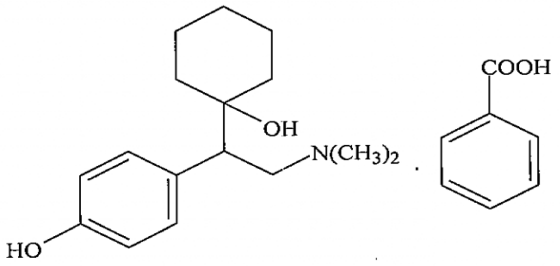
APO-DESVENLAFAXINE MR EXTENDED RELEASE TABLETS

NAME OF THE MEDICINE

Desvenlafaxine (as benzoate).

Chemical Name: 4-[2-dimethylamino-1-(1-hydroxy cyclohexyl) ethyl] phenol benzoate

Structural Formula: (as benzoate)



Molecular Formula: $C_{23}H_{31}NO_4$ (as benzoate)
Molecular Weight: 385.50 (as benzoate)
CAS Registry Number: 93413-62-8 (free base), 1147940-37-1 (as benzoate)

DESCRIPTION

Desvenlafaxine benzoate is a white to pale yellow powder that is sparingly soluble in N, N-Dimethylformamide, in methanol and in water.

Each extended release tablet contains 50 mg or 100 mg of desvenlafazine (as benzoate salt). In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, purified talc, stearic acid, colloidal anhydrous silica, magnesium stearate and hypromellose. The 50 mg tablets are film coated with OPADRY® II complete film coating system 85F94487 PINK (PI No. 106952), the 100 mg tablets are coated with OPADRY® II complete film coating system 85F94527 PINK (PI No. 106953).

PHARMACOLOGY

Pharmacological Actions

Non-clinical studies have shown that desvenlafaxine is a selective serotonin and noradrenaline reuptake inhibitor (SNRI).

Desvenlafaxine lacked significant affinity for numerous receptors, including muscarinic-cholinergic, H1-histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors has been hypothesised to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In the same comprehensive binding profile assay, desvenlafaxine also lacked significant affinity for various ion channels, including calcium, chloride, potassium and sodium ion channels and also lacked monoamine oxidase (MAO) inhibitory activity. Desvenlafaxine lacked significant activity in the *in vitro* cardiac potassium channel (hERG) assay.

In preclinical rodent models, desvenlafaxine demonstrated activity predictive of antidepressant, anxiolytic and thermoregulatory actions, and pain inhibitory properties.

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 ($t_{1/2}$) 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.

The pharmacokinetics of desvenlafaxine have been thoroughly evaluated in women and men. There are minimal differences based on gender; data from all subjects are presented below.

Absorption

Desvenlafaxine is well absorbed, with an absolute oral bioavailability of 80%. Mean time to peak plasma concentrations (T_{max}) is about 7.5 hours after oral administration. AUC and C_{max} of 6,747 ng.hr/mL and 376 ng/mL, respectively, are predicted after a single dose of 100 mg.

Administration with food has minimal impact on drug absorption. Following administration with low, medium, and high-fat meals, increases in C_{max} of approximately 16% (observed confidence interval: 107.8-125.1%; required confidence interval for bioequivalence 80-125%) were observed only following a high-fat meal. There was no statistically significant change in AUC values for any of the meals; therefore, desvenlafaxine can be taken without regard to meals.

Distribution

The plasma protein binding of desvenlafaxine *in vitro* is low (approximately 30%) and is independent of drug concentration over the range 100-500 ng/mL. Desvenlafaxine's volume of distribution at steady-state following intravenous administration is 3.4 L/kg, indicating distribution into nonvascular compartments.

Metabolism

Approximately 45% of desvenlafaxine is excreted unchanged in urine. Desvenlafaxine is primarily metabolised by conjugation (shown to be mediated by UGT isoforms UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17 *in vitro*) and to a minor extent through oxidative metabolism. *In vitro* studies showed that CYP3A4 is the predominant cytochrome P450 isozyme mediating the oxidative metabolism (N-demethylation) of desvenlafaxine.

Excretion

Approximately 19% of the administered dose is excreted as the glucuronide metabolite and <5% as the oxidative metabolite (N,O-didesmethylvenlafaxine) in urine.

Special Populations

Elderly (>65 years)

In a trial of healthy subjects administered doses up to 300 mg, there was an age-dependent decrease in desvenlafaxine clearance, resulting in a 32% increase in C_{max} and a 55% increase in AUC values in subjects greater than 75 years of age as compared with subjects 18 - 45 years of age. No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose.

Children and Adolescents

Safety and effectiveness in the paediatric population have not been established.

Renal Impairment

The pharmacokinetics of desvenlafaxine 100 mg were studied in subjects with mild (n = 9), moderate (n = 8), severe (n = 7) and end-stage renal disease (ESRD) requiring dialysis (n = 9) and in healthy, age-matched control subjects (n = 8). Elimination was significantly correlated with creatinine clearance. Total body clearance was reduced by 29% in mild, 39% in moderate, 51% in severe renal impairment, and 58% in ESRD compared to healthy subjects. This reduced clearance resulted in increases in AUCs of 42% in mild (24-hr CrCl = 50-80 mL/min), 56% in moderate (24-hr CrCl = 30-50mL/min), 108% in severe (24-hr CrCl <30 mL/min) renal impairment, and 116% in ESRD subjects.

The mean terminal half-life ($t_{1/2}$) was prolonged from 11.1 hours in the control subjects to 13.5, 15.5, 17.6, and 22.8 hours in mild, moderate, severe renal impairment and ESRD subjects, respectively.

Less than 5% of the drug in the body was cleared during a standard 4-hour haemodialysis procedure. Therefore, supplemental doses should not be given to patients after dialysis. Dosage adjustment is recommended in patients with significant impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment

The pharmacokinetics of desvenlafaxine 100 mg were studied in subjects with mild (Child-Pugh A, n = 8), moderate (Child-Pugh B, n = 8), and severe (Child-Pugh C, n = 8) hepatic impairment and in healthy subjects (n = 12).

Average AUC was increased by approximately 31% and 35% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. Average AUC values were comparable in subjects with mild hepatic impairment and healthy subjects (<5% difference).

Systemic clearance (CL/F) was decreased by approximately 20% and 36% in patients with moderate and severe hepatic impairment, respectively, as compared to healthy subjects. CL/F values were comparable in mild hepatic impairment and healthy subjects (<5% difference).

The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively.

Thorough QTc Trial

In a thorough QTc trial with prospectively determined criteria, in healthy women, desvenlafaxine did not cause QT prolongation. Additionally, no effect on QRS interval was observed.

CLINICAL TRIALS

Major Depressive Disorder

The efficacy of desvenlafaxine as a treatment for depression was established in four, 8-week, randomised, double-blind, placebo-controlled, fixed-dose trials in adult outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder (MDD). In the first study, patients received 100 mg (n = 114), 200 mg (n = 116), or 400 mg (n = 113) of desvenlafaxine once daily, or placebo (n = 118). In a second study, patients received either 200 mg (n = 121) or 400 mg (n = 124) of desvenlafaxine once daily, or placebo (n = 124). In two additional trials, patients received 50 mg (n = 150 and n = 164) or 100 mg (n = 147 and n = 158) of desvenlafaxine once daily or placebo (n = 150 and n = 161).

Desvenlafaxine showed superiority over placebo as measured by improvement in the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}) total score in four trials and, as measured by the Clinical Global Impressions Scale - Improvement (CGI-I), in three of the four trials. There was no clear evidence that doses greater than 50 mg/day conferred any additional benefit. Two other studies that treated patients with doses of 200 mg to 400 mg also showed superiority to placebo when appropriately analysed to take early drop-outs for adverse effects into account.

In a long-term study, adult outpatients meeting DSM-IV criteria for major depressive disorder and who responded to 12 weeks of acute treatment with desvenlafaxine were assigned randomly to the same dose (200 or 400 mg/day) they had received during acute treatment or to placebo for up to 26 weeks of observation for relapse. Response during the open-label phase was defined as a HAM-D_{17} total score of ≤ 11 at the day 84 evaluation. Relapse during the double-blind phase was defined as follows: (1) a HAM-D_{17} total score of ≥ 16 at any office visit, (2) a CGI-I score of ≥ 6 (versus day 84) at any office visit, or (3) discontinuation from the study due to unsatisfactory response. Patients receiving continued desvenlafaxine treatment experienced significantly lower relapse rates over the subsequent 26 weeks compared with those receiving placebo.

Analyses of the relationships between treatment outcome and age and treatment outcome and gender did not suggest any differential responsiveness on the basis of these patient characteristics.

INDICATIONS

APO-Desvenlafaxine MR tablets are indicated for the treatment of major depressive disorder, including the prevention of relapse.

APO-Desvenlafaxine MR tablets are not indicated for paediatric use.

CONTRAINDICATIONS

Hypersensitivity to desvenlafaxine, venlafaxine hydrochloride or to any excipients in the desvenlafaxine formulation.

Monoamine Oxidase Inhibitors (MAOIs)

Desvenlafaxine must not be used in combination with monoamine oxidase inhibitors (MAOIs) or reversible MAOIs (RIMA) (e.g. moclobemide, linezolid and intravenous methylene blue), or within 14 days of discontinuing treatment with a MAOI. Similarly, desvenlafaxine must be discontinued for at least 7 days before starting treatment with a MAOI. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SNRI in combination with MAOIs and RIMA, and in patients who have recently discontinued an SNRI and have been started on a MAOI (see also **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Clinical Worsening and Suicide Risk

Patients with major depression, both adult and paediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, 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. Antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. As improvement may not occur during the first few weeks or more of treatment, patients should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases.

Pooled analyses of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed that these medicines increase the risk of suicidality in children, adolescents, and young adults (ages 18-24 years) with major depression and other psychiatric disorders, generally during initial treatment (1-2 months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 years and older.

The pooled analysis of placebo-controlled trials in children and adolescents with major depression, obsessive compulsive disorder, or other psychiatric disorders included a total of 24 short-term trials of nine antidepressant medicines in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with major depression or other psychiatric disorders included a total of 295 short-term trials (medium duration 2 months) of 11 antidepressant medicines in over 77,000 patients. There was considerable variation in risk of suicidality among medicines, but a tendency toward an increase in the younger patients for almost all medicines studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence with major depression.

No suicides occurred in any of the paediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about the medicine 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 trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms (see **Discontinuation Effects** below).

It is particularly important that monitoring be undertaken during the initial course of antidepressant treatment or at times of dose increase or decrease.

Patients with co-morbid depression associated with other psychiatric or non-psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depression as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and /or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Prescriptions for desvenlafaxine tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the possibility of overdosage. This is particularly so at the times of treatment initiation or dosage change.

Information for Patients and Caregivers

Patients and their caregivers should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Mania/Hypomania

In clinical trials, mania was reported for approximately 0.1% of patients treated with desvenlafaxine Activation of mania/hypomania has also been reported in a small proportion of patients with mood disorders who were treated with other marketed antidepressants. A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) 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 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.

As with all antidepressants, desvenlafaxine should be used cautiously in patients with a history or family history of mania or hypomania.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions

The development of a potentially life-threatening serotonin or neuroleptic malignant syndrome (NMS)-like reactions syndrome may occur with desvenlafaxine treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (e.g. MAOIs, including reversible MAOIs such as moclobemide, linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists (see **CONTRAINDICATIONS**).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, confusion, hallucinations, and coma), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, myoclonus, tremor) and/or gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhoea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes (see **INTERACTIONS WITH OTHER MEDICINES**).

If concomitant treatment with desvenlafaxine and other agents that may affect the serotonergic and/or dopaminergic neurotransmitter system (such as an SSRI, another SNRI or a 5-hydroxytryptamine receptor agonist (triptan)) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of desvenlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended.

Treatment with desvenlafaxine should be discontinued if serotonin syndrome or NMS-Like reactions occur and supportive symptomatic treatment initiated.

Narrow-Angle Glaucoma

Patients with raised intraocular pressure (IOP) or narrow angle glaucoma were excluded from all desvenlafaxine studies. Mydriasis has been reported in association with desvenlafaxine it is recommended that patients with raised intra-ocular pressure or patients at risk for acute narrow-angle glaucoma (angle closure glaucoma) should be closely monitored.

Co-administration of Drugs Containing Venlafaxine and/or Desvenlafaxine

Desvenlafaxine is the major active metabolite of venlafaxine, a medication used to treat major depressive, generalised anxiety, social anxiety and panic disorders. Products containing desvenlafaxine should not be used concomitantly with products containing venlafaxine hydrochloride or other products containing desvenlafaxine.

Effects on Blood Pressure

Increases in blood pressure were observed in some patients in clinical trials, particularly with higher doses. Pre-existing hypertension should be controlled before treatment with desvenlafaxine. Patients receiving desvenlafaxine should have regular monitoring of 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 tablets, either dose reduction or discontinuation should be considered. Caution should be exercised in treating patients with underlying conditions that might be compromised by increases in blood pressure.

Cardiovascular/Cerebrovascular Disease

Caution is advised in administering desvenlafaxine to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders (see **ADVERSE EFFECTS**). Increases in blood pressure and heart rate were observed in clinical trials with desvenlafaxine. Desvenlafaxine has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical trials.

Serum Lipids

In the short-term, placebo-controlled, pre-marketing trials for MDD, desvenlafaxine treatment was associated with mean increases of 5.7, 1.4, 3.6 and 5.5 mg/dl in total cholesterol, HDL, LDL cholesterol and triglycerides, respectively (0.11, 0.03, 0.07 and 0.04 mmol/L, respectively). The changes in fasting serum total cholesterol, LDL, and triglycerides were dose-related. Measurement of serum lipids should be considered during treatment with desvenlafaxine.

Seizures

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

Discontinuation Effects

During marketing of SNRIs (Serotonin and Noradrenaline 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., paraesthesias, 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 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 (see **ADVERSE EFFECTS** and **DOSAGE AND ADMINISTRATION**).

Abnormal Bleeding

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), including desvenlafaxine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to

this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, haematoma, epistaxis, and petechiae to life-threatening haemorrhages. 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.

Hyponatraemia

Cases of hyponatraemia and/or the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) secretion have been described with SNRIs (including desvenlafaxine) and SSRIs, usually in volume-depleted or dehydrated patients, including elderly patients and patients taking diuretics (see **ADVERSE EFFECTS**).

Physical and Psychological Dependence

Although desvenlafaxine has not been systematically studied in preclinical or clinical trials for its potential for abuse, no indication of drug-seeking behaviour was seen in the clinical trials. However, it is not possible to predict on the basis of pre-marketing experience, the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of desvenlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

Electroconvulsive Therapy

There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with desvenlafaxine treatment for MDD.

Effects on Fertility

Fertility in male rats was unaffected by oral administration of desvenlafaxine resulting in exposure (plasma AUC) up to 4 times that in humans treated with 200 mg/day. When treated male rats were mated with treated females, female fertility was variably reduced with oral doses resulting in exposures (plasma AUC) 2 to 7 times that in humans treated with 200 mg/day; there was some evidence that this was associated with disruption of oestrus cycles.

Use in Pregnancy (Category B2)

The safety of desvenlafaxine in human pregnancy has not been established. Only administer desvenlafaxine to pregnant women if the expected benefits outweigh any possible risk. If desvenlafaxine is used until, or shortly before birth, discontinuation effects in the newborn should be considered.

Neonates exposed to venlafaxine, other SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyper-reflexia, 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.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the new born (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with desvenlafaxine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

<u>Teratogenicity</u>

Desvenlafaxine was not teratogenic in rats at an oral dose resulting in a drug exposure (plasma AUC) that was 7 times that in humans treated with 200 mg/day. There were tendencies for reduced numbers and bodyweights of foetuses with this dose in some studies. No teratogenicity was observed in a rabbit embryo-foetal development study, but the oral doses resulted in drug exposures (AUC) that were below the value in humans treated with 200 mg/day. Potential effects on embryo-foetal development may therefore not have been fully defined due to excessive maternal toxicity at higher dosages in rabbits.

Oral administration of desvenlafaxine to pregnant rats from early gestation to weaning was associated with increased *post-partum* pup mortality and reduced birth weight persisting to maturity, but no effect on developmental indices, at maternal exposure (plasma AUC) 7 times that in humans treated with 200 mg/day. Maternal toxicity was observed at this dose; at the no-effect dose maternal exposure was 2 times that in humans treated with 200 mg/day.

Use in Lactation

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 or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer desvenlafaxine to breastfeeding women if the expected benefits outweigh any possible risk.

Paediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

Use in the Elderly

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see **DOSAGE AND ADMINISTRATION** and **PHARMACOLOGY - Pharmacokinetics**).

Greater sensitivity to desvenlafaxine in some older patients cannot be ruled out.

Of the 3,292 patients in pre-marketing clinical trials of desvenlafaxine for major depressive disorder, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger subjects; however, in the short-term placebo-controlled trials, there was a higher incidence of systolic orthostatic hypotension in patients ≥ 65 years of age compared to patients <65 years of age treated with desvenlafaxine.

Genotoxicity

Desvenlafaxine was not genotoxic in *in vitro* assays for bacterial gene mutation, mammalian gene mutation, chromosomal aberrations and cell transformation, or in *in vivo* tests for clastogenic activity in mice and rats.

Carcinogenicity

Desvenlafaxine did not increase the incidence of tumours in long-term mouse and rat carcinogenicity studies at oral doses up to 7 (mice), 14 (male rats) and 23 (female rats) times the maximal recommended human dose of 200 mg/day, on a mg/m^2 basis.

Effects on Ability to Drive and Use of Machines

The results of a clinical study that assessed the effects of desvenlafaxine on behavioural performance of healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behaviour performance. However, since any CNS-active drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that desvenlafaxine therapy does not adversely affect their ability to engage in such activities.

Effect on Laboratory Tests

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.

INTERACTIONS WITH OTHER MEDICINES

Monoamine Oxidase Inhibitors

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (including reversible MAOIs such as moclobemide, linezolid and intravenous methylene blue) and started on antidepressants with

pharmacological properties similar to desvenlafaxine (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI (see **PRECAUTIONS**).

Concomitant use of desvenlafaxine in patients taking monoamine oxidase inhibitors is contraindicated (see **CONTRAINDICATIONS**).

Central Nervous System (CNS)-Active Agents

The risk of using desvenlafaxine in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when desvenlafaxine is taken in combination with other CNS-active drugs.

Serotonin Syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life threatening condition, may occur with desvenlafaxine treatment, particularly with concomitant use of other agents that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone, pentazocine or St. John's wort *[Hypericum perforatum]*), with drugs which impair metabolism of serotonin (such as MAOIs including moclobemide, linezolid [an antibiotic which is a reversible non-selective MAOI] and intravenous methylene blue), or with serotonin precursors (such as tryptophan supplements). Serotonin syndrome symptoms may include mental status changes, autonomic instability, neuromuscular aberrations and/or gastrointestinal symptoms (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

If concomitant treatment with desvenlafaxine and other agents that may affect the serotonergic neurotransmitter system (such as an SSRI, another SNRI or a 5-hydroxytryptamine receptor agonist [triptan]) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of desvenlafaxine with serotonin precursors (such as tryptophan supplements) is not recommended (see **PRECAUTIONS**).

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.

Potential for Other Drugs to Affect Desvenlafaxine

Inhibitors of CYP3A4

CYP3A4 is minimally involved in desvenlafaxine elimination. In a clinical study, ketoconazole (200 mg BID) increased the AUC of desvenlafaxine (400 mg single dose) by approximately 43%, a weak interaction. Concomitant use of desvenlafaxine with potent inhibitors of CYP3A4 may result in higher exposure to desvenlafaxine.

Inhibitors of other CYP enzymes

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.

Potential for Desvenlafaxine to Affect Other Drugs

Drugs metabolised by CYP2D6

When desvenlafaxine was administered at a dose of 400 mg daily in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased approximately 90%. Concomitant use of desvenlafaxine with a drug metabolised by CYP2D6 may result in higher concentrations of that drug.

Drugs metabolised by CYP3A4

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

In a clinical study, desvenlafaxine (400 mg daily) decreased the AUC of midazolam (a single 4 mg dose), by approximately 31%. Concomitant use of desvenlafaxine with a drug metabolised by CYP3A4 may result in lower exposures to that drug.

Drugs metabolised by CYP1A2, 2A6, 2C8, 2C9 and 2C19

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

P-glycoprotein Transporter

In vitro, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter.

ADVERSE EFFECTS

Clinical Trials Experience

The safety of desvenlafaxine was established in a total of 4,724 patients, who were exposed to at least one dose of desvenlafaxine ranging from 50 to 400 mg/day in clinical trials. Long-term safety was evaluated in 1,576 patients, who were exposed to desvenlafaxine for at least 6 months and with 575 patients exposed for 1 year.

The following list of adverse reactions was reported by patients treated with desvenlafaxine throughout the dose range studied (50 to 400 mg) during both short- and long-term trials. In general, the adverse reactions were most frequent in the first week of treatment.

Adverse reactions are listed below in CIOMS frequency categories:

Very Common	≥10%
Common	≥1% and <10%
Uncommon	≥0.1% and <1%
Rare	≥0.01% and <0.1%
Very Rare	<0.01%

SYSTEM ORGAN CLASS	**ADVERSE REACTION**
Cardiac Disorders	
Common	Palpitations, Tachycardia
Ear and Labyrinth Disorders	
Common	Tinnitus, Vertigo**
Eye Disorders	
Common	Vision blurred, mydriasis
Gastrointestinal disorders	
Very Common	Nausea, dry mouth, constipation
Common	Diarrhoea, vomiting
Rare	Pancreatitis acute
General disorders and administration site conditions	
Very Common	Fatigue
Common	Chills, asthenia, feeling jittery
Immune system disorders	
Uncommon	Hypersensitivity
Investigations	
Common	Liver function test abnormal, weight increased, weight decreased, blood cholesterol increased
Uncommon	Blood triglycerides increased, blood prolactin increased
Metabolism and nutritional disorders	
Common	Decreased appetite
Rare	Hyponatraemia
Musculoskeletal, connective tissue and bone disorders	
Common	Musculoskeletal stiffness
Nervous system disorders	
Very Common	Dizziness, headache, somnolence
Common	Tremor, paraesthesia, dysgeusia, disturbance in attention
Uncommon	Syncope, extrapyramidal disorder, dyskinesia
Rare	Convulsion, serotonin syndrome**, dystonia
Psychiatric disorder	
Very Common	Insomnia

SYSTEM ORGAN CLASS	ADVERSE REACTION
Common	Anxiety, abnormal dreams, nervousness, libido decreased, anorgasmia, orgasm abnormal, withdrawal syndrome, irritability
Uncommon	Depersonalisation, hypomania
Rare	Hallucinations, mania
Renal and urinary disorders	
Common	Urinary hesitation
Uncommon	Proteinuria, urinary retention**
Reproductive system and breast disorders	
Common	Erectile dysfunction*, ejaculation delayed*, ejaculation disorder*, ejaculation failure*
Uncommon	Sexual dysfunction
Respiratory, thoracic and mediastinal disorders	
Common	Yawning
Uncommon	Epistaxis
Skin and subcutaneous tissue disorders	
Very Common	Hyperhidrosis
Common	Rash
Uncommon	Alopecia**
Rare	Angioedema**, photosensitivity reaction, Stevens-Johnson syndrome**
Vascular disorders	
Common	Hot flush, blood pressure increased
Uncommon	Orthostatic hypotension, peripheral coldness

* Frequency is calculated based on men only.
** Adverse reaction identified during post-approval use.

Adverse Reactions reported with other SNRIs

Although the following are not considered adverse reactions for desvenlafaxine they are adverse reactions for other SNRIs and may also occur with desvenlafaxine: gastrointestinal bleeding and severe cutaneous reactions (such as Stevens - Johnson syndrome, toxic epidermal necrolysis and/or erythema multiforme).

Ischaemic Cardiac Adverse Events

In clinical trials, there were uncommon reports of ischaemic cardiac adverse events including myocardial ischaemia, myocardial infarction, and coronary occlusion requiring revascularisation; these patients had multiple underlying cardiac risk factors. More patients experienced these events during desvenlafaxine treatment as compared to placebo (see **PRECAUTIONS - Cardiovascular/ Cerebrovascular Disease**).

Discontinuation Symptoms

Adverse drug reactions reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical trials at a rate of ≥ 5% include: dizziness, withdrawal syndrome, nausea, headache, irritability, diarrhoea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation symptoms occurred more frequently with higher doses and longer duration of therapy (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS - Discontinuation Effects**).

Orthostatic hypotension

Of the 3,292 patients in clinical trials with desvenlafaxine, 5% of patients 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 trials, there was a higher incidence of systolic orthostatic hypotension in patients ≥ 65 years of age compared to patients < 65 years of age treated with desvenlafaxine.

Adverse Reactions Leading to Discontinuation of Therapy

The most common adverse reactions leading to discontinuation in at least 2% of the desvenlafaxine-treated patients in the short-term trials, up to 8 weeks, were: nausea (4%); dizziness and vomiting (2% each); in the long-term trial, up to 9 months, the most common was vomiting (2%).

DOSAGE AND ADMINISTRATION

APO-Desvenlafaxine MR extended release tablets are intended for oral administration. They should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

Initial Treatment

The recommended dose for APO-Desvenlafaxine MR is 50 mg once daily, with or without food. In clinical trials, doses of 50-400 mg/day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg/day. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur gradually and at intervals of not less than 7 days. The maximum dose should not exceed 200 mg/day.

When discontinuing therapy, gradual dose reduction is recommended whenever possible to minimise discontinuation symptoms (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy. The efficacy of desvenlafaxine (200-400 mg) in major depressive disorder was demonstrated in the 24-week double-blind phase of a relapse prevention trial in patients who had responded during an initial, 12-week open-label phase (see **CLINICAL TRIALS**). Patients should continue on the same dose at which they were stabilised. They should be periodically reassessed to determine the need for continued treatment.

Children and Adolescents

Safety and efficacy in patients less than 18 years of age have not been established.

Dosage Adjustment in Renal Impairment

The recommended starting 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. Because of individual variability in clearance in these patients, individualisation of dosage may be desirable. Supplemental doses should not be given to patients after dialysis (see **PHARMACOLOGY**).

Dosage Adjustment in Hepatic Impairment

No adjustment of dose is necessary in patients with mild, moderate, and severe hepatic impairment (see **PHARMACOLOGY**).

Dosage Adjustment in the Elderly

No dosage adjustment is required solely on the basis of age; however, possible reduced renal clearance of desvenlafaxine should be considered when determining dose (see **PHARMACOLOGY**).

Discontinuing Desvenlafaxine

When discontinuing therapy gradual dose reduction should be considered to minimise discontinuation symptoms (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

Symptoms associated with discontinuation of desvenlafaxine, as well as other SNRIs and SSRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. 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 (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

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 followed by a washout period may be necessary to minimise discontinuation symptoms and the possibility of drug-drug interactions from a pharmacokinetic or pharmacodynamic perspective.

Residual Inert Tablet Matrix

Patients receiving APO-Desvenlafaxine MR may notice an inert matrix tablet passing in the stool or via colostomy.

Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert matrix tablet.

OVERDOSAGE

Symptoms

There is limited clinical experience with desvenlafaxine overdosage in humans. In clinical trials, no cases of fatal acute overdose of desvenlafaxine were reported.

Among the patients included in the major depressive disorder trials of desvenlafaxine, there were four adults who ingested doses greater than 800 mg of desvenlafaxine (4000 mg [desvenlafaxine alone], 900, 1800 mg and 5200 mg [in combination with other drugs]); all patients recovered. In addition, a patient's 11-month-old child accidentally ingested 600 mg of desvenlafaxine, was treated, and recovered.

Treatment

In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control Centre for additional information on the treatment of any overdose.

Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI.

General supportive and symptomatic measures are recommended. Ensure an adequate airway, oxygenation and ventilation. Cardiac rhythm and vital signs must be monitored. Administration of activated charcoal may also limit drug absorption. Where there is a risk of aspiration, induction of emesis is not recommended. No specific antidotes for desvenlafaxine are known. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Desvenlafaxine MR extended release tablets are intended for oral administration.

Each tablet contains 50 mg or 100 mg desvenlafaxine (as benzoate), as the active ingredient.

50 mg Extended Release Tablet:

A light pink, biconvex, round shaped film coated tablet debossed with "DV" on one side and "50"on the other side.

Clear PVC/Aclar as forming (base) material and either Peel Push Aluminium foil or Aluminium foil as the lidding of 7, 14 and 28 tablets (AUST R 218307).

100 mg Extended Release Tablet:

A reddish-orange, biconvex, round shaped film coated tablet, debossed with "DV" on one side and "100"on the other side.

Clear PVC/Aclar as forming (base) material and either Peel Push Aluminium foil or Aluminium foil as the lidding of 7, 14 and 28 tablets (AUST R 227802).

Not all pack sizes may be available.

Storage

Store below 25°C in a dry place.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

12 November 2014

DATE OF MOST RECENT AMENDMENT

20 April 2017