PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

ODIVEN 37,5 tablets

ODIVEN 50 tablets

ODIVEN 75 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ODIVEN 37,5: Each tablet contains venlafaxine hydrochloride equivalent to 37,5 mg venlafaxine.

ODIVEN 50: Each tablet contains venlafaxine hydrochloride equivalent to 50 mg venlafaxine.

ODIVEN 75: Each tablet contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine.

Excipient with known effect:

Contains sugar:

45 mg lactose monohydrate per ODIVEN 37,5 tablet.

60 mg lactose monohydrate per ODIVEN 50 tablet.

90 mg lactose monohydrate per ODIVEN 75 tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ODIVEN 37,5: Peach coloured, round, flat, bevelled edge, uncoated tablets with a bisect on one side; one side of the bisect is debossed with the logo "ZC" and other side is debossed with "65", the other side is plain.

ODIVEN 50: Peach coloured, round, flat, bevelled edge, uncoated tablets with a bisect on one side; one side of the bisect is debossed with the logo "ZC" and other side is debossed with "66",

the other side is plain.

ODIVEN 75: Peach coloured, round, flat, bevelled edge, uncoated tablets with a bisect on one side; one side of the bisect is debossed with the logo "ZC" and other side is debossed with "67", the other side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ODIVEN is indicated for the treatment of depression, including depression with associated anxiety.

ODIVEN is indicated for the prevention of relapses of an episode of depression in patients responding to an initial 6 to 8 weeks treatment. In patients responding to 6 months of relapse prevention, ODIVEN may be used to prevent recurrence. Safety and efficacy beyond one year have not been demonstrated in clinical studies.

4.2 Posology and method of administration

Posology

The usual recommended dose is 75 mg per day given in two divided doses (37,5 mg twice daily). The dose may be increased to 150 mg per day given in two divided doses (75 mg twice daily), if necessary.

In severely depressed hospitalised patients, the recommended starting dose is 150 mg per day given in two divided doses (or 50 mg three times daily). The daily dose should then be increased by 50 – 75 mg every two or three days until the desired response is achieved. The maximum recommended dose is 375 mg per day. The dose should then be gradually reduced to the usual dosage, consistent with patient response and tolerance. It is recommended that ODIVEN be taken with food.

Special populations

Patients with renal or hepatic impairment

Patients with renal and/or hepatic impairment should receive lower doses of ODIVEN. The total

daily dose of ODIVEN must be reduced by 25 – 50 % for patients with renal impairment with a glomerular filtration rate (GFR) of 10 – 70 mL/min. The total daily dose of ODIVEN must be reduced by 50 % in haemodialysis patients. Administration must be withheld until the dialysis session is completed.

Patients with hepatic impairment

The total daily dose of ODIVEN must be reduced by 50 % in patients with moderate hepatic impairment. Reductions of more than 50 % may be appropriate for some patients.

Children

See section 4.3.

Elderly patients

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

Maintenance, continuation and extended treatment

The need for long-term therapy with venlafaxine must be periodically reassessed. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuing ODIVEN

Dose tapering is recommended when discontinuing ODIVEN therapy. Tapering over at least a two-week period is recommended if venlafaxine has been used for more than 6 weeks (see section 4.4). The period required for tapering may depend on the dose, duration of therapy and the individual patient. Patients should be advised to consult their doctor before abruptly discontinuing ODIVEN (section 4.4).

Method of administration

Oral administration.

4.3 Contraindications

- Hypersensitivity to venlafaxine or any excipients listed in section 6.1.
- Children under the age of 18 years.
- Pregnancy and lactation (see section 4.6).
- Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Overdose

Patients should be advised not to use alcohol, considering its central nervous system (CNS) effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with ODIVEN including CNS depressant effects (section 4.5). Overdose with venlafaxine has been reported, predominantly in combination with alcohol and/or other medicines, including cases with fatal outcome (see section 4.9).

Severe adverse reactions have been reported when ODIVEN therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of ODIVEN. Reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death. Safety and efficacy in children under 18 years of age have not been established (see sections 4.3 and 4.8).

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. This risk may persist until significant remission occurs.
As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
A causal role, however, for antidepressant medicine in inducing such behaviour has not been established.
Close supervision of patients, and in particular those at high risk, should accompany medicine therapy, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately if these symptoms present.

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.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

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 to the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing ODIVEN, 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 should be tapered (see sections 4.4 and 4.2).

The risk of suicide must be considered in all depressed patients. Prescriptions for ODIVEN should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the possibility of overdose.

ODIVEN should be introduced with care in patients with a history of seizures and should be discontinued in any patient developing a seizure.

Patients should be advised to notify their doctor if they develop a rash, urticaria, or a related allergic phenomenon.

Blood pressure

Dose-related increases in blood pressure have been commonly reported with venlafaxine, as in ODIVEN. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in post-marketing experience. All patients should be carefully screened for high blood pressure, and pre-existing hypertension should be controlled before initiation of treatment. Blood pressure should be reviewed periodically, after initiation of treatment and after dose increases. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure, e.g. those with impaired cardiac function.

Treatment with ODIVEN has been associated with an increase in blood pressure in some patients. Mean increases in supine diastolic blood pressure of approximately 2 mm Hg were observed. The presence of treated hypertension or elevated blood pressure at baseline does not seem to predispose patients to further increases during ODIVEN therapy. For patients treated with doses greater than 200 mg/day, blood pressure monitoring may be advisable. Either dose reduction or

discontinuation should be considered for patients who experience a sustained increase in blood pressure while receiving ODIVEN.

Mania/hypomania

Mania/hypomania may occur in a small proportion of patients with mood disorders who have received antidepressants, including venlafaxine. As with all antidepressants, ODIVEN should be used with caution in patients with a history or family history of bipolar disorder.

Aggression

Aggression may occur in some patients who have received antidepressants, including ODIVEN. This has been reported under initiation, dose changes and discontinuation of treatment. ODIVEN should be used cautiously 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 may occur in patients during changes in ODIVEN dosing regimen, including during discontinuation. Therefore, patients should be closely monitored when the dose is reduced or during discontinuation (see section 4.4 – ***Suicide/suicidal thoughts or clinical worsening*** and ***Aggression***).

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8).

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, visual impairment and hypertension are the most commonly reported reactions.

Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They 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. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 – 3 months or more). It is therefore advised that ODIVEN should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2). In some patients, discontinuation could take months or longer.

Co-administration with weight loss medicines

The safety and efficacy of ODIVEN therapy in combination with weight loss medicines, including phentermine, have not been established.

Co-administration of ODIVEN and weight loss medicines is not recommended. ODIVEN is not indicated for weight loss alone or in combination with other products (see section 4.5).

Treatment-associated anorexia has frequently been reported with venlafaxine. Dose-related weight loss has also been noted. Significant weight loss, especially in underweight depressed patients, may be an undesirable effect of venlafaxine treatment. Weight gain has been experienced less frequently.

Misuse or abuse of ODIVEN

There are no signs of drug-seeking behaviour, development of tolerance, or dose escalation over time among patients taking ODIVEN. Nonetheless, it is recommended that doctors carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of ODIVEN (e.g. development of tolerance, increase in dose, drug-seeking behaviour).

Diseases or conditions affecting haemodynamic responses or metabolism

Clinical experience with ODIVEN in patients with concomitant systemic illnesses is limited. Caution is advised in administering ODIVEN to patients with diseases or conditions that could affect haemodynamic responses or metabolism.

Heart rate

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

Cardiac disease and risk of arrhythmia

ODIVEN has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.

In post-marketing experience, cases of QTc prolongation, torsades de pointes (TdP), ventricular tachycardia and fatal cardiac arrhythmias have been reported with the use of venlafaxine, as in ODIVEN, especially in overdose or in patients with other risk factors for QTc prolongation/TdP.

No serious arrhythmias were observed in patients treated with ODIVEN and mean PR, QRS or QTc intervals were not significantly prolonged. The mean heart rate was increased by approximately 4 beats/minute during treatment. As increases in heart rate were observed, caution should be exercised in patients whose underlying medical conditions might be compromised by increases in heart rate (e.g. patients with hyperthyroidism, heart failure, or recent myocardial infarction).

Convulsions

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

Hyponatraemia

Cases of hyponatraemia and/or the syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur with ODIVEN. This has most frequently been reported in volume-depleted or dehydrated patients. Elderly patients, patients taking diuretics, and patients who are otherwise

volume-depleted may be at greater risk for this event.

Abnormal bleeding

Medicines that inhibit serotonin uptake may lead to reduced platelet function. Bleeding events related to selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) use have ranged from ecchymosis, haematomas, epistaxis and petechiae to gastrointestinal and life-threatening haemorrhages. SSRIs/SNRIs, including venlafaxine, may increase the risk of post-partum haemorrhage (see sections 4.6 and 4.8). The risk of haemorrhage may be increased in patients taking ODIVEN.
ODIVEN should be used cautiously in patients predisposed to bleeding, including patients on anticoagulants and platelet inhibitors (see section 4.5).

Serum cholesterol

Clinically relevant increases in serum cholesterol were recorded in 5,3 % of venlafaxine-treated patients and 0,0 % of placebo-treated patients treated for at least 3 months in placebo-controlled clinical trials. Measurement of serum cholesterol levels should be considered during long-term treatment.

Patients with renal or liver impairment

ODIVEN should be used with caution in patients with moderate to severe renal impairment or cirrhosis of the liver. A lower or less frequent dose may be necessary (see section 4.2).

Use in elderly patients

ODIVEN appears to pose no exceptional safety problems for healthy elderly patients. No dosage adjustment is recommended on the basis of age alone, although other clinical circumstances, such as renal impairment, which may be more common in the elderly, may warrant a dose reduction.

Carcinogenesis, mutagenesis, impairment of fertility

No evidence was noted in non-clinical toxicology studies.

Paediatric use

ODIVEN is contraindicated in children and adolescents under the age of 18 years (see section 4.3). In clinical trials in major depressive disorder, there were increased reports of hostility (predominantly aggression, oppositional behaviour and anger) and suicide-related adverse events such as suicidal ideation and self-harm. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with ODIVEN treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (see sections 4.3 and 4.5).

Serotonin syndrome symptoms 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 in its most severe form, can resemble neuroleptic malignant syndrome (NMS), which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes.

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

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

Narrow-angle glaucoma

Mydriasis may occur in association with venlafaxine, as in ODIVEN. It is recommended that patients with raised intraocular pressure or patients at risk for acute narrow-angle glaucoma (angle-closure glaucoma) be closely monitored.

Sexual dysfunction

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

Akathisia/psychomotor restlessness

The use of ODIVEN has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Dry mouth

Dry mouth is reported in 10 % of patients treated with venlafaxine, as in ODIVEN. This may increase the risk of caries, and patients should be advised about the importance of dental hygiene.

Diabetes

In patients with diabetes, treatment with an SSRI or ODIVEN may alter glycaemic control. Insulin and/or oral antidiabetic dosage may need to be adjusted.

Medicine-laboratory test interactions

False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking venlafaxine, as in ODIVEN. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following

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

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take ODIVEN tablets.

Sodium

ODIVEN tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say it is essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (see section 4.4)

Irreversible non-selective MAOIs

ODIVEN must not be used in combination with irreversible non-selective MAOIs. ODIVEN must not be initiated for at least 14 days after discontinuation of treatment with an irreversible non-selective MAOI. ODIVEN must 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 MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of ODIVEN with a reversible and selective MAOI, such as moclobemide, is not recommended. Following treatment with a reversible MAO inhibitor, a shorter withdrawal period than 14 days may be used before initiation of ODIVEN treatment. It is recommended that ODIVEN should be discontinued for at least 7 days before starting treatment with a reversible MAOI (see section 4.4).

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with ODIVEN (see section 4.4).

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI and started on ODIVEN or have recently had ODIVEN discontinued prior to initiation of an MAOI (see section 4.3). These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness and hyperthermia with features resembling neuroleptic malignant syndrome, seizure and death.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with ODIVEN treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, SNRIs, tricyclic antidepressants, amphetamines, lithium, sibutramine, St John's wort [*Hypericum perforatum*], opioids [e.g. fentanyl and its analogues, tramadol, dextromethorphan, tapentadol, pethidine, methadone, pentazocine, buprenorphine and buprenorphine/naloxone combination]), with medicines that impair metabolism of serotonin (such as MAOIs, e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (see sections 4.3 and 4.4).

If concomitant treatment with ODIVEN and an SSRI, an SNRI or a serotonin receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of ODIVEN with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

CNS active medicines

Based on known mechanism of action of ODIVEN and the potential for serotonin syndrome, caution is advised when ODIVEN is co-administered with other medicines that may affect serotonergic neurotransmitter system (such as triptans, selective serotonin reuptake inhibitors or lithium).

Ethanol

Patients should be advised to avoid alcohol consumption while taking ODIVEN, considering its CNS effects and potential of clinical worsening of psychiatric conditions, and the potential for adverse interactions with ODIVEN, including CNS depressant effects.

Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval. Co-administration of such medicines should be avoided (see section 4.4). Relevant classes include:

- class la and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines
- some quinolone antibiotics (e.g. moxifloxacin).

The above list is not exhaustive and other individual medicines known to significantly increase QT interval should be avoided.

Effect of other medicines on ODIVEN

Ketoconazole (CYP3A4 inhibitor)

A pharmacokinetic study with ketoconazole in CYP2D6 extensive (EM) and poor metabolisers (PM) resulted in higher AUC of venlafaxine (70 % and 21 % in CYP2D6 PM and EM subjects, respectively) and *O*-desmethylvenlafaxine (33 % and 23 % in CYP2D6 PM and EM subjects, respectively) following administration of ketoconazole. Concomitant use of CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, posaconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin) and ODIVEN may increase levels of venlafaxine and *O*-desmethylvenlafaxine. Therefore, caution is advised if a patient's therapy includes a CYP3A4 inhibitor and ODIVEN concomitantly.

Effect of ODIVEN on other medicines

Indinavir

Pharmacokinetics shows a 28 % decrease in AUC and a 36 % decrease in C_{max} for indinavir. Indinavir does not affect the pharmacokinetics of ODIVEN and *O*-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

Warfarin

Potential of anticoagulant effects may occur in patients taking warfarin following addition of ODIVEN.

Haloperidol

Haloperidol may have a 42 % decrease in total clearance after oral administration, a 70 % increase in AUC, an 88 % increase in C_{max} but without any change in half-life. This should be taken into account in patients treated with haloperidol and ODIVEN concomitantly.

Cimetidine

Cimetidine inhibits the first-pass metabolism of ODIVEN but had no apparent effect on the formation or elimination of *O*-desmethylvenlafaxine, which is present in a much greater quantity in the systemic circulation. Consequently, the overall pharmacological activity of ODIVEN plus *O*-desmethylvenlafaxine is expected to increase only slightly.
No dosage adjustments seem necessary when ODIVEN is co-administered with cimetidine. However, for elderly patients or patients with hepatic dysfunction concomitantly taking ODIVEN and cimetidine, the extent of interaction is not known and potentially could be more pronounced. For such patients, clinical monitoring is indicated.

Risperidone

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

Metoprolol

Concomitant administration of venlafaxine and metoprolol to healthy volunteers in a pharmacokinetic interaction study for both medicines resulted in an increase of plasma concentrations of metoprolol by approximately 30 – 40 % without altering the plasma concentrations of its active metabolite, α-hydroxymetoprolol. The clinical relevance of this finding in hypertensive patients is unknown. Metoprolol did not alter the pharmacokinetic profile of venlafaxine or its active metabolite, *O*-desmethylvenlafaxine. Caution should be exercised with co-administration of ODIVEN and metoprolol.

Diazepam

Diazepam does not appear to affect the pharmacokinetics of either ODIVEN or *O*-desmethylvenlafaxine. ODIVEN has no effects on the pharmacokinetics and pharmacodynamics of diazepam and its active metabolite, desmethyldiazepam.

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 *O*-desmethylvenlafaxine. The clinical significance of this interaction is unknown. Caution should be exercised with co-administration of ODIVEN and imipramine.

Lithium

Serotonin syndrome may occur with the concomitant use of venlafaxine and lithium (see **Serotonin syndrome**).

Medicines highly bound to plasma proteins

ODIVEN is not highly bound to plasma proteins (27 % bound); therefore, administration of ODIVEN

to a patient taking another medicine that is highly protein bound is not expected to cause increased free concentration of the other medicine.

Medicines metabolised by cytochrome P450 isoenzymes

ODIVEN is a relatively weak inhibitor of CYP2D6. ODIVEN does not inhibit CYP3A4 (alprazolam and carbamazepine), CYP1A2 (caffeine) and 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 venlafaxine, as in ODIVEN. There is no clear evidence these pregnancies were a result of medicine interaction with venlafaxine. No interaction study with hormonal contraceptives has been performed.

4.6 Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established (see section 4.3).

Pregnancy

There are no adequate data from the use of venlafaxine, as in ODIVEN, in pregnant women. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown.
Discontinuation symptoms may occur in the newborns if ODIVEN is used until or shortly before birth. Some newborns exposed to ODIVEN 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 taking into account the related mechanism of action (inhibition of the reuptake 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 in sleeping. These symptoms may be due to either serotonergic effects or exposure symptoms. In the majority of cases, these complications are observed immediately or within 24 hours postpartum.

Breastfeeding

ODIVEN and *O*-desmethylvenlafaxine are excreted in human milk. There have been post-marketing reports of breastfed infants who experienced crying, irritability and abnormal sleep patterns. Symptoms consistent with venlafaxine discontinuation have also been reported after stopping breastfeeding. A risk to the suckling child cannot be excluded. Therefore, a decision should be made whether not to breastfeed or to discontinue venlafaxine. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.

Fertility

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

4.7 Effects on ability to drive and use machines

ODIVEN may impair judgement, thinking or motor skills and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the medicine does not affect them adversely.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Agranulocytosis, aplastic anaemia, haemorrhage, neutropenia, pancytopenia.

Endocrine disorders

Less frequent: Pancreatitis, syndrome of inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Frequent: Anorexia (decreased appetite), weight loss.

Psychiatric disorders

Less frequent: Mania, hypomania, hallucinations, derealisation, apathy.

Frequency unknown: Suicidal ideation, suicidal behaviours[a], aggression[b].

Nervous system disorders

Frequent: Headache, abnormal dreams, anxiety or nervousness, dizziness, sedation, dryness of mouth, insomnia, confusional state, depersonalisation, agitation, paraesthesia, dysgeusia, somnolence, tremor.

Less frequent: Central nervous system (CNS) effects (abnormal thinking, emotional lability), seizures, syncope, myoclonus, neuroleptic malignant syndrome-like events (convulsions, difficulty breathing, fast heartbeat, high fever), serotonin syndrome (agitation, confusion, diarrhoea, fever), convulsions, tardive dyskinesia (lip smacking or puckering).

Frequency unknown: Catatonia, delirium, involuntary movements, panic, shock-like electrical sensations, impaired coordination, dysphoric mood, irritability, lethargy.

Eye disorders

Frequent: Vision disturbances, including abnormal accommodation and blurred vision, visual impairment, mydriasis.

Less frequent: Angle-closure glaucoma.

Frequency unknown: Eye haemorrhage.

Ear and labyrinth disorders

Frequent: Tinnitus.

Frequency unknown: Vertigo.

Cardiac disorders

Frequent: Tachycardia, palpitations.

Less frequent: Cardiovascular effects including chest pain, torsades de pointes, ventricular fibrillation, ventricular tachycardia, electrocardiogram QT prolonged.

Frequency unknown: Atrial fibrillation, cardiac arrhythmias, supraventricular tachycardia, ventricular extrasystoles.

Vascular disorders

Frequent: Hypertension, hot flush.

Less frequent: Oedema, orthostatic hypotension.

Frequency unknown: Deep vein thrombophlebitis.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea, yawning.

Less frequent: Pulmonary eosinophilia, rhinitis.

Frequency unknown: Pharyngitis.

Gastrointestinal disorders

Frequent: Constipation, diarrhoea, dyspepsia, nausea, stomach pain, vomiting, dry mouth.

Less frequent: Gastrointestinal haemorrhage.

Hepato-biliary disorders

Frequency unknown: Fatty liver, liver damage, liver failure, liver necrosis.

Skin and subcutaneous tissue disorders

Frequent: Hyperhidrosis (including night sweats), pruritus, rash.

Less frequent: Epidermal necrolysis, erythema multiforme, Stevens Johnson syndrome, photosensitivity reaction.

Musculoskeletal and connective tissue disorders

Frequent: Hypertonia (muscle tension).

Less frequent: Rhabdomyolysis.

Frequency unknown: Fasciculation, back and neck pain, myalgia, arthralgia.

Renal and urinary disorders

Frequent: Urinary hesitation, urinary retention.

Less frequent: Impaired urination, urinary frequency, urinary incontinence.

Frequency unknown: Renal failure.

Reproductive system and breast disorders

Frequent: Sexual dysfunction (anorgasmia, decreased libido, ejaculation disorder[b], impotence), menorrhagia, metrorrhagia, erectile dysfunction[b].

Less frequent: Abnormal orgasm.

Congenital, familial and genetic disorders

Frequency unknown: Congenital anomalies.

General disorders and administration site conditions

Frequent: Fatigue, asthenia, chills.

Less frequent: Trismus (lockjaw), taste perversion.

Investigations

Frequent: Weight decreased, weight increased, blood cholesterol increased.

[a] Cases of suicidal ideation and suicidal behaviours have been reported during venlafaxine therapy or early after treatment discontinuation (see section 4.4).

[b] See section 4.4.

[c] In pooled clinical trials, the incidence of headache with venlafaxine and placebo were similar.

[d] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

In children: reports of hostility, suicidal ideation and self-harm.

The occurrence of many frequently observed adverse events is dose related. Adverse events generally decrease in intensity and frequency with continued therapy and generally do not lead to cessation of treatment.

Post-marketing adverse reactions

Blood and lymphatic system disorders

Less frequent: Thrombocytopenia.

Immune system disorders

Less frequent: Anaphylactic reaction.

Endocrine disorders

Less frequent: Increased blood prolactin.

Metabolism and nutrition disorders

Less frequent: Hyponatraemia, hypoglycaemia.

Psychiatric disorders

Less frequent: Bruxism, delirium.

Nervous system disorders

Frequent: Akathisia.

Less frequent: Balance disorder, abnormal coordination, dyskinesia, dystonia.

Cardiac disorders

Frequency unknown: Stress cardiomyopathy (takotsubo cardiomyopathy).

Vascular disorders

Less frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Interstitial lung disease.

Gastrointestinal disorders

Less frequent: Pancreatitis.

Hepato-biliary disorders

Less frequent: Liver function test abnormal, hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Urticaria, alopecia, ecchymosis, angioedema.

Renal and urinary disorders

Frequent: Pollakiuria.

Reproductive system and breast disorders

Frequency unknown: Postpartum haemorrhage[d].

General disorders and administration site conditions

Less frequent: Mucosal haemorrhage.

Investigations

Less frequent: Bleeding time prolonged.

Discontinuation of treatment

Discontinuation of ODIVEN (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, flu syndrome, visual impairment and hypertension 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 treatment is no longer required, gradual discontinuation by dose tapering should be carried out. However, in some patients, severe aggression and suicidal ideation occurred when the dose was reduced or during discontinuation (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

In post-marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicines, including cases with fatal outcome. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsions and vomiting. Other reported events include electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation [see section 5.1]), ventricular tachycardia, bradycardia, hypotension, hypoglycaemia, vertigo and deaths. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressants, but lower than that for tricyclic antidepressants.

Epidemiological studies have shown that venlafaxine-treated patients have a higher burden of suicide risk factors than SSRI patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine, as in ODIVEN, in overdosage, as opposed to some characteristics of venlafaxine-treated patients, is not clear.

Treatment

Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving ODIVEN, prompt treatment is required.

General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs

must be monitored.

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

Administration of activated charcoal may also limit absorption of the active substance. Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine, as in ODIVEN, are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Other antidepressants.

ATC code: NO6AX16.

Mechanism of action

Venlafaxine and its major metabolite, *O*-desmethylvenlafaxine, are inhibitors of serotonin and noradrenalin reuptake and also weakly inhibit dopamine reuptake. This leads to potentiation of neurotransmitter activity in the central nervous system (CNS). Venlafaxine and *O*-desmethylvenlafaxine reduce beta-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter reuptake and receptor binding.

5.2 Pharmacokinetic properties

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 *O*-desmethylvenlafaxine (ODV) occur in 2 and 3 hours, respectively.

Following the administration of ODIVEN prolonged-release dosage, 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 dosage, the prolonged-release dosage 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

Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172 ng/mL after 25 to 150 mg single doses and are reached in approximately 2,4 hours.
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. *In vitro* and *in vivo* studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolised to a minor, less active metabolite, *N*-desmethylvenlafaxine, by CYP3A4. *In vitro* and *in vivo* studies indicate that venlafaxine, as in ODIVEN, is a weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2, CYP2C9 or CYP3A4.
Venlafaxine is extensively metabolised in the liver. *O*-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and *O*-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak *O*-desmethylvenlafaxine plasma concentrations range from approximately 61 to 325 ng/mL after 25 to 150 mg single doses of venlafaxine and are reached in approximately 4,3 hours. Plasma concentrations of venlafaxine and *O*-desmethylvenlafaxine generally correlated well with dose levels. Venlafaxine and *O*-desmethylvenlafaxine are less than 35 % bound to plasma proteins (venlafaxine and *O*-desmethylvenlafaxine are 27 % and 30 % bound to plasma proteins, 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.

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, unconjugated *O*-desmethylvenlafaxine, conjugated *O*-desmethylvenlafaxine, or other minor metabolites. 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.

Administration of venlafaxine with food slightly prolonged the time-to-peak concentration (by 20 – 30 minutes) but had no effect on the peak concentration (C_{max}) or extent of absorption of venlafaxine. Similarly, food has no effect on the C_{max} or extent of formation of *O*-desmethylvenlafaxine. A 20 % reduction in clearance was noted for *O*-desmethylvenlafaxine in subjects over 60 years old.

Special populations

Age and gender

Subject 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.

Patients with renal impairment

In patients with moderate to severe impairment of renal function, the total clearance of both venlafaxine and *O*-desmethylvenlafaxine was reduced, and $t_{½}$ was prolonged. The reduction in

total clearance was most pronounced in subjects with creatinine clearance less than 30 mL/min. Dosage adjustment is recommended in these patients (see section 4.2).

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).

Patients with hepatic impairment

In patients with compensated hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and *O*-desmethylvenlafaxine was significantly altered. The reduction in both the metabolism of venlafaxine and elimination of *O*-desmethylvenlafaxine resulted in higher plasma concentrations of both. Dosage adjustment is recommended in these patients (see section 4.2).

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 intersubject variability was noted. There are limited data in patients with severe hepatic impairment (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose

Sodium starch glycolate (Type A)

Iron oxide yellow (E172)

Iron oxide red (E172)

Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

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

6.5 Nature and contents of container

ODIVEN 37,5, ODIVEN 50 and ODIVEN 75 tablets are packed in an aluminium/PVC/PVDC foil blister strip containing ten tablets.

Pack sizes: 10, 30, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Tel: 012 748 6400

8. REGISTRATION NUMBERS

ODIVEN 37,5: 41/1.2/0440

ODIVEN 50: 41/1.2/0441

ODIVEN 75: 41/1.2/0442

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

09 July 2007

10. DATE OF REVISION OF THE TEXT

30 June 2026