administration

General Instruction for use

The recommended dose for desvenlafaxine extended-release tablets are 50 mg once daily, with or without food. The 50 mg dose is both a starting dose and the therapeutic dose. Desvenlafaxine extended-release tablets 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.

The 25 mg per day dose is intended for a gradual reduction in dose when discontinuing treatment. When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimize discontinuation symptoms.

Dosage recommendations for patients with renal impairment

The maximum recommended dose in patients with moderate renal impairment (24-hr creatinine clearance [ClCr] = 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 15 to 29 mL/min, C-G) or end-stage renal disease (ESRD, ClCr <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.

Dosage recommendations for patients with hepatic impairement

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.

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. Patients should be periodically reassessed to determine the need for continued treatment.

Discontinuing Desvenlafaxine

Adverse reactions may occur upon discontinuation of desvenlafaxine. Gradually reduce the dosage rather than stopping desvenlafaxine abruptly when discontinuing therapy with desvenlafaxine. In some patients, discontinuation may need to occur over a period of several months

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.

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 extended-release tablets. Conversely, at least 7 days should be allowed after stopping desvenlafaxine extended-release tablets before starting an MAOI intended to treat psychiatric disorders

Use of Desvenlafaxine extended-release tablets with other MAOIs such as Linezolid or Methylene Blue

Do not start desvenlafaxine extended-release tablets 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.

In some cases, a patient already receiving desvenlafaxine extended-release tablets therapy

may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not Cr 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 extended-release tablets 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 extended-release tablets may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

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 extended-release tablet is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use.

4.3. Contraindications

- Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the desvenlafaxine formulation. Angioedema has been reported in patients treated with desvenlafaxine.
- 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
- 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

4.4. Special warnings and precautions for use

Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

Patients with 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 as 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

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated**
	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
<18	14 additional 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.

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 extended-release tablets 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.

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.

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.

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.

Elevated Blood Pressure

Patients receiving desvenlafaxine should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies *(6.1)]*. Pre-existing hypertension should be controlled before initiating treatment with desvenlafaxine. Caution should be exercised in treating patients with preexisting 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 extended-release tablets, either dose reduction or discontinuation should be considered.

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. 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.

Angle Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including desvenlafaxine extended-release tablets 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 extended-release tablets in patients with untreated anatomically narrow angles.

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.

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.

There have been post marketing reports of serious discontinuation symptoms with desvenlafaxine, which can be protracted and severe. Completed suicide, suicidal thoughts, and severe aggression (including hostility, rage, and homicidal ideation) have been observed in patients during reduction in desvenlafaxine dosage, including during discontinuation. Other post marketing reports describe visual changes (such as blurred vision or trouble focusing) and increased blood pressure after stopping or reducing the dose of desvenlafaxine.

Patients should be monitored when discontinuing treatment with desvenlafaxine. A gradual reduction in the dose, rather than abrupt cessation, is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the healthcare provider may continue decreasing the dose, but at a more gradual rate. In some patients, discontinuation may need to occur over a period of several months

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 succinate should be prescribed with caution in patients with a seizure disorder.

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. 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.

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.

Sexual Dysfunction

Use of SNRIs, including desvenlafaxine, may cause symptoms of sexual dysfunction. 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.

4.5. Drugs interactions

Drugs Having Clinically Important Interactions with Desvenlafaxine

Table: Clinically Important Drug Interactions with Desvenlafaxine

Monoamine Oxidase Inhibitors (MAOI)	
Clinical Impact	The concomitant use of SSRIs and SNRIs including desvenlafaxine with MAOIs increases the risk of serotonin syndrome.
Intervention	Concomitant use of desvenlafaxine is

	contraindicated: With an MAOI intended to treat psychiatric disorders or within 7 days of stopping treatment with desvenlafaxine. Within 14 days of stopping an MAOI intended to treat psychiatric disorders. In a patient who is being treated with linezolid or intravenous methylene blue.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Other Serotonergic Drugs	
Clinical Impact	Concomitant use of desvenlafaxine with other serotonergic drugs increases the risk of serotonin syndrome.
Intervention	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
Examples	other SNRIs, SSRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort
Drugs that Interfere with Hemostasis	
Clinical Impact	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.
Intervention	Closely monitor for bleeding for patients receiving an antiplatelet or anticoagulant drug when desvenlafaxine is initiated or discontinued
Examples	NSAIDs, aspirin, and warfarin
Drugs that are Primarily Metabolized by CYP2D6	
Clinical Impact	Concomitant use of desvenlafaxine increases C and AUC of a drug primarily metabolized by CYP2D6 which may increase the risk of toxicity of the CYP2D6 substrate drug
Intervention	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
Examples	desipramine, atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine

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.

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.

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 folowing discontinuation of desvenlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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.

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. There are risks associated with untreated depression in pregnancy and with exposure to SNRIs and SSRIs, including desvenlafaxine, during pregnancy .

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. Al 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.

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.

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 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.

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 oraly 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.

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. 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.

Pediatric Use

The safety and effectiveness of desvenlafaxine, have not been established in pediatric patients for the treatment of MDD. Efficacy was not demonstrated in two adequate and wel controled, 8-week, randomized, double-blind, placebo-controled, paralel group studies conducted in 587 patients (7 to 17 years of age) for the treatment of MDD.

Antidepressants, such as desvenlafaxine, increase the risk of suicidal thoughts and behaviors in pediatric patients. Desvenlafaxine was associated with a decrease in body weight in placebo controled trials in pediatric patients with MDD. The incidence of weight loss (≥3.5% of baseline weight) was 22%, 14%, and 7% for patients treated with low dose desvenlafaxine, high dose desvenlafaxine, and placebo, respectively.

The risks associated with longer term desvenlafaxine use were assessed in 6-month, open-label extension studies in pediatric patients (7 to 17 years of age) with MDD. Pediatric patients (7 to 17 years of age) had mean changes in weight that approximated expected changes, based on data from age-and sex-matched peers.

In clinical trials, when compared to adult patients receiving the same dose of desvenlafaxine, exposure to desvenlafaxine was similar in adolescent patients 12 to 17 years of age, and was about 30% higher in pediatric patients 7 to 11 years of age.

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 al 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.

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 ≥65 years of age compared to patients < 15 mL/min, C-G).

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

Renal Impairment

Adjust the maximum recommended dosage in patients with moderate or severe renal impairment (CLcr 15 to 50 mL/min, C-G), or end-stage renal disease (CLcr < 15 mL/min, C-G).

Hepatic Impairment

Adjust the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15).

4.7. Effects on ability to drive and use machines.

Desvenlafaxine has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

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

- Hypersensitivity
- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

- Serotonin Syndrome
- Elevated Blood Pressure
- Increased Risk of Bleeding
- Angle Closure Glaucoma
- Activation of Mania/ Hypomania
- Discontinuation Syndrome
- Seizure
- Hyponatremia
- Interstitial Lung Disease and Eosinophilic Pneumonia
- Sexual Dysfunction

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 succinate (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 ≥ 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 shows the incidence of common adverse reactions that occurred in ≥ 2% of desvenlafaxine extended-release tablets treated MDD patients and twice the rate of placebo at any dose in the pre-marketing pooled 8-week, placebo-controlled, fixed dose clinical studies

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

	Percentage of Patients Reporting Reaction Desvenlafaxine Extended-Release Tablets				
System Organ Class	Placebo (n=636)	50 mg (n=317)	100 mg (n=424)	200 mg (n=307)	400 mg (n=317)
Cardiac disorders					
Blood pressure increased	1	1	1	1	1
Gastrointestinal disorders					
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
General disorders and administration site conditions					
Fatigue	4	7	7	10	11
Chills	1	1	<1	3	4
Feeling jittery	1	1	2	3	3
Metabolism and nutrition disorders					
Decreased appetite	2	5	8	10	10
Nervous system disorders					
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
Psychiatric disorders					
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
Renal and urinary disorders					
Urinary hesitation	0	<1	1	4	3
Respiratory, thoracic and mediastinal disorders					
Yawning	<1	1	1	4	3
Skin and subcutaneous tissue disorders					
Hyperhidrosis	4	10	11	18	21
Special Senses					
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
Vascular disorders					

	Percentage of Patients Reporting Reaction Desvenlafaxine Extended-Release Tablets				
Hot Flush	<1	1	1	2	2

Sexual Function Adverse Reactions

Table shows the incidence of sexual function adverse reactions that occurred in ≥ 2% of desvenlafaxine extended-release tablets treated MDD patients in any fixed-dose group (pre-marketing pooled 8-week, placebo-controlled, fixed -dose, clinical studies)

Table: Sexual Function Adverse Reactions (≥2% in Men or Women in any Desvenlafaxine Succinate Group) During the On-Therapy Period

	Desvenlafaxine Extended-Release Tablets				
	Placebo (n=239)	**50 mg (n=108)**	**100 mg (n=157)**	**200 mg (n=131)**	**400 mg (n=154)**
Men Only					
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
Desvenlafaxine Extended-Release Tablets					
	Placebo (n=397)	**50 mg (n=209)**	**100 mg (n=267)**	**200 mg (n=176)**	**400 mg (n=163)**
Women only					
Anorgasmia	0	1	1	0	3

Other Adverse Reactions Observed in Premarketing and Post marketing Clinical Studies

Other infrequent adverse reactions, not described elsewhere in the label, occurring at an incidence of < 2% in MDD patients treated with desvenlafaxine extended-release tablets 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 controled, 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

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

	Desvenlafaxine Extended Release Tablets				
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Total Cholesterol * (Increase of ≥ 50 mg/dl and an absolute value of ≥ 261 mg/dl)					
	2	3	4	4	10
LDL Cholesterol * (Increase ≥ 50 mg/dl and an absolute value of ≥ 190 mg/dl)					
	0	1	0	1	2
Triglycerides, fasting * (Fasting: ≥ 327 mg/dl)					
	3	2	1	4	6

Proteinuria:

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

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

	Desvenlafaxine Extended-Release Tablets				
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Proteinuria	4	6	8	5	7

Vital Sign Changes:

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

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

	Desvenlafaxine Extended Release Tablets				
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Blood Pressure					
Supine Systolic bp(mm Hg)	-1.4	1.2	2.0	2.5	2.1
Supine Diastolic bp(mm Hg)	-0.6	0.7	0.8	1.8	2.3
Pulse rate					
Supine pulse (bpm)	-0.3	1.3	1.3	0.9	4.1
Weight (kg)	0.0	-0.4	-0.6	-0.9	-1.1

Treatment with desvenlafaxine at al 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) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits. Analyses of patients in desvenlafaxine succinate 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 al 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

Treatment Group	Proportion of patients with sustained hypertension
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	1.3%

Orthostatic Hypotension:

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

Post marketing 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:

Skin and subcutaneous tissue disorders – Stevens-Johnson syndrome

Gastrointestinal disorders – Pancreatitis acute

Cardiovascular system – Takotsubo cardiomyopathy

Respiratory, thoracic and mediastinal disorders – Anosmia, hyposmia

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

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 Overdosage section of the venlafaxine package insert.

In post marketing 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.

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 Centre at 1 800-222-1222 for latest recommendations.

5. Pharmacological properties

5.1. 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).

5.2. Pharmacodynamic properties

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic cholinergic, H-histaminergic, or a-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.

5.3. Pharmacokinetic properties

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 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.

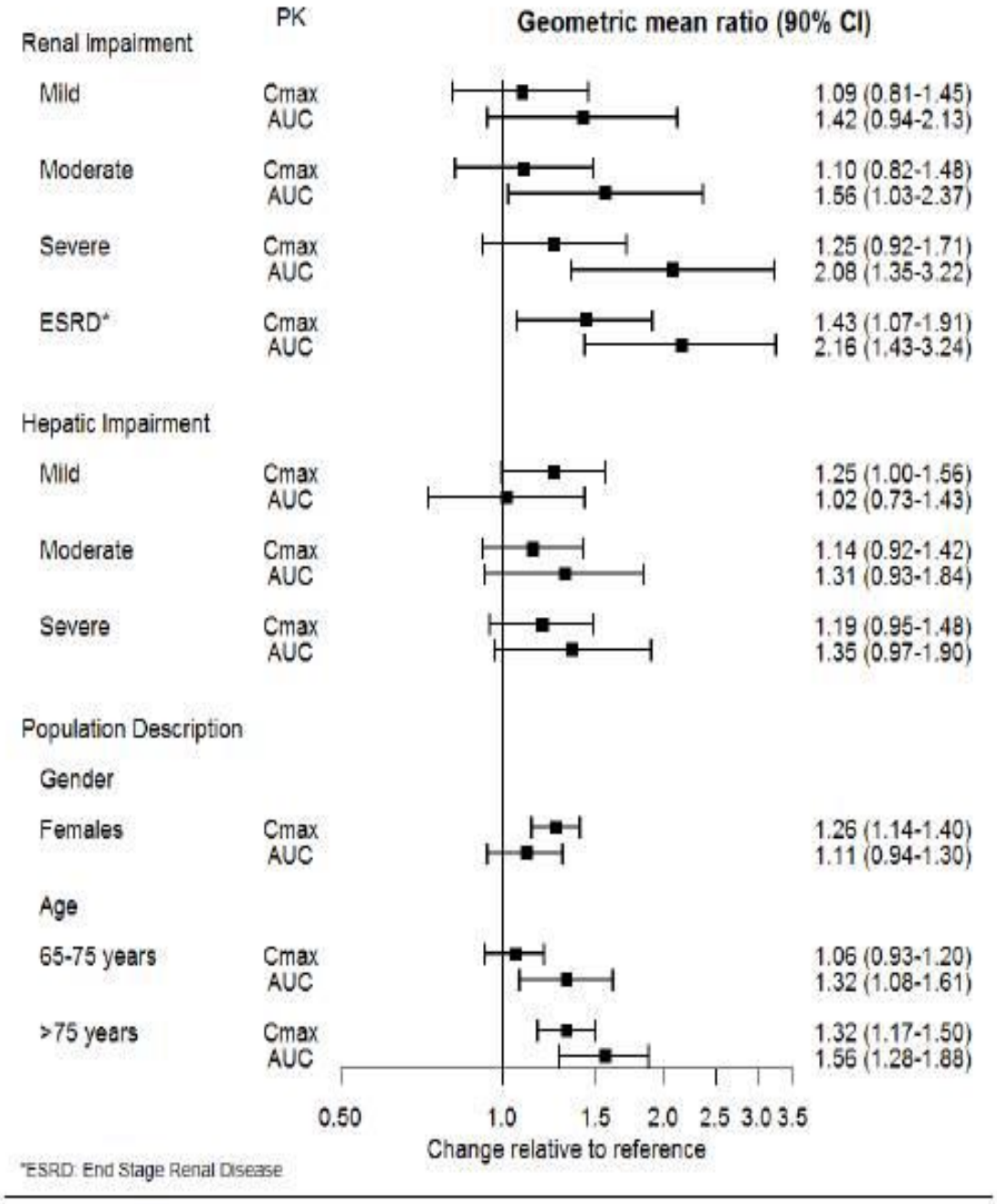
Excretion:

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.

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



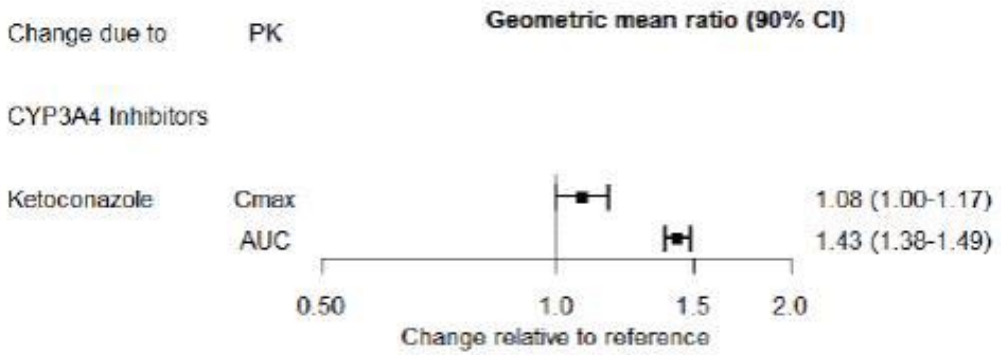
Drug Interaction Studies

Clinical Studies:

Other Drugs on Desvenlafaxine

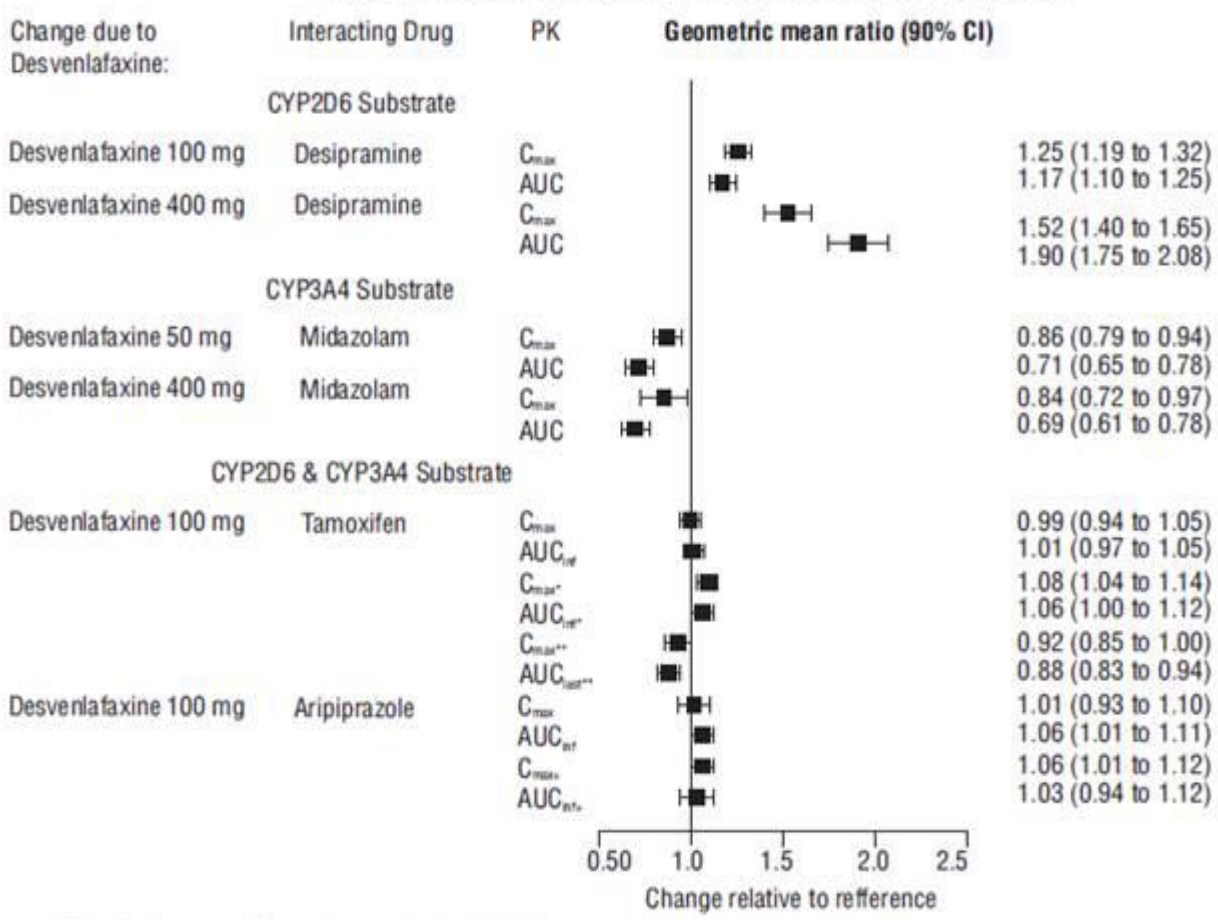
The effect of ketoconazole on the exposures of desvenlafaxine is summarized in Figure 2.

Figure 2. Effect of Other Drugs on Desvenlafaxine Pharmacokinetics



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



*Results for tamoxifen active metabolite 4-hydroxy-tamoxifen

**Results for tamoxifen active metabolite Endroxifen

+Results for aripiprazole active metabolite dehydro-aripiprazole

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.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

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

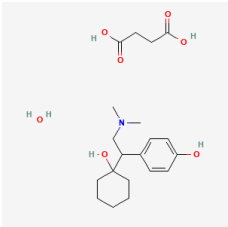
Desvenlafaxine was not mutagenic in the *in vitro* bacterial mutation assay (Ames test) and was not clastogenic in an *in vitro* chromosome aberration assay in cultured CHO cells, an *in vivo* mouse micronucleus assay, or an *in vivo* chromosome aberration assay in rats. Additionally, desvenlafaxine 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.

7. Description

Desvenlafaxine Succinate Monohydrate is butanedioicacid;4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol;hydrate. The empirical formula is $C_{20}H_{33}NO_7$and its molecular weight is 399.5 g/mol. The chemical structural formula is:



Newven OD 50

Newven OD 50 is Peach colour, circular shape, biconvex, film coated extended-release tablets having both sides plain. The list of excipients used are Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyvinylpyrrolidone, Isopropyl alcohol, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Polyethylene glycol, Titanium dioxide, Red oxide of Iron, Dichloromethane.

Newven OD 100

Newven OD 100 is yellow colour, circular shape, biconvex, film coated extended-release tablets having both sides plain. The list of excipients used are Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyvinylpyrrolidone, Isopropyl alcohol, Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Polyethylene glycol, Titanium dioxide, Quinoline Yellow Lake Colour, Methylene Chloride.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

Newven OD is available in Pack of 10 Tablets.

8.4. Storage and handing instructions.

Store in a dry & dark place at a temperature not exceeding 25^0C.

Keep out of reach of children.

Tablets to be swallowed whole, not to be crushed or chewed.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Ravenbhel Healthcare Pvt. Ltd.

(WHO & cGMP Certified company)

16-17, EPIP, SIDCO, Kartholi,

Bari Brahmana, Jammu -181133

11. Details of permission or licence number with date

Mfg. Lic. No.: JK/01/56. Issue on 19.07.2019

12. Date of revision

MAR 2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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