Denla XR

50mg & 100mg Tablet

(Desvenlafaxine Succinate)

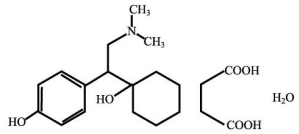
ڈینلا ایکس آر

۵۰ اور ۱۰۰ ملی گرام

(ڈیس وینلافیکسین سکسینیٹ)

Composition:
Each extended release tablet contains:
Desvenlafaxine Succinate equivalent to
Desvenlafaxine base 100mg
Each extended release tablet contains:
Desvenlafaxine Succinate equivalent to
Desvenlafaxine base 50mg

Description:
Denla XR is an extended-release tablet for oral administration that contains desvenlafaxine succinate, a structurally novel SNRI for the treatment of MDD. Desvenlafaxine (O desmethylvenlafaxine) is the major active metabolite of the antidepressant venlafaxine, a medication used to treat major depressive, generalized anxiety, social anxiety and panic disorders. Desvenlafaxine is designated RS-4-[2-dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol and has the empirical formula of C16H25NO2 (free base) and C16H25NO2oC4H6O4oH2O (succinate monohydrate). Desvenlafaxine succinate monohydrate has a molecular weight of 399.48. The structural formula is shown below.



Clinical Pharmacology:
Pharmacodynamics
Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or ?1-adrenergic receptors in vitro. Denla XR also lacked monoamine oxidase (MAO) inhibitory activity.
Pharmacokinetics
The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 100 to 600 mg/day. The mean terminal half-life, t1/2, is approximately 11 hours. With once-daily dosing, steady-state plasma concentrations are achieved within approximately 4-5 days. At steady-state, multiple-dose accumulation of desvenlafaxine is linear and predictable from the single-dose pharmacokinetic profile.
Absorption and Distribution
The absolute oral bioavailability of Denla XR after oral administration is about 80%. Mean time to peak plasma concentrations (Tmax) is about 7.5 hours after oral administration. A food-effect study involving administration of Denla XR to healthy subjects under fasting and fed conditions (high-fat meal) indicated that the Cmax was increased about 16% in the fed state, while the AUCs were similar. This difference is not clinically significant; therefore, Denla XR can be taken without regard to meals [see Dosage and Administration (2.1)]. The plasma protein binding of desvenlafaxine is low (30%) and is independent of drug concentration. The desvenlafaxine volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.
Metabolism and Elimination
Desvenlafaxine is primarily metabolized by conjugation (mediated by UGT isoforms) and, to a minor extent, through oxidative metabolism. CYP3A4 is the cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine. The CYP2D6 metabolic pathway is not involved, and after administration of 100 mg, the pharmacokinetics of desvenlafaxine was similar in subjects with CYP2D6 poor and extensive metabolizer phenotype. 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.
Indications and Usage
Denla XR, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD) [see Clinical Studies (14) and Dosage and Administration (2.1)]. The efficacy of Denla XR has been established in four 8-week, placebo-controlled studies of outpatients who met DSM-IV criteria for major depressive disorder. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.
Dosage and Administration:
Initial Treatment
The recommended dose for Denla XR is 50 mg once daily, with or without food. In clinical studies, doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day and adverse events 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 (2.4) and Warnings and Precautions (5.9)]. Denla XR should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.
Special Populations
Pregnant women during the third trimester
Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding [see Use in Specific Populations (8.1)]. When treating pregnant women with Denla XR during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Denla XR in the third trimester.
Patients with renal impairment,
No dosage adjustment is necessary in patients with mild renal impairment (24 hr CrCl = 50 80 mL/min).
The recommended dose in patients with moderate renal impairment (24 hr CrCl = 30 50 mL/min) is 50 mg per day. The recommended dose in patients with severe renal impairment (24-hr CrCl < 30 mL/min) or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis. The doses should not be escalated in patients with moderate or severe renal impairment, or ESRD [see Warnings and Precautions (5.10), Use in Specific Populations (8.6) and Clinical Pharmacology (12.6)].
Patients with hepatic impairment
The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see Clinical Pharmacology (12.6)].
Elderly patients, No dosage adjustment is required solely on the basis of age; however, the possibility of reduced renal clearance of Denla XR should be considered when determining the dose [see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6)].
Contraindications
Hypersensitivity
Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Denla XR formulation.
4.2 Monoamine Oxidase Inhibitors Denla XR must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Denla XR before starting an MAOI [see Dosage and Administration (2.6)].
Side Effects
The following adverse reactions are discussed in greater detail in other sections of the label;
" Hypersensitivity [see Contraindications (4.1)]
" Effects on blood pressure [see Warnings and Precautions (5.3)]
" Abnormal bleeding [see Warnings and Precautions (5.4)]
" Mydriasis [see Warnings and Precautions (5.5)]
" Hypomania and mania [see Warnings and Precautions (5.6)]
" Serum cholesterol and triglyceride elevation [see Warnings and Precautions (5.8)]
" Seizure [see Warnings and Precautions (5.11)]
with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients.
Clinical Studies Experience
The most commonly observed adverse reactions in PRISTIQ treated MDD patients in short-term 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.
Adverse Reactions Identified During Post-Approval Use
The following adverse reaction has been identified during post-approval use of PRISTIQ. Because post-approval 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 - Angioedema.
Adverse Reactions Reported With Other SNRIs
Although the following are not considered adverse reactions for desvenlafaxine succinate, they are adverse reactions for other SNRIs and may also occur with desvenlafaxine succinate: gastrointestinal bleeding, hallucinations, and photosensitivity reactions.
Drug Interactions:
Central Nervous System (CNS)-Active Agents
The risk of using Denla XR in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Denla XR is taken in combination with other CNS-active drugs [see Warnings and Precautions (5.13)].
Warnings:
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 18-24) 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 1000 patients treated) are provided in Table 1.
Pediatric Use
Safety and effectiveness in the pediatric population have not been established [seeÊÊand Warnings and Precautions ()]. Anyone considering the use of Denla XR in a child or adolescent must balance the potential risks with the clinical need.
Geriatric Use:
Of the 3,292 patients in clinical studies with Denla XR, 5% 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 < 65 years of age treated with Denla XR [see Adverse Reactions (6)]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)]. If Denla XR is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Denla XR, 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 (5.12)].
Greater sensitivity of some older individuals cannot be ruled out.
Overdose:
Human Experience
There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In pre-marketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. Among the patients included in the MDD pre-marketing studies of Denla XR, there were four adults who ingested desvenlafaxine succinate (4000 mg [desvenlafaxine alone], 900, 1800 and 5200 mg [in combination with other drugs]); all patients recovered. In addition, one patient's 11-month-old child accidentally ingested 600 mg of desvenlafaxine succinate, was treated, and recovered. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Denla XR included: headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Denla XR) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Denla XR) is presented below; the identical information can be found in the Overdosage section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Denla XR) 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. Prescriptions for Denla XR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Management of Overdose:
Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.
Instructions:
Store below 25°C. Protect from sunlight & moisture. Keep all medicines out of the reach of children.
How Supplied
Denla XR (desvenlafaxine) Extended Release Tablet are available as follows:
14 Tablets in Alu Alu blister, 1 blister in a box.

دوا کو دھوپ اور نمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

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Marketed by:
ORGANIC Pharmaceuticals