Generic Name Desvenlafaxine and Clonazepam

Trade Name Nexvenla OD Plus

ALKEM

1. NAME OF THE MEDICINAL PRODUCT: Desvenlafaxine & Clonazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated extended release tablet contains:
Desvenlafaxine succinate equivalent to
Desvenlafaxine ……..50mg
Clonazepam……0.5mg

3. PHARMACEUTICAL FORM: Film coated extended release tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications: For the treatment of major depressive disorder

4.2 Posology and Method of Administration

The combination of Desvenlafaxine and Clonazepam should be administered once daily.

Patients with renal impairment
Desvenlafaxine: The maximum recommended dose in patients with moderate renal impairment (24-hr creatinine clearance [CrCl] = 30 to 50 mL/min, Cockcroft-Gault [C-G]) is 50 mg per day. The maximum recommended dose in patients with severe renal impairment (24-hr CrCl less than 30 mL/min, C-G) or end-stage renal disease (ESRD) is 25 mg every day or 50 mg every other day. Supplemental doses should not be given to patients after dialysis.

Clonazepam: Based on kinetic criteria no dose adjustment is required in patients with renal failure.

Patients with hepatic impairment:
Desvenlafaxine: The recommended dose in patients with moderate to severe hepatic impairment is 50 mg per day. Dose escalation above 100 mg per day is not recommended.

Clonazepam: In patients with mild to moderate hepatic impairment the dose should be adjusted to individual requirements and will probably be lower.

Pediatric Use: Should not be used.

Geriatric Use:

Desvenlafaxine: For elderly patients, possible reduced renal clearance of Desvenlafaxine should be considered when determining dose. 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.

Clonazepam:

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 Special Precautions for Use

Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults:

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (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 shortterm 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.

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 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

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Desvenlafaxine, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome 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/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Desvenlafaxine with MAOIs intended to treat psychiatric disorders is contraindicated. Desvenlafaxine should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking Desvenlafaxine. Desvenlafaxine should be discontinued before initiating treatment with the MAOI.

If concomitant use of Desvenlafaxine with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Desvenlafaxine and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Elevated Blood Pressure

Patients receiving Desvenlafaxine should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies. 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.

Abnormal Bleeding

SSRIs and SNRIs, 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. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Desvenlafaxine and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

Angle Closure Glaucoma:

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Pristiq may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

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

Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Desvenlafaxine during clinical studies in Major Depressive Disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy.

During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Desvenlafaxine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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 physician may continue decreasing the dose, but at a more gradual rate.

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.

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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Monoamine Oxidase Inhibitors (MAOI):

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.

Serotonergic drugs:
Based on the mechanism of action of desvenlafaxine and the potential for serotonin syndrome, caution is advised when desvenlafaxine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin):
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Desvenlafaxine is initiated or discontinued.

Potential for Other Drugs to Affect Desvenlafaxine:
ased on in vitro data, no dose adjustment is required for Desvenlafaxine when used concomitantly with inhibitors of CYP3A4 and CYP1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, 2E1, and the Pglycoprotein transporter. Clinical studies have demonstrated no clinically significant pharmacokinetic interaction between Desvenlafaxine and strong CYP 3A4 inhibitors.

Potential for Desvenlafaxine to Affect Other Drugs:
Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Substrates primarily metabolized by CYP2D6 (e.g., desipramine , atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine) should be dosed at the original level when co-administered with Desvenlafaxine 100 mg or lower or when Desvenlafaxine is discontinued. Reduce the dose of these substrates by up to one-half if co-administered with 400 mg of Desvenlafaxine.

No additional dose adjustment is required for concomitant use of substrates of CYP3A4, 1A2, 2A6, 2C8, 2C9, and 2C19 isozymes, and P-glycoprotein transporter. Clinical studies have demonstrated no clinically significant pharmacokinetic interaction between Desvenlafaxine and CYP3A4 substrates.

Clinical studies have shown that desvenlafaxine (100 mg daily) does not have a clinically relevant effect on tamoxifen and aripiprazole, compounds that are metabolized by a combination of both CYP2D6 and CYP3A4 enzymes.

In vitro studies showed minimal inhibitory effect of desvenlafaxine on the CYP2D6 isoenzyme.

In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme.

In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19, isozymes, and P-glycoprotein transporter and would not be expected to affect the pharmacokinetics of drugs that are substrates of these CYP isozymes and transporter.

Other Drugs Containing Desvenlafaxine or Venlafaxine:

Avoid use of Desvenlafaxine with other desvenlafaxine-containing products or venlafaxine products. The concomitant use of Desvenlafaxine with other desvenlafaxine-containing products or venlafaxine will increase desvenlafaxine blood levels and increase dose-related adverse reactions.

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

4.6 Fertility, Pregnancy and Lactation:
Pregnancy Category C:

Risk summary There are no adequate and well-controlled studies of Desvenlafaxine in pregnant women. In reproductive developmental studies in rats and rabbits with desvenlafaxine succinate, evidence of teratogenicity was not observed at doses up to 30 times a human dose of 100 mg per day (on a mg/m2 basis) in rats, and up to 15 times a human dose of 100 mg per day (on a mg/m2 basis) in rabbits. An increase in rat pup deaths was seen during the first 4 days of lactation when dosing occurred during gestation and lactation, at doses greater than 10 times a human dose of 100 mg per day (on a mg/m2 basis). Desvenlafaxine should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

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

Human data: Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), 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.

Nursing Mothers: Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Desvenlafaxine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Undesirable Effects

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

Hypersensitivity
Suicidal Thoughts and Behaviors in Adolescents and Young Adults.
Serotonin Syndrome
Elevated Blood Pressure
Abnormal Bleeding
Angle Closure Glaucoma
Activation of Mania/Hypomania
Discontinuation Syndrome
Seizure
Hyponatremia
Interstitial Lung Disease and Eosinophilic Pneumonia

Adverse reactions reported as reasons for discontinuation of treatment

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 premarketing 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.

The common adverse reactions that occurred in ≥ 2% of Desvenlafaxine 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

Cardiac disorders: blood pressure increased
Gastrointestinal disorders: Nausea, dry mouth, constipation, vomiting
General disorders and administration site conditions: Fatigue, chills, feeling jittery
Metabolic and nutrition disorders: dizziness, somnolence, tremor, disturbance in attention
Psychiatric disorders: insomnia, anxiety, nervousness, abnormal dreams
Renal and urinary disorders: Urinary hesitation
Respiratory, thoracic and mediastinal disorders: Yawning
Skin and subcutaneous tissue disorders: hyperhidrosis
Special senses: vision blurred, mydriasis, vertigo, tinnitus, dysgeusia
Vascular disorders: Hot flush

Sexual function adverse reactions

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

Men only:
Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction

Women only:
Anorgasmia

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.

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

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.

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.

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) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits.

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.

Orthostatic hypotension In the pre-marketing short-term, placebo-controlled 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.

Postmarketing Experience:
Skin and subcutaneous tissue disorders – Stevens-Johnson syndrome.

4.9 Overdose

There is limited clinical trial experience with desvenlafaxine succinate overdosage in humans. However, desvenlafaxine (Desvenlafaxine) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Desvenlafaxine) is presented below.

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.

Management of Overdosage: No specific antidotes for Desvenlafaxine are known. In managing over dosage, consider the possibility of multiple drug involvement

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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).

Pharmacodynamics:Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or α1-adrenergic receptors in vitro. Desvenlafaxine also lacked monoamine oxidase (MAO) inhibitory activity.

ECG changes

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.

5.2 Pharmacokinetic Properties

The single-dose pharmacokinetics of desvenlafaxine are linear and dose-proportional in a dose range of 50 to 600 mg 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 and distribution:

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

A food-effect study involving administration of Desvenlafaxine to healthy subjects under fasting and fed conditions (high-fat meal, 800 to 1000 calories) indicated that desvenlafaxine Cmax was increased about 16% in the fed state, while the AUCs were similar. This difference is not expected to be clinically significant; therefore, Desvenlafaxine can be taken without regard to meals.

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.

5.3 Preclinical Safety Data

Desvenlafaxine

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 300 mg/kg/day dose is 15 times a human dose of 100 mg per day on a mg/m2 basis.
Rats received desvenlafaxine succinate at dosages up to 300 mg/kg/day (males) or 500 mg/kg/day (females). The highest dose is 29 (males) or 48 (females) times a human dose of 100 mg per day on a mg/m2 basis.

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 30 times a human dose of 100 mg per day (on a mg/m2 basis). There was no effect on fertility at 100 mg/kg/day, approximately 10 times a human dose of 100 mg per day (on a mg/m2 basis).

Clonazepam
Carcinogenicity studies have not been conducted with clonazepam. The data currently available are not sufficient to determine the genotoxic potential of clonazepam. In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life: 2 yrs

6.2 Special Precautions for Storage: Store below 30°C. Protect from Sunlight

6.3 Nature and Contents of Container: 10’s. PVC-Alu blister

Marketed By
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