PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

ODIVEN XR 37,5 capsules

ODIVEN XR 75 capsules

ODIVEN XR 150 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ODIVEN XR 37,5: Each extended-release capsule contains 37,5 mg venlafaxine (as venlafaxine HCl).

ODIVEN XR 75: Each extended-release capsule contains 75 mg venlafaxine (as venlafaxine HCl).

ODIVEN XR 150: Each extended-release capsule contains 150 mg venlafaxine (as venlafaxine HCl).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ODIVEN XR 37,5: White to off-white free flowing pellets, filled in size “3” hard gelatine capsule shells with an opaque grey cap and opaque white body, printed with “375 mg” in black ink on the body.

ODIVEN XR 75: White to off-white free flowing pellets, filled in size “1” hard gelatine capsule shells with an opaque peach cap and opaque peach body, printed with “75 mg” in black ink on the body.

ODIVEN XR 150: White to off-white free flowing pellets, filled in size “0” hard gelatine capsule shells with an opaque grey cap and opaque white body, printed with “150 mg” in black in on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ODIVEN XR is indicated for the following:

- The treatment of depression, including depression with associated anxiety.
- The prevention of relapses of an episode of depression in patients responding to an initial six to eight weeks of treatment.
- Prevention of recurrence in patients responding to six months of relapse prevention. Safety and efficacy of treatment beyond one year have not been established. When ODIVEN XR is used long term, it should periodically be re-evaluated for the usefulness of the medicine in the individual patient.
- The treatment of generalised anxiety disorder.
- Treatment of social anxiety disorder. The effectiveness of ODIVEN XR has not been demonstrated for longer than 12 weeks for this indication.

4.2 Posology and method of administration

Posology

The recommended daily dose for ODIVEN XR is 75 mg once daily. If after several weeks further clinical improvement is required, the dose may be increased to 150 mg once daily.
This dose can be further increased to 225 mg once daily. Dose increments should be made at intervals of 2 weeks or more, but not less than 4 days. The dose for depressed patients may be further increased, if needed, up to 375 mg once daily.
ODIVEN XR should be taken with food. Swallow the capsule whole, with fluid. Do not open, divide, crush, chew or place ODIVEN XR capsule in water.
ODIVEN XR should be taken once daily at more or less the same time, either in the morning or in the evening. ODIVEN XR capsules contain pellets, which release the active ingredient into the digestive system over an extended period of time. The insoluble portion of these pellets is eliminated and may be seen in stools.
Depressed patients who are currently being treated at a therapeutic dose with ODIVEN, may be

switched to ODIVEN XR at the nearest equivalent dose (mg/day). Individual dosage adjustments may, however, be necessary.

Special populations

Patients with renal impairment

A lower dose of ODIVEN XR is recommended in patients with renal impairment. In patients with renal impairment with a glomerular filtration rate (GFR) of 10 – 70 mL/min, the total daily dose of ODIVEN XR must be reduced by 25 – 50 %. In haemodialysis patients, the total daily dose of ODIVEN XR must be reduced by 50 %. Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment, the total daily dose of ODIVEN XR must be reduced by 50 %. For some patients, reductions of more than 50 % may be appropriate.

Paediatric population

ODIVEN XR is not recommended for use in children and adolescents. The efficacy and safety of venlafaxine for other indications in children and adolescents under the age of 18 years have not been established (see sections 4.3, 4.4 and 4.8).

Elderly patients

No specific dosage adjustments of ODIVEN XR are recommended based on patient age.

Maintenance, continuation and extended treatment

Periodic re-assessment of the need for long-term therapy with ODIVEN XR is recommended. It is unknown if the dose of antidepressant needed to induce remission is the same as the dose needed to maintain and/or sustain euthymia.

Discontinuing ODIVEN XR

Dose tapering is recommended when discontinuation of ODIVEN XR therapy is indicated.

If ODIVEN XR has been used for more than 6 weeks, tapering over at least a 2-week period is recommended. Successful tapering can be achieved by reducing the daily dose by 75 mg at 1-week intervals. The tapering period is influenced by the dose, duration of therapy and the individual patient. Patients should be advised to consult their medical practitioner before abruptly discontinuing ODIVEN XR (see section 4.4).

Method of administration

For oral use.

It is recommended that ODIVEN XR be taken with food. Each capsule should be swallowed whole with fluid. Do not divide, crush, chew or place capsule in water.

4.3 Contraindications

- Hypersensitivity to venlafaxine or to any of the excipients listed in section 6.1.
- Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia (see section 4.5). ODIVEN XR should not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. ODIVEN XR should be discontinued at least 7 days before starting treatment with an irreversible MAOI (see sections 4.4 and 4.5).
- Severe adverse reactions have been reported when ODIVEN XR treatment is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of ODIVEN XR, including tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome (NMS), seizures and death (see section 4.5).
- Children under the age of 18 years (see section 4.4).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. The risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with ODIVEN XR should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania. Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing ODIVEN XR, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, ODIVEN XR should be tapered (see section 4.2).

Paediatric population

ODIVEN XR should not be used in the treatment of children and adolescents under the age of 18 years. Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility (predominantly aggression, oppositional behaviour and anger) and suicide-related events, such as suicidal

ideation and self-harm (see section 4.3).

If, based on clinical need, a decision is made to nevertheless treat the patient, the patient should be carefully monitored for suicidal symptoms. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with ODIVEN XR treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, amphetamines, lithium, sibutramine, St John's wort (*Hypericum perforatum*), fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicines that impair metabolism of serotonin (such as MAOIS), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.5).

Symptoms of serotonin syndrome may include mental status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Serotonin syndrome can resemble neuroleptic malignant syndrome (NMS) in its most severe form, with symptoms including hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

Careful observation of the patient is advised, particularly during treatment initiation and dose increases, where concomitant treatment with ODIVEN XR and other medicines that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted.

Concomitant use of ODIVEN XR with serotonin precursors (such as tryptophan supplements) is not recommended.

Narrow-angle glaucoma

Patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma should be closely monitored, as mydriasis may occur when using ODIVEN XR.

Blood pressure

Dose-related increase in blood pressure have commonly been reported with ODIVEN XR. Severely elevated blood pressure requiring immediate treatment has been reported in some cases in post-marketing experience. Before treatment is initiated all patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g. those with impaired cardiac function.

Heart rate

Caution should be exercised in patients whose underlying conditions might be compromised by increases in heart rate, as increases in heart rate can occur, particularly with higher doses.

Cardiac disease and risk of dysrhythmia

ODIVEN XR should be used with caution in patients with a recent history of myocardial infarction or unstable heart disease, as the use of ODIVEN XR has not been evaluated in these patients. Cases of QTc prolongation, torsade de pointes (TdP), ventricular tachycardia and fatal cardiac dysrhythmias have been reported with the use of venlafaxine (as in ODIVEN XR) in post-marketing experiences, especially in overdose or in patients with other risk factors for QTc prolongation/TdP. The balance of risks and benefits should be considered before prescribing ODIVEN XR to patients at high risk of serious cardiac dysrhythmia or QTc prolongation (see section 5.1).

Convulsions

Convulsions may occur with ODIVEN XR therapy. As with all antidepressants, ODIVEN XR should be introduced with caution in patients with history of convulsions, and concerned patients should be closely monitored. Treatment should be discontinued in any patient who develops seizures.

Hyponatraemia

Hyponatraemia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur with the use of ODIVEN XR, most frequently in volume-depleted or dehydrated patients. Patients taking diuretics, elderly patients and patients who are otherwise volume-depleted may be at greater risk.

Abnormal bleeding

The use of serotonin uptake inhibitors (SSRIs and SNRIs) may lead to reduced platelet function. Bleeding events have ranged from ecchymoses, haematomas, epistaxis and petechia to gastrointestinal and life-threatening haemorrhages. SSRIs/SNRIs, including venlafaxine, may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). There may be an increased risk of haemorrhage in patients taking ODIVEN XR. ODIVEN XR should be used with caution in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors.

Serum cholesterol

Patients on ODIVEN XR treatment may have clinically relevant increases in serum cholesterol.

Co-administration with weight loss medicines

Co-administration of ODIVEN XR and weight loss medicines, including phentermine, is not recommended as safety and efficacy of combination therapy have not been established. ODIVEN XR is not indicated for weight loss alone or in combination with other medicines.

Mania/hypomania

A small number of patients who have received antidepressants, including ODIVEN XR, may present with mania/hypomania. ODIVEN XR should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression

Aggression may occur in a small number of patients who have been treated with antidepressants, including ODIVEN XR. This has been reported with initiation, dose changes and discontinuation of treatment. ODIVEN XR should be used with caution in patients with a history of aggression.

Discontinuation of treatment

Discontinuation effects are well known to occur with antidepressants, and sometimes these effects can be protracted and severe. Suicide/suicidal thoughts and aggression have been observed in patients during changes in venlafaxine dosing regimen, including discontinuation. Therefore, patients should be closely monitored when the dose is reduced or during discontinuation (see above in section 4.4 – Suicide/suicidal thoughts or clinical worsening, and Aggression). When treatment is discontinued, particularly if discontinuation is abrupt, withdrawal symptoms are common (see section 4.8).

The risk of withdrawal symptoms depends on several factors, including the dose and duration of therapy as well as the rate of dose reduction. The most commonly reported reactions include dizziness, sleep disturbances (insomnia and intense dreams), sensory disturbances (paraesthesia), agitation, anxiety, nausea, vomiting, tremor and headache. These symptoms are generally mild to moderate, but may be severe in some patients. These symptoms usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. These symptoms are generally self-limiting and usually resolve within 2 weeks, although it may be prolonged (2 – 3 months or more) in some individuals. Therefore, it is advised that ODIVEN XR should be gradually tapered when discontinuing treatment over a period of several weeks or months (see section 4.2). In some patients, discontinuation could take months or longer.

Sexual dysfunction

Serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports on long-lasting sexual dysfunction where the symptoms

have continued despite discontinuation of SNRIs.

Akathisia/psychomotor restlessness

ODIVEN XR use has been associated with the development of akathisia, most likely within the first few weeks of treatment. Akathisia is characterised by a subjective unpleasant or distressing restlessness, a need to move often and an inability to stand or sit still. Increasing the dose in patients who develop these symptoms, may be detrimental.

Dry mouth

ODIVEN XR can cause a dry mouth, which may increase the risk of caries. Patients should be advised on the importance of dental hygiene.

Diabetes

Treatment with ODIVEN XR or a SSRI may alter glycaemic control in patients with diabetes. Dosage adjustment may be needed for patients on insulin and/or oral antidiabetic treatment.

Laboratory test interactions

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

Use in elderly patients

ODIVEN XR appears to pose no exceptional safety problems for healthy elderly patients.

Abuse and dependence

Clinical studies did not show evidence of drug-seeking behaviour, development of tolerance, or

dose escalation over time. *In vitro* studies revealed that ODIVEN XR has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP) or N-methyl-D-aspartic acid (NMDA) receptors. ODIVEN XR was not found to have any significant CNS stimulant activity in rodents. In primate medicine discrimination studies, ODIVEN XR showed no significant stimulant or depressant abuse liability.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOI)

Severe adverse reactions have been reported in patients who have recently discontinued an MAOI and started ODIVEN XR treatment, or have recently discontinued ODIVEN XR before initiating an MAOI. These adverse reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness and hyperthermia with features resembling neuroleptic malignant syndrome (NMS), seizures and death.

Irreversible non-selective MAOIs

ODIVEN XR should not be used in combination with irreversible non-selective MAOIs and should also not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI. ODIVEN XR should be discontinued for at least 7 days before starting treatment with an irreversible non-selective MAOI (see sections 4.3 and 4.4).

Reversible, selective MAOIs (moclobemide)

The combination of ODIVEN XR with a reversible selective MAOI (such as moclobemide), is not recommended, due to a risk of serotonin syndrome. A withdrawal period of shorter than 14 days may be required before initiating ODIVEN XR treatment. ODIVEN XR should be discontinued for at least 7 days before starting treatment with a reversible MAOI.

Reversible, non-selective MAOIs (linezolid)

The antibiotic, linezolid, is a weak reversible and non-selective MAOI. Linezolid should not be

given to patients of ODIVEN XR treatment.

Serotonin syndrome

Serotonin syndrome, a potential life-threatening condition, may occur with ODIVEN XR treatment, particularly with concomitant use with other medicines that may affect the serotonergic neurotransmitter system (SSRIs, SNRIs, amphetamines, lithium, sibutramine, St John's wort (*Hypericum perforatum*), fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone and pentazocine), with medicines that impair serotonin metabolism (MOAIs), with serotonin precursors (tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.4).

Where concomitant treatment with ODIVEN XR and an SSRI, an SNRI or a serotonin receptor agonist (triptan) is clinically warranted, patients should be carefully observed, especially during initiation of treatment and with dosage increases. Concomitant use of serotonin precursors (such as tryptophan supplements) with ODIVEN XR is not recommended (see section 4.4).

Central nervous system (CNS) active medicines

Caution is advised when ODIVEN XR is taken in combination with other CNS active medicines, as the risk has not been systematically evaluated.

Ethanol

ODIVEN XR may not increase the impairment of mental and motor skills caused by ethanol. However, patients should be advised to avoid alcohol consumption while taking ODIVEN XR.

Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular dysrhythmias (e.g. TdP) is increased with concomitant use of other medicines which prolong the QTc interval. Co-administration with such medicines should be avoided (see section 4.4).

Relevant classes include:

- Class Ia and III antidysrhythmics (e.g. amiodarone, quinidine, sotalol).
- Some antipsychotics (e.g. thioridazine).
- Some macrolides (e.g. erythromycin).
- Some antihistamines.
- Some quinolone antibiotics (e.g. moxifloxacin).

Other medicines known to significantly increase the QT interval should also be avoided.

Cimetidine

The first pass metabolism of ODIVEN XR is inhibited by cimetidine at steady-state, but it had no apparent effect on the pharmacokinetics of O-desmethylvenlafaxine (ODV). The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly in most patients. In the elderly and in patients with hepatic or renal dysfunction this interaction may be more pronounced.

Ketoconazole (CYP3A4 inhibitor)

Concomitant use of CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and venlafaxine may increase levels of venlafaxine and ODV. Therefore, caution is advised when combining ODIVEN XR with a CYP3A4 inhibitor.

Lithium

Serotonin syndrome may occur with the concomitant use of ODIVEN XR and lithium.

Diazepam

ODIVEN XR has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam. Diazepam does not appear to affect the pharmacokinetics of either venlafaxine or ODV.

Imipramine

Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. There was a dose-dependent increase of 2-OH-desipramine AUC by 2,5 to 4,5-fold when venlafaxine 75 mg to 150 mg daily was administered. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. Caution should be exercised with co-administration of ODIVEN XR and imipramine.

Haloperidol

Changes in the pharmacokinetics of oral haloperidol include a possible decrease of 42 % in total oral clearance, a 70 % increase in AUC, and an 88 % increase in the C_{max}. The half-life is not affected. This should be considered in the co-administration of haloperidol and ODIVEN XR.

Risperidone

Venlafaxine increased the risperidone AUC by 50 % but does not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

Metoprolol

Concomitant administration of venlafaxine and metoprolol resulted in an increase in plasma concentrations of metoprolol by approximately 30 – 40 % without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. ODIVEN XR appeared to reduce the blood pressure-lowering effect of metoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of ODIVEN XR or its active metabolite, O-desmethylvenlafaxine. Caution should be exercised with co-administration of ODIVEN XR and metoprolol.

Indinavir

A pharmacokinetic study with indinavir shows a decrease of 28 % in the AUC and a decrease of 36 % in C_{max} for indinavir. The pharmacokinetics of ODIVEN XR and ODV are not affected by

indinavir. The clinical significance of this interaction is unknown.

Medicines highly bound to plasma proteins

ODIVEN XR is not highly bound to plasma proteins (27 % bound); therefore, administration of ODIVEN XR with other highly protein bound medicines is not expected to result in increased free concentration of the other medicines.

Medicines metabolised by cytochrome P450 isoenzymes

In vivo studies indicate that ODIVEN XR is a relatively weak inhibitor of CYP2D6. ODIVEN XR did not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine), CYP2C9 (tolbutamide) or CYP2C19 (diazepam) *in vivo*.

Oral contraceptives

In post-marketing experience, unintended pregnancies have been reported in subjects taking oral contraceptives while on ODIVEN XR. There is no clear evidence that these pregnancies were a result of medicine interactions with ODIVEN XR. No interaction study with hormonal contraceptives has been performed.

4.6 Fertility, pregnancy and lactation

Patients falling pregnant or planning a pregnancy during ODIVEN XR therapy should inform their health care professional.

Pregnancy

The safety of ODIVEN XR during pregnancy has not been established.

Discontinuation symptoms may occur in newborns if ODIVEN XR is used until or shortly before birth, as with other serotonin reuptake inhibitors (SSRIs/SNRIs).

Some neonates exposed to ODIVEN XR late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalisation. Such complications can

arise immediately upon delivery.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRIs/SNRIs exposure within the month prior to birth (see sections 4.4 and 4.8).

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 newborn (PPHN). Although no studies have investigated an association of PPHN to SNRI treatment, this potential risk cannot be ruled out with ODIVEN XR, taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

The following symptoms may be observed in neonates if the mother has used an SSRI/SNRI late in pregnancy: irritability, tremor, hypotonia, persistent crying and difficulty in suckling or sleeping. These symptoms may be due to either serotonergic effects or exposure symptoms. In most cases, these complications are observed immediately or within 24 hours postpartum.

Breastfeeding

The safety of ODIVEN XR during breastfeeding has not been established. Both venlafaxine and O-desmethylvenlafaxine are excreted in breast milk. There have been post-marketing reports of breastfed infants who experienced crying, irritability and abnormal sleep patterns. Symptoms consistent with ODIVEN XR discontinuation have also been reported after stopping breastfeeding. A decision should be made as to whether ODIVEN XR should be discontinued, or whether the patient should stop breastfeeding.

Fertility

Reduced fertility was observed in a study in which both female and male rats were exposed to the major metabolite, O-desmethylvenlafaxine. The human relevance of this finding is unknown.

4.7 Effects on ability to drive and use machines

ODIVEN XR may impair judgement, thinking and motor skills. Therefore, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are

reasonably certain that ODIVEN XR does not affect them adversely.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: agranulocytosis, aplastic anaemia, pancytopenia, neutropenia, thrombocytopenia

Immune system disorders

Frequency unknown: anaphylactic reaction, angioedema

Endocrine disorders

Less frequent: inappropriate antidiuretic hormone secretion, hyperprolactinaemia

Metabolism and nutrition disorders

Frequent: increased serum cholesterol (possibly dose related and after prolonged use), decreased body mass, decreased appetite

Less frequent: hyponatraemia, weight gain

Psychiatric disorders

Frequent: confusional state, depersonalisation, abnormal dreams, nervousness, agitation, insomnia, decreased libido

Less frequent: mania, hypomania, hallucinations, derealisation, bruxism, apathy, delirium

Frequency unknown: suicidal ideation, suicidal behaviour, aggression

Nervous system disorders

Frequent: headache, dizziness, sedation, akathisia, tremor, paraesthesia, dysgeusia

Less frequent: syncope, myoclonus, balance disorder, abnormal coordination, dyskinesia, neuroleptic malignant syndrome (NMS), serotonin syndrome, convulsions,

dystonia, tardive dyskinesia

Eye disorders

Frequent: visual impairment, accommodation disorder, blurred vision, mydriasis

Less frequent: angle closure glaucoma

Ear and labyrinth disorders

Frequent: tinnitus

Frequency unknown: vertigo

Cardiac disorders

Frequent: tachycardia, palpitations, chest pain, hypertension

Less frequent: torsade de pointes, ventricular tachycardia, ventricular fibrillation, electrocardiogram QT prolongation

Frequency unknown: stress cardiomyopathy (takotsubo cardiomyopathy)

Vascular disorders

Frequent: hypertension, vasodilation (mostly hot flushes*)*

Less frequent: orthostatic hypotension, hypotension

Respiratory, thoracic and mediastinal disorders

Frequent: yawning, dyspnoea

Less frequent: interstitial lung disease, pulmonary eosinophilia

Gastrointestinal disorders

Frequent: nausea, dry mouth, constipation, diarrhoea, vomiting, decreased appetite, abdominal pain

Less frequent: gastrointestinal haemorrhage, pancreatitis, altered taste sensation

Hepatobiliary disorders

Less frequent: abnormal liver function test, hepatitis

Skin and subcutaneous tissue disorders

Frequent: hyperhidrosis (including night sweats), rash, pruritus

Less frequent: urticaria, alopecia, ecchymosis, angioedema, photosensitivity reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and connective tissue disorders

Frequent: hypertonia, back pain

Less frequent: rhabdomyolysis

Renal and urinary disorders

Frequent: urinary hesitation, urinary retention, pollakiuria, impaired urination (mostly hesitancy)

Less frequent: urinary incontinence

Reproductive system and breast disorders

Frequent: menorrhagia, metrorrhagia, erectile dysfunction, ejaculation disorder, abnormal ejaculation/orgasm (males), anorgasmia, decreased libido

Less frequent: abnormal orgasm (females)

Frequency unknown: postpartum haemorrhage

General disorders and administration site conditions

Frequent: fatigue, asthenia, chills, pain

Less frequent: mucosal haemorrhage

Investigations

Frequent: weight decreased, weight increased, blood cholesterol increased

Less frequent: prolonged bleeding time.

Description of selected adverse reactions

Discontinuation of treatment

Discontinuation of ODIVEN XR (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, vertigo, headache and flu syndrome are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting, however, in some patients, they may be severe and/or prolonged. It is therefore advised that when ODIVEN XR treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4). However, in some patients, severe aggression and suicidal ideation occurred when the dose was reduced or during discontinuation (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ODIVEN XR is important. It allows continued monitoring of the benefit/risk balance of ODIVEN XR. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

The most commonly reported symptoms are tachycardia, changes in the level of consciousness (ranging from somnolence to coma), mydriasis, convulsions and vomiting. Other events include electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS

prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo and death (see section 4.8).

Treatment

The recommended treatment of an overdose should be supportive and symptomatic, including the monitoring of vital signs and cardiac rhythm.

When there is a risk of aspiration, induction of emesis is not recommended.

Administration of activated charcoal may also limit medicine absorption.

Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be beneficial.

There are no known specific antidotes for ODIVEN XR.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics.

Pharmacotherapeutic group: Nervous system phsychoanaleptics, antidepressants, other antidepressants.

ATC code: NO6AX16.

Mechanism of action

Venlafaxine and its major metabolite, O-desmethylvenlafaxine, are inhibitors of serotonin and noradrenaline re-uptake and also weakly inhibit dopamine uptake. This leads to potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and O-desmethylvenlafaxine are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

Venlafaxine has virtually no affinity for rat brain muscarinic, cholinergic, H1-histaminergic or α1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant medicines, such as anticholinergic, sedative and

cardiovascular side effects. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity. *In vitro* studies revealed that venlafaxine has virtually no affinity for opiate or benzodiazepine sensitive receptors.

Clinical efficacy and safety

Major depressive episodes

The efficacy of venlafaxine immediate-release and prolonged-release as treatment for major depressive episodes was established.

Generalised anxiety disorder

The efficacy of venlafaxine prolonged-release capsules as a treatment for generalised anxiety disorder (GAD) was established.

Social anxiety disorder

The efficacy of venlafaxine prolonged-release capsules was established as a treatment for social anxiety.

Panic disorder

The efficacy of venlafaxine prolonged-release capsules was established as a treatment for panic disorder.

Cardiac electrophysiology

Post-marketing cases of QTc prolongation/TdP and ventricular dysrhythmia have been reported, especially in overdose or in patients with other risk factors for QTc prolongation/TdP (see sections 4.4, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). Mean ± SD plasma half-lives of venlafaxine and ODV are 5 ± 2 hours and 11 ± 2 hours, respectively. Steady-state concentrations of venlafaxine and ODV are attained within 3 days of oral multiple-dose therapy. Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Absorption

At least 92 % of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40 % to 45 % due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5,5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.

Food does not affect the bioavailability of venlafaxine and ODV.

Distribution

Venlafaxine and ODV are minimally bound at therapeutic concentrations to human plasma proteins (27 % and 30 % respectively). The volume of distribution for venlafaxine at steady state is 4,4 ± 1,6 L/kg following intravenous administration.

Biotransformation

Venlafaxine undergoes extensive hepatic metabolism and is biotransformed to its major active metabolite, ODV, by CYP2D6. Venlafaxine is also metabolised to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. Venlafaxine is a weak inhibitor of CYP2D6. Venlafaxine did

not inhibit CYP1A2, CYP2C9 or CYP3A4.

Elimination

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87 % of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5 %), unconjugated ODV (29 %), conjugated ODV (26 %), or other minor inactive metabolites (27 %). Mean ± SD plasma steady-state clearances of venlafaxine and ODV are 1,3 ± 0,6 L/h/kg and 0,4 ± 0,2 L/h/kg, respectively.

Special populations

Age and gender

Age and gender do not significantly affect the pharmacokinetics of venlafaxine and ODV.

CYP2D6 extensive/poor metabolisers

Plasma concentrations of venlafaxine are higher in CYP2D6 poor metabolisers than extensive metabolisers. Because the total exposure (AUC) of venlafaxine and ODV is similar in poor and extensive metabolisers, there is no need for different venlafaxine dosing regimens for these two groups.

Hepatic impairment

In Child-Pugh A (mildly hepatically impaired) and Child-Pugh B (moderately hepatically impaired) subjects, venlafaxine and ODV half-lives were prolonged compared to normal subjects. The oral clearance of both venlafaxine and ODV was reduced. A large degree of inter-subject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).

Renal impairment

In dialysis patients, venlafaxine elimination half-life was prolonged by about 180 % and clearance reduced by about 57 % compared to normal subjects, while ODV elimination half-life was

prolonged by about 142 % and clearance reduced by about 56 %. Dosage adjustment is necessary in patients with severe renal impairment and in patients that require haemodialysis (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets

Hydroxypropyl cellulose

Microcrystalline cellulose

Polymer coating (containing ethyl cellulose and hypromellose)

Talc.

Hard gelatine capsules

Gelatine

Iron oxide black (E172) (for ODIVEN XR 37,5)

Iron oxide red (E 172) (for ODIVEN XR 75 and ODIVEN XR 150)

Sodium laurilsulfate (SLS)

Titanium dioxide (E 171).

Black ink

Iron oxide black (E 172)

Potassium hydroxide (E 525)

Propylene glycol (E 1520)

Shellac (E 904).

Sugar free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove capsules from blister strips until required for use.

Keep blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Transparent PVC/PVDC film and silver aluminium foil blister strip containing 10 capsules.

OR

Transparent OPA/PVC and silver aluminium foil blister strip containing 10 capsules.

Pack size: 30.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion 0157

8. REGISTRATION NUMBERS

ODIVEN XR 37,5: 54/1.2/0072

ODIVEN XR 75: 54/1.2/0073

ODIVEN XR 150 54/1.2/0074

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10 September 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.