Front Side

535 mm

400 mm

MACLAFAX XR 75/150
(Extended release capsules)
PM03626301

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

MACLAFAX XR 75 mg (Extended release capsules)
MACLAFAX XR 150 mg (Extended release capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MACLAFAX XR 75 mg CAPSULES: Each extended release capsule contains venlafaxine hydrochloride equivalent to 75 mg venlafaxine. Sugar free.
MACLAFAX XR 150 mg CAPSULES: Each extended release capsule contains venlafaxine hydrochloride equivalent to 150 mg venlafaxine. Sugar free.
Excipients:
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

MACLAFAX XR 75 mg (Extended release capsules).
Peach Cap/peach body, size '1' capsules containing white to off white extended release beads with 'L 87' on cap and '75' on body imprinted with red ink.
MACLAFAX XR 150 mg (Extended release capsules).
Dark orange cap/dark orange body, size '0el' capsules containing white to off white extended release beads with 'L 88' on cap and '150' on body imprinted with white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
MACLAFAX XR is indicated for the following:
- The treatment of depression, including depression with associated anxiety.
- Prevention of relapse of an episode of depression in patients that responded to an initial 6 to 8 weeks period of treatment.
- Prevention of recurrence in patients responding to 6 months of relapse prevention.
  The safety and efficacy of treatment beyond one year have not been demonstrated. When **MACLAFAX XR** is used for long-term it should periodically be re-evaluated for the usefulness of the product in the individual patient.
- The treatment of generalised anxiety disorder.
- Treatment of Social Anxiety Disorder. The effectiveness of **MACLAFAX XR** in the treatment of Social Anxiety Disorder for more than 12 weeks has not been demonstrated.

4.2 Posology and method of administration
Posology:
The usual recommended dose for **MACLAFAX XR** is 75 mg, given once daily. If after several weeks further clinical improvement is required, the dose may be increased to 150 mg, given once daily. If needed, the dose can be further increased up to 225 mg given once daily. Dose increments should be made at intervals of approximately 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, given once daily.
MACLAFAX XR should be administered once daily, at approximately the same time either in the morning or in the evening. The extended-release formulation contains spheroids, which release the medicine slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in stools.
Depressed patients who are currently being treated at a therapeutic dose with an immediate release formulation may be switched to **MACLAFAX XR** at the nearest equivalent dose (mg/day). Individual dosage adjustments may however be necessary.
Special populations
Patients with renal impairment:
Patients with renal impairment should receive lower doses of **MACLAFAX XR**.
The total daily dose of **MACLAFAX XR** should 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 **MACLAFAX XR** should be reduced by 50 % in haemodialysis patients.
Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Patients with hepatic impairment:
The total daily dose of **MACLAFAX XR** should be reduced by 50 % in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been studied; therefore, caution should be used if considering treating these patients with **MACLAFAX XR** and a further reduction should be considered. Since there is a variability in clearance between hepatically impaired patients, individualisation of dosing, including further dose reductions (> 50 %), may be desirable in some patients.
Because of individual variability in clearance in these patients, individualisation of dosage may be desirable.

Elderly:
No dosage adjustment is recommended for elderly patients on the basis of age.

Pediatric population
See section 4.3.

Maintenance, continuation and extended treatment:
The need for long-term therapy with **MACLAFAX XR** 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 MACLAFAX XR:
Dose tapering is recommended whenever possible when discontinuing **MACLAFAX XR** therapy (see section 4.4). Tapering over at least a two-week period is recommended if **MACLAFAX XR** has been used for more than 6 weeks. In clinical trials with venlafaxine extended-release capsules, tapering was achieved by reducing the daily dose by 75 mg at 1-week intervals. 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 **MACLAFAX XR** (see section 4.4).

Method of administration
For oral use.
It is recommended that **MACLAFAX 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
MACLAFAX XR is contraindicated in:
- Patients with hypersensitivity to venlafaxine hydrochloride, or to any of the inactive ingredients of **MACLAFAX XR** listed in section 6.1.
- Concomitant use of monoamine oxidase inhibitors (MAOIs). **MACLAFAX XR** must not be initiated for at least 14 days after discontinuation of treatment with a MAOI. **MACLAFAX XR** must be discontinued for at least 7 days before starting treatment with any MAOI. Severe adverse reactions have been reported when **MACLAFAX XR** therapy is initiated soon after discontinuation of an MAOI and when an MAOI is initiated soon after discontinuation of **MACLAFAX XR**. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Children under 18 years (see section 4.4).

4.4 Special warnings and precautions for use
Suicide:
All patients treated with **MACLAFAX XR** should be monitored appropriately and observed closely for clinical worsening and suicidality. Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restless), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially when initiating therapy or during any change in dose or dosage regimen. The risk of suicide attempt must be considered especially in depressed patients, and the smallest quantity of medicine, consistent with good patient management, should be provided to reduce the risk of overdose. Risk assessment for suicide should be performed regularly.
Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are strong predictors of suicide. 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 (aged 18 – 24 years) with major depression and other psychiatric disorders.

Patients with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicine. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with **MACLAFAX 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 disorder 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 **MACLAFAX 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, **MACLAFAX XR** should be tapered (see section 4.2).

Serotonin syndrome:
Serotonin syndrome, a potentially life-threatening condition may occur with **MACLAFAX 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 e.g. methylene blue), with serotonin precursors (such as tryptophan supplements) or with antipsychotics or other dopamine antagonists (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 **MACLAFAX XR** 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 **MACLAFAX XR** with serotonin precursors (such as tryptophan supplements) is not recommended.

Mydriasis:
Mydriasis may occur in association with **MACLAFAX XR**. It is recommended that patients with raised intra-ocular pressure or patients at risk for acute narrow angle glaucoma (angle closure glaucoma) be closely monitored.

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 dysrhythmia:
MACLAFAX XR has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, it should be used with caution in these patients.
In postmarketing experience, cases of QTc prolongation, Torsade de Pointes (TdP), ventricular tachycardia, and fatal cardiac dysrhythmias have been reported with the use of venlafaxine, 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 **MACLAFAX XR** to patients at high risk of serious cardiac dysrhythmia or QTc prolongation (see section 5.1).

Blood pressure:
Dose-related increases in blood pressure have been frequently reported with venlafaxine. In some cases, severely elevated blood pressure requiring immediate treatment has been reported in postmarketing experience. Regular blood pressure monitoring is recommended for patients receiving **MACLAFAX XR**. Pre-existing hypertension should be controlled before treatment with **MACLAFAX XR**. Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.
Convulsions:
Convulsions may occur with **MACLAFAX XR** therapy. **MACLAFAX XR** should be introduced with care in patients with a history of convulsions.

Activation of mania/hypomania:
Mania/hypomania may occur in a small proportion of patients with mood disorders who have received **MACLAFAX XR**. **MACLAFAX XR** should be used cautiously in patients with a history or family history of bipolar disorder.

Aggression:
Aggression may occur in a small proportion of patients who have received **MACLAFAX XR** treatment, dose reduction or discontinuation. **MACLAFAX XR** should be used cautiously in patients with a history of aggression.

Hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH):
Cases of hyponatraemia and/or the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion may occur with **MACLAFAX XR**, usually 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 abnormalities of platelet aggregation. The risk of skin and mucous membrane bleeding, including gastrointestinal haemorrhage, may be increased in patients taking **MACLAFAX XR**. **MACLAFAX XR** should be used cautiously in patients predisposed to bleeding, including patients on anti-coagulants and platelet inhibitors.

Allergic reaction:
Patients should be advised to notify their doctor if they develop a rash, hives, or a related allergic phenomenon.

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

Cholesterol:
Clinically relevant increases in serum cholesterol were recorded in 5,3 % of venlafaxine-treated patients and 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.

Discontinuation of treatment:
Discontinuation effects are well-known to occur. It is therefore recommended that **MACLAFAX XR** be tapered gradually and the patient monitored (see section 4.2).
The following symptoms have been reported in association with abrupt discontinuation or dose-reduction, or tapering of venlafaxine treatment: Hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paraesthesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea and vomiting. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment.

Sexual dysfunction:
Serotonin-norepinephrine reuptake inhibitors (SNRIs) including **MACLAFAX XR** 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 venlafaxine 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. This may increase the risk of caries, and patients should be advised upon the importance of dental hygiene.

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

Post-partum haemorrhage
There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.
Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Paediatric use:
Safety and efficacy in individuals below 18 years of age have not been established. In clinical trials in Major Depressive Disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see section 4.3).
Use in elderly patients:
MACLAFAX 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 venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP) or N-methyl-D-aspartic acid (NMDA) receptors. Venlafaxine was not found to have any significant CNS stimulant activity in rodents. In primate medicine discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

4.5 Interaction with other medicines and other forms of interaction
Monoamine oxidase inhibitors (MAOIs):
Severe adverse reactions have been reported in patients who have recently been discontinued from a MAOI and started on venlafaxine or have recently had venlafaxine therapy discontinued prior to initiation of a MAOI (see section 4.3). These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures and death.

CNS active medicines:
The risk of using venlafaxine in combination with other CNS-active medicines has not been systematically evaluated. Consequently, caution is advised when **MACLAFAX XR** is taken in combination with other CNS-active medicines.
Serotonin syndrome, a potentially life threatening condition which may occur with **MACLAFAX XR** treatment, particularly with concomitant use of other medicines that may affect the serotonergic neurotransmitter system (including triptans, SSRIs, other SNRIs, lithium, sibutramine, tramadol, or St. John's Wort [*Hypericum perforatum*]), with medicines which impair metabolism of serotonin (such as MAOIs; including linezolid [an antibiotic which is a reversible non-selective MAOI], see Section 4.3), 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 section 4.3 and 4.4).
If concomitant treatment of **MACLAFAX XR** with an SSRI, an 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 **MACLAFAX XR** with serotonin precursors (such as tryptophan supplements) is not recommended (see section 4.4).

Indinavir:
A pharmacokinetic study with indinavir has shown a 28 % decrease in AUC and a 36 % decrease in C_{max} for indinavir. Indinavir did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. The clinical significance of this interaction is unknown.

Ethanol:
Venlafaxine has been shown not to increase the impairment of mental and motor skills caused by ethanol. However, patients should be advised to avoid alcohol consumption while taking **MACLAFAX XR**.

Haloperidol:
A pharmacokinetic study with haloperidol has shown for haloperidol a 42 % decrease in total oral clearance, a 70 % increase in AUC, an 88 % increase in C_{max}, but no change in half-life. This should be taken into account in patients treated with haloperidol and **MACLAFAX XR** concomitantly.

Cimetidine:
At steady-state, cimetidine has been shown to inhibit first-pass metabolism of venlafaxine; however, cimetidine had no effect on the pharmacokinetics of O-desmethylvenlafaxine. The overall pharmacological activity of venlafaxine plus O-desmethylvenlafaxine 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.
Imipramine:
Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35 % in the presence of venlafaxine. There was an increase of 2-OH-desipramine AUC by 2,5 to 4,5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and O-desmethylvenlafaxine. This should be taken into account in patients treated with imipramine and **MACLAFAX XR** concomitantly.

Ketoconazole:
A pharmacokinetic study with ketoconazole in extensive (EM) and poor metabolisers (PM) of CYP2D6 resulted in higher plasma concentrations of both venlafaxine and O-desmethylvenlafaxine in subjects following administration of ketoconazole.

Metoprolol:
Concomitant administration of venlafaxine (50 mg every 8 hours for 5 days) and metoprolol (100 mg every 24 hours for 5 days) 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.
Venlafaxine appeared to reduce the blood pressure lowering effect of metoprolol in this study of healthy volunteers. 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 **MACLAFAX XR** and metoprolol.

Risperidone:
Venlafaxine increased the risperidone AUC by 32 % but did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). The clinical significance of this interaction is unknown.

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

Lithium:
The steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine are not affected when lithium is co-administered. Venlafaxine also has no effects on the pharmacokinetics of lithium.

Medicines highly bound to plasma proteins:
Venlafaxine is not highly bound to plasma proteins (27 % bound); therefore, administration of **MACLAFAX XR** to a patient taking another medicine that is highly protein bound is not expected to cause increased free concentrations of the other medicine.

Medicines metabolised by cytochrome P450 isoenzymes:
Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP3A4, CYP1A2 and CYP2C9 *in vitro*. This was confirmed by *in vivo* studies with the following medicines: alprazolam (CYP3A4), caffeine (CYP1A2), carbamazepine (CYP3A4), diazepam (CYP3A4 and CYP2C19) and tolbutamide (CYP2C9).

Potential for other medicines to affect MACLAFAX XR:
The metabolic pathways for **MACLAFAX XR** include CYP2D6 and CYP3A4. **MACLAFAX XR** is primarily metabolised to its active metabolite, O-desmethylvenlafaxine, by the cytochrome P450 enzyme CYP2D6. CYP3A4 is a minor pathway relative to CYP2D6 in the metabolism of **MACLAFAX XR**.
CYP2D6 inhibitors:
Concomitant use of CYP2D6 inhibitors and **MACLAFAX XR** may reduce the metabolism of **MACLAFAX XR** to O-desmethylvenlafaxine, resulting in increased plasma concentrations of **MACLAFAX XR** and decreased concentrations of O-desmethylvenlafaxine. As **MACLAFAX XR** and O-desmethylvenlafaxine are both pharmacologically active, no dosage adjustment is required when **MACLAFAX XR** is co-administered with a CYP2D6 inhibitor.
CYP3A4 inhibitors:
Concomitant use of CYP3A4 inhibitors and **MACLAFAX XR** may increase levels of **MACLAFAX XR** and O-desmethylvenlafaxine. Therefore, caution is advised when combining **MACLAFAX XR** with a CYP3A4 inhibitor.
CYP2D6 and 3A4 inhibitors:
The concomitant use of venlafaxine with medicine treatment(s) that potentially inhibit both CYP2D6 and CYP3A4, the primary metabolizing enzymes for **MACLAFAX XR**, has not been studied. However, this concomitant use would be expected to increase **MACLAFAX XR** plasma concentrations. Therefore, caution is advised when combining **MACLAFAX XR** with any medicine(s) that produce simultaneous inhibition of these two enzyme systems.

Medicines that Prolong the QT Interval
The risk of QTc prolongation and/or ventricular arrhythmias (e.g., TdP) 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 Ia 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.

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

4.6 Fertility, pregnancy and lactation
Pregnancy
MACLAFAX XR must not be administered to pregnant or lactating women. Safety during human pregnancy and lactation has not been established (see section 4.3). Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalization. Such complications can arise immediately upon delivery. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy.
Breastfeeding
Venlafaxine and O-desmethylvenlafaxine are excreted in human milk; therefore, mothers on treatment with **MACLAFAX XR** should not breastfeed.

4.7 Effects on ability to drive and use machines
MACLAFAX XR causes dizziness and sedation; it may therefore impair judgement, thinking and motor skills. Therefore, patients receiving **MACLAFAX XR** should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable effects
The most frequently observed adverse events associated with the use of **MACLAFAX XR** are nausea, dry mouth, headache and sweating (including night sweats). The occurrence of many frequently observed adverse events is dose related.
The following adverse reactions have been reported in association with **MACLAFAX XR**:

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Less frequent	Ecchymosis
	Frequency unknown	Mucous membrane bleeding, prolonged bleeding time, thrombocytopenia*, blood dyscrasias (including agranulocytosis*, aplastic anaemia*, neutropenia* and pancytopenia*)
Immune system disorders	Frequency unknown	Anaphylactic reaction*, angioedema
Endocrine disorders	Frequency unknown	Increased prolactin*, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)*.
Metabolism and nutrition disorders	Frequent	Increased serum cholesterol (dose related and after prolonged use), weight loss, decreased appetite
	Frequency unknown	Hyponatraemia*
Psychiatric disorders	Frequent	Abnormal dreams, decreased libido, insomnia, nervousness
	Less frequent	Apathy, hallucinations, manic reaction
	Frequency unknown	Confusion*, depersonalization*, agitation*, delirium*, aggression, amnesia, anxiety, depression, emotional lability, abnormal thinking, suicidal ideation and suicidal behaviours.
Nervous system disorders	Frequent	Dizziness, dry mouth, hypertonia, paraesthesia, sedation, tremor, Dysgeusia
	Less frequent	Myoclonus, convulsion,
	Frequency unknown	Headache*, impaired coordination and balance*, akathisia*/psychomotor restlessness, neuroleptic malignant syndrome (NMS)*, serotonergic syndrome*, extrapyramidal reactions (including dystonia* and dyskinesia), tardive dyskinesia*, hypoaesthesia, somnolence, trismus
Eye disorders	Frequent	Abnormality of accommodation, mydriasis, visual disturbance
	Frequency unknown	Angle-closure glaucoma*
Ear and labyrinth disorders	Frequent	Tinnitus*
	Frequency unknown	Vertigo
Cardiac disorders	Less frequent	Tachycardia
	Frequency unknown	Palpitations*, QT prolongation*, ventricular tachycardia* and fibrillation (including Torsade de Pointes)*
Vascular disorders	Frequent	Hypertension, vasodilation (mostly flushes) and hypertension
	Less frequent	Postural hypotension, syncope
	Frequency unknown	Hypotension*
Respiratory, thoracic and mediastinal disorders	Frequent	Yawning Dyspnoea*
	Frequency unknown	Pulmonary eosinophilia*, pharyngitis and rhinitis
Gastrointestinal disorders	Frequent	Decreased appetite, constipation, nausea, vomiting
	Frequency not known	Bruxism*, diarrhoea*, gastrointestinal haemorrhage*, pancreatitis*, anorexia, increased appetite, dyspepsia, eructation, flatulence
Hepatobiliary disorders	Frequency not known	Abnormal liver function tests*, hepatitis*
Skin and subcutaneous tissue disorders	Less frequent	Rash, photosensitivity reaction
	Frequency not known	Sweating* (including night sweats*), alopecia*, Stevens-Johnson syndrome*, erythema multiforme*, pruritus*, urticaria*, toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	Frequency not known	Myalgia, rhabdomyolysis*
Renal and urinary disorders	Frequent	Impaired urination (mostly hesitancy)
	Less frequent	Urinary retention
	Frequency not known	Increased urinary frequency*, urinary incontinence
Reproductive system and breast disorders	Frequent	Abnormal ejaculation / orgasm(males), erectile dysfunction, anorgasmia
	Less frequent	Abnormal orgasm (females)
	Frequency unknown	Menstrual disorders associated with increased bleeding* or increased irregular bleeding* (e.g. menorrhagia*, metrorrhagia*), post-partum haemorrhage**.
General disorders and administration site conditions	Frequent	Asthenia, fatigue, pain, abdominal pain, back pain, chest pain
	Frequency not known	Chills*
Investigations	Frequent	Weight decrease, Weight increased, Blood cholesterol increased
	Less frequent	Bleeding time prolonged*

*ADR identified during post-marketing
** There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.
Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Discontinuation of treatment
Discontinuation of venlafaxine (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 venlafaxine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose
In post-marketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other medicines. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other events reported include electrocardiographic changes (e.g. prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death.
Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher 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 in overdosage as opposed to some characteristics of venlafaxine-treated patients is not clear. Prescriptions for **MACLAFAX XR** should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.
Recommended treatment:
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 medicine absorption.
Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for **MACLAFAX XR** are known.

5. PHARMACOLOGICAL PROPERTIES

ATC code: N06AX21
A 1.2 Psychoanaleptics (antidepressants)

5.1 Pharmacodynamic properties
Studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine are inhibitors of serotonin and norepinephrine re-uptake and also weakly inhibit dopamine re-uptake.
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 re-uptake and receptor binding.
Venlafaxine has virtually no affinity for rat brain muscarinic, histaminergic or adrenergic receptors *in vitro*. Venlafaxine does not possess monoamine oxidase (MAO) inhibitory activity.

5.2 Pharmacokinetic properties
Absorption:
Venlafaxine is well absorbed and undergoes extensive first-pass metabolism.
After administration of venlafaxine extended release capsules, peak plasma concentrations of venlafaxine and O-desmethylvenlafaxine are attained within 6,0 +/- 1,5 and 8,8 +/- 2,2 hours, respectively.
Administration of venlafaxine with food has no effect on the extent of absorption of venlafaxine or on the subsequent formation of O-desmethylvenlafaxine.
Metabolism:
Venlafaxine is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine.
Distribution:
The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively.
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).
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.
Special populations
Elderly: A 20 % reduction in clearance was noted for O-desmethylvenlafaxine in subjects over 60 years old: *The magnitude of the differences that were seen is insufficient to warrant dosage adjustment based solely on age.*

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 for these patients (see section 4.2).

Hepatic impairment: In patients with compensated hepatic cirrhosis (mild to moderate hepatic impairment), 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 significantly higher plasma concentrations of both. Dosage adjustment is recommended in these patients (see sections 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Low substituted hydroxy propyl cellulose, corn starch, microcrystalline cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, purified talc, hard gelatine capsules containing titanium dioxide, iron oxide red, gelatine and sodium lauryl sulfate. In addition **MACLAFAX XR 75 mg CAPSULES** contain iron oxide yellow.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months from the date of manufacturing.

6.4 Special precautions for storage
Store at or below 25 °C.
Protect from light and moisture.
Keep the blisters in the carton until required for use.
Keep HDPE containers tightly closed.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container
Blister pack:
Plain, silver coloured, 25 µ aluminium foil/ 6-8 gsm HSL as the lidding material and clear, transparent PVC/PE/PVdC, 250 µ/25 µ/90 gsm, as the forming material, packed in a pre-printed unit carton with 10, 28 or 30 capsules.
HDPE container pack:
Capsules are packed in white, opaque, round 40 ml or 60 ml HDPE container for **MACLAFAX XR** 75 mg and 60 ml HDPE container for **MACLAFAX XR** 150 mg with 33 mm neck finish closed with 33 mm white polypropylene closure with wad having induction sealing liner. Each container contains 28 or 30 capsules with a silica gel. The containers are placed in a pre-printed outer carton with a package insert.
Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD
Office block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext. 12,
Alberton, South Africa.

8. REGISTRATION NUMBER(S)

MACLAFAX XR 75 mg (Extended release capsules): 51/1.2/0061.057
MACLAFAX XR 150 mg (Extended release capsules): 51/1.2/0062.058

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2021

10. DATE OF REVISION OF THE TEXT

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PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S5

MACLAFAX XR 75 mg (Extended release capsules)
Venlafaxine hydrochloride 75 mg
Sugar free

MACLAFAX XR 150 mg (Extended release capsules)
Venlafaxine hydrochloride 150 mg
Sugar free

Read all of this leaflet carefully before you start taking MACLAFAX XR
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- MACLAFAX XR has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What MACLAFAX XR is and what it is used for
2. What you need to know before you take MACLAFAX XR
3. How to take MACLAFAX XR
4. Possible side effects
5. How to store MACLAFAX XR
6. Contents of the pack and other information

1. What MACLAFAX XR is and what it is used for

MACLAFAX XR contains the active substance venlafaxine.
MACLAFAX XR is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). MACLAFAX XR is used in adults to treat:
- depression, including depression with associated anxiety
- and the following anxiety disorders: generalised anxiety disorder and social anxiety disorder (fear or avoidance of social situations).

2. What you need to know before you take MACLAFAX XR

Do not take MACLAFAX XR:
- If you are allergic (hypersensitive) to venlafaxine or any of the other ingredients of MACLAFAX XR listed in Section 6.
- If you are also taking or have taken any time within the last 14 days any medicines known as irreversible monoamine oxidase inhibitors (MAOIs), used to treat depression or Parkinson's disease. Taking an irreversible MAOI together with MACLAFAX XR, can cause side effects such as nausea, vomiting, dizziness, tremor, flushing, muscle twitching, elevated body temperature, profuse sweating, seizures or even life-threatening side effects. Also, you must wait at least 7 days after you stop taking MACLAFAX XR before you take any MAOI.
- If you are pregnant or breastfeeding.
- If you are under 18 years of age.

Warnings and precautions
Take special care with MACLAFAX XR:
- if you are taking other medicines to treat depression.
- if you have had seizures (fits).
- If you previously have had mental illness (mania) or if you or a family member has a history of bipolar disorder as MACLAFAX XR may cause mood swings (mood of excitement, over-activity and uninhibited behaviour).
- if you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- if you have high blood sugar (diabetes).
- if you are depressed and/or have anxiety disorders, you can sometimes have thoughts of harming or killing yourself. These may be increased when you first start taking antidepressants or when you doctor makes changes to the dose. If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
  You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.
- if you have any pre-existing heart condition or disease which might affect your blood pressure. MACLAFAX XR may cause your blood pressure to increase and in some cases requiring immediate treatment to lower your blood pressure. Your doctor will test your blood pressure before start of treatment, after a dose increase and regularly thereafter.
- if you suffer from bleeding tendencies or if you are taking medicines known as anti-coagulants (e.g. warfarin) or platelet inhibitors (e.g. aspirin) as the risk of skin and mucous membrane bleeding, including bleeding from the stomach wall, may be increased in patients taking MACLAFAX XR.
- if you are taking any medicines for weight loss (e.g. phentermine). MACLAFAX XR is not indicated for weight loss, alone or in combination with other products.
- There has been a relation between a group of medicines called SSRI and SNRI and heavy bleeding following birth. MACLAFAX XR belongs to the group of medicines called SSRIs. If you have any bleeding disorders or are pregnant, your doctor will have to change your treatment to an alternative group of medicines

While taking MACLAFAX XR:
- Contact your doctor immediately if you experience an allergic reaction to MACLAFAX XR with symptoms of swelling of the face, lips, tongue, and throat, difficulty breathing as well as a diffuse skin rash.
- Tell your doctor if you notice the following changes in behaviour while taking MACLAFAX XR: anxiety, agitation, panic attacks, insomnia, irritability, become hostile and aggressive, impulsive, feeling restless and unable to stand or sit still or suffering from mental illness. Your doctor may consider discontinuing therapy with MACLAFAX XR if you did not have these symptoms prior to therapy with MACLAFAX XR. Your dose will be gradually reduced if your doctor decides to discontinue your therapy with MACLAFAX XR.
- Serotonin syndrome, a potentially life-threatening condition may occur with MACLAFAX XR treatment, particularly when taken with other medicines. Examples of these medicines include:
  - Triptans (used for migraine)
  - Other medicines to treat depression, for instance SNRIs, SSRIs, tricyclics, or medicines containing lithium
  - Medicines containing amphetamines (used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy and obesity)
  - Medicines containing linezolid, an antibiotic (used to treat infections)
  - Medicines containing moclobemide, a MAOI (used to treat depression)
  - Medicines containing sibutramine (used for weight loss)

Back Side

535 mm

400 mm

- Medicines containing tramadol, fentanyl, tapentadol, pethidine, or pentazocine (used to treat severe pain)
  - Medicines containing dextromethorphan (used to treat coughing)
  - Medicines containing methadone (used to treat opioid drug addiction or severe pain)
  - Medicines containing methylene blue (used to treat high levels of methaemoglobin in the blood)
  - Products containing St. John's Wort (also called Hypericum perforatum, a natural or herbal remedy used to treat mild depression)
  - Products containing tryptophan (used for problems such as sleep and depression)
  - Antipsychotics (used to treat a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, unclear reasoning and becoming withdrawn)

Inform your doctor or go to the nearest hospital if you notice a combination of the following: restlessness, hallucinations, loss of coordination, fast heartbeat, increased body temperature, changes in blood pressure, overactive reflexes, diarrhoea, coma, nausea and vomiting.

- MACLAFAX XR may cause eye problems such as dilated pupils, raised pressure and glaucoma. Inform your doctor if you notice any changes to your eyes.
- Tell your doctor if you have been told you have an abnormal heart rhythm as MACLAFAX XR may cause an increase in heart rate, especially at high doses.
- If you experience palpitations or irregular heart beat or fainting spells during the period of treatment, you should inform your doctor immediately.
- Inform your doctor if you experience aggressive behaviour during treatment with MACLAFAX XR especially upon start, dose reduction or discontinuation of treatment.
- MACLAFAX XR may cause low levels of sodium in the blood and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH); a condition that causes your body to make too much antidiuretic hormone (ADH). ADH is a chemical that helps keep the right balance of fluids in your body. Increased ADH may cause too much water to remain inside your body and chemicals in your blood, such as salt, may decrease. This may prevent your organs from working properly. This side effect may occur especially if you are elderly, are taking diuretics (water pills) or are dehydrated.
- Your doctor will monitor your cholesterol levels periodically as MACLAFAX XR may increase the cholesterol levels in your blood.
- If your doctor thinks that you no longer need MACLAFAX XR, he/she may ask you to reduce your dose slowly before stopping treatment altogether. Side effects are known to occur when people stop using MACLAFAX XR, especially when MACLAFAX XR is stopped suddenly or the dose is reduced too quickly (see POSSIBLE SIDE EFFECTS).
- MACLAFAX XR may cause symptoms of sexual dysfunction. In some cases, these symptoms have continued after stopping treatment.
- MACLAFAX XR may cause a sensation of restlessness or an inability to sit or stand still during the first few weeks of treatment. You should tell your doctor if this happens to you.
- MACLAFAX XR may cause dry mouth. Take special care in your dental hygiene as a dry mouth may increase the risk of dental caries.
- Your blood glucose levels may be altered due to MACLAFAX XR. Therefore, the dosage of your diabetes medicines may need to be adjusted.
- You are unlikely to develop tolerance or become addicted to MACLAFAX XR when taken over a long period of time, however, your doctor will monitor your treatment for signs of tolerance or addiction.
- MACLAFAX XR can be used safely in healthy elderly patients.

Children and adolescents

- MACLAFAX XR should not be given to children under 18 years of age as it has not been proven to be safe and effective in this age group.

Other medicines and MACLAFAX XR

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).
Only take other medicines while you are on MACLAFAX XR if your doctor tells you that you can.
You should tell your doctor if you are taking the following medicines:

- Monoamine oxidase inhibitors (MAOIs) such as moclobemide (an antidepressant) and linezolid (an antibiotic).
- Medicines to treat depression, for instance, medicines known as SNRIs or SSRIs and medicines containing lithium.
- Medicines that increase the level of serotonin: Triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), SNRIs (such as venlafaxine), tricyclic antidepressants (such as clomipramine, amitriptyline), pethidine, St John's Wort (herbal medicine for depression) and MAOIs (such as moclobemide and linezolid). These medicines increase the risk of side effects; if you experience any unusual symptoms while taking any of these medicines together with MACLAFAX XR, you should see your doctor.
- Supplements containing tryptophan (used for problems such as sleep and depression).
- Indinavir (for HIV treatment)
- Desipramine (for depression)
- Sibutramine (used for weight loss).
- Ketoconazole (an antifungal medicine).
- Haloperidol or risperidone (to treat psychiatric conditions).
- Metoprolol (a beta blocker to treat high blood pressure and heart problems)
- Medicines that can affect your heart rhythm. Examples of these medicines include:
  - Antidysrhythmics such as quinidine, amiodarone, sotalol or dofetilide (used to treat abnormal heart rhythm)
  - Antipsychotics such as thioridazine (See also Serotonin syndrome above)
  - Antibiotics such as erythromycin or moxifloxacin (used to treat bacterial infections)
  - Antihistamines (used to treat allergy).

Inform your doctor that you are taking MACLAFAX XR if blood tests are required to test for phencyclidine (PCP) or amphetamine.

MACLAFAX XR with food and drink and alcohol

Alcohol should be avoided while being treated with MACLAFAX XR.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking MACLAFAX XR.

- Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking MACLAFAX XR. You should not take MACLAFAX XR if you are pregnant.
- If you take MACLAFAX XR near the end of your pregnancy, your baby might have some symptoms when it is born. These usually begin at birth or within a few days of your baby being born. These symptoms may include not feeding properly, trouble with breathing and prolonged hospitalisation.
- Tell your doctor if you are breastfeeding. You should not take MACLAFAX XR while breastfeeding.

Driving and using machines

MACLAFAX XR may cause impairment of judgement, thinking or muscle control. It is not always possible to predict to what extent MACLAFAX XR may interfere with your daily activities. You should not engage in the above activities until you are aware of the extent to which MACLAFAX XR affects you.

3. How to take MACLAFAX XR

- Do not share medicines prescribed for you with any other person.
- Always take MACLAFAX XR exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- Your doctor will tell you how long your treatment with MACLAFAX XR will last. Do not stop treatment early.
- If you have the impression that the effect of MACLAFAX XR is too strong or too weak, tell your doctor or pharmacist.
- Stay under a healthcare provider's care when taking MACLAFAX XR. Do not change your treatment or stop treatment without first talking with your healthcare provider.

Recommended dose of MACLAFAX XR:

- MACLAFAX XR capsules are for oral use.
- Your doctor will tell you how many MACLAFAX XR to take and how long you should continue to take them.
- The usual recommended starting dose for treatment of depression, generalised anxiety disorder and social anxiety disorder is 75 mg per day. The dose can be raised by your doctor gradually, and if needed, even up to a maximum dose of 375 mg daily for depression. The maximum dose for generalised anxiety disorder and social anxiety disorder is 225 mg/day.
- Take MACLAFAX XR at approximately the same time each day, either in the morning or in the evening. Capsules must be swallowed whole with fluid and not opened, crushed, chewed or dissolved. MACLAFAX XR should be taken with food.
- If you have liver or kidney problems, your doctor will adjust your dose of MACLAFAX XR.
- Do not be concerned if you see small white granules or particles in your stools after taking MACLAFAX XR. MACLAFAX XR formulation contains, spheroids, which release the medicine slowly into the digestive tract. The insoluble portion of these spheroids is eliminated and may be seen in stools.

If you take more MACLAFAX XR than you should

In the event of overdosage consult your doctor or pharmacist. If neither is available contact the nearest hospital or poison control centre.
The symptoms of a possible overdose may include a rapid heartbeat, changes in level of alertness (ranging from sleepiness to coma), blurred vision, seizures or fits, and vomiting.

If you forget to take MACLAFAX XR

If you forget to take a dose, take it as soon as you remember, and then continue as before.
Do not take a double dose to make up for forgotten individual doses.

If you stop taking MACLAFAX XR

Do not stop taking your capsules just because you feel better. It is important that you carry on taking MACLAFAX XR for as long as your doctor tells you.
If your doctor thinks that you no longer need MACLAFAX XR, he/she may ask you to reduce your dose slowly before stopping treatment altogether. After stopping long and short-term MACLAFAX XR treatment, you need to know that you may experience certain side effects. Some patients may experience symptoms such as mood swings, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, sleepiness, tingling, dizziness, seizures, spinning sensation (vertigo), headache, flu-like symptoms, ringing in the ears (tinnitus), impaired coordination and balance, tremor, sweating, dry mouth, loss of appetite, diarrhoea, nausea and vomiting.
Your doctor will advise you on how you should gradually discontinue MACLAFAX XR treatment. If you experience any of these or other symptoms that are troublesome, ask your doctor for further advice.

4. Possible side effects

MACLAFAX XR can have side effects.
Not all side effects reported for MACLAFAX XR are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking MACLAFAX XR, please consult your doctor, pharmacist or other healthcare professional for advice.
If any of the following happens, stop taking MACLAFAX XR and tell your doctor immediately or go to the casualty department at your nearest hospital:
Get emergency medical help if you have any of these **signs of an allergic reaction:**

- Hives; shortness of breath or difficulty breathing; swelling of your face, lips, tongue, or throat.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to MACLAFAX XR. You may need urgent medical attention or hospitalization.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Feeling dehydrated, having low levels of sodium in the blood (mostly in elderly people; the symptoms may include feeling dizzy, weak, confused, sleepy or very tired, or feeling or being sick, more serious symptoms are fainting, fits or falls), retention of water by the body (syndrome of inappropriate secretion of anti-diuretic hormone (SIADH)).
- Having convulsions (fits).
- Thoughts of suicide and self-harm.
- Serotonin syndrome, a potentially life-threatening condition may occur with MACLAFAX XR treatment. Inform your doctor or go to the nearest hospital if you notice a combination of the following: restlessness, hallucinations, loss of coordination, fast heartbeat, increased body temperature, changes in blood pressure, overactive reflexes, diarrhoea, nausea, vomiting and coma.
- In its most severe form, serotonin syndrome can resemble Neuroleptic Malignant Syndrome (NMS). Signs and symptoms of NMS may include a combination of fever, fast heartbeat, sweating, severe muscle stiffness, confusion, increased muscle enzymes (determined by a blood test).
- Symptoms of rhabdomyolysis (breakdown of muscle tissue): dark, red, or cola-coloured urine, decreased urine output, general weakness, muscle stiffness or aching, muscle tenderness, weakness of the affected muscles.
- Fast and/or irregular heartbeat or abnormal fast heart rate, changes on the ECG referred to as a prolongation of the QT-interval, i.e., delayed conduction of electrical signals.
- Coughing, wheezing, shortness of breath and a high temperature, which are symptoms of inflammation of the lungs associated with an increase in white blood cells (pulmonary eosinophilia).
- Vomiting blood, or black tarry stools (faeces).
- Inflammation of the pancreas with symptoms including upper abdominal pain, nausea and vomiting.
- Inflammation of the liver or liver failure that may cause abdominal pain and yellowing of the skin or whites of the eyes (jaundice).
- Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals).
- Severe skin rash, itching or hives (elevated patches of red or pale skin that often itch)
- Prolonged bleeding - if you cut or injure yourself, it may take slightly longer than usual for bleeding to stop.
- Contraction of the jaw muscle (lockjaw).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:
Frequent side effects:

- unusual dreams, less sex drive, trouble sleeping, nervousness
- dizziness, dry mouth, feeling sluggish, numbness, including numbness, pricking or tingling of the skin, feeling sleepy, tremor, altered or impaired sense of taste
- eye problems such as blurred eyesight, dilated pupils, inability of the eye to automatically change focus from distant to near objects
- tinnitus (hearing sound in the ear when there is no external sound)
- increased blood pressure, flushing
- increased yawning, difficulty breathing
- decreased appetite, feeling sick (nausea), constipation, being sick (vomiting)
- difficulties passing urine
- problems getting an erection, changes in ejaculation/orgasm in males
- weakness, fatigue, pain, stomach pain, back pain, chest pain.

Less frequent side effects:

- bruising of the skin
- feeling indifferent, hallucinations, psychiatric problems, such as hyperactivity and feeling unusually overexcited
- sudden involuntary jerks or twitches of the muscles
- difficulty sleeping, feeling disorientated, lack of motivation
- fainting, light headedness or fainting on standing up
- inflammation of the large intestine (leading to diarrhoea), burping, difficulty swallowing, inflammation of the mouth, bad breath
- skin rash, sensitivity to sunlight
- difficulty or inability to pass urine
- abnormal orgasm in females
- feeling cold or hot, thirst, shivering, feeling unwell, abnormal gait
- weight gain
- changes in blood test results (decrease in blood sodium, decrease in white blood cell count, blood sugar increased, platelet count decreased, weight increased, weight decreased, liver enzymes increased.

Frequency unknown:

- bleeding gums
- reduced number of platelets in your blood, leading to an increased risk of bruising or bleeding
- signs of infection, such as high temperature, chills, shivering, headaches, sweating, flu-like symptoms. This may be the result of a blood disorder (reduction in certain white blood cells) which leads to an increased risk of infection.
- increased prolactin levels in the blood (abnormal breast milk production)
- confusion; feeling separated (or detached) from yourself, agitation, disorientation and confusion often accompanied by hallucination (delirium), aggression, loss of memory, anxiety, depression, lack of feeling or emotion; abnormal thinking, inappropriate behaviour
- headache, difficulty controlling movement e.g. lack of coordination or involuntary movements of the muscles, muscle stiffness, sensation of restlessness or an inability to sit or stand still, repetitive, involuntary movements such as grimacing and eye blinking, numbness or a decreased sense of touch, poor sleep quality
- increased pressure in the eyes (glaucoma)
- vertigo (spinning sensation)
- feeling the heart pumping in the chest
- low blood pressure
- sore throat, runny or stuffed nose
- grinding or clenching the teeth, increased appetite, diarrhoea, heartburn or indigestion, burping or belching, breaking wind
- muscle pain, muscle spasm
- sweating (including night sweats), hives, itchy skin rash, abnormal hair loss
- needing to pass more urine than normal
- menstrual disorders associated with increased bleeding or increased irregular bleeding, haemorrhage (heavy bleeding) after giving birth.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of MACLAFAX XR.

5. How to store MACLAFAX XR

Store at or below 25 °C.
Protect from light and moisture.
Keep the blisters in the carton until required for use.
Keep HDPE containers tightly closed.
KEEP OUT OF REACH OF CHILDREN
Do not store in a bathroom.
Do not use after the expiry date stated on the label / carton / bottle.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of pack and other information

What MACLAFAX XR contains

- The active substance is venlafaxine hydrochloride 75 mg/150 mg.
- The other ingredients are low substituted hydroxy propyl cellulose, corn starch, microcrystalline cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, purified talc, hard gelatin capsules containing titanium dioxide, iron oxide red, gelatin and sodium lauryl sulfate. In addition MACLAFAX XR 75 mg contain iron oxide yellow.

What MACLAFAX XR looks like and contents of the pack

MACLAFAX XR 75 mg (Extended Release Capsules)
Peach Cap/peach body, size '1' capsules containing white to off white extended release beads with 'L 87' on cap and '75' on body imprinted with red ink.
MACLAFAX XR 150 mg (Extended Release Capsules)
Dark orange cap/dark orange body, size '0el' capsules containing white to off white extended release beads with 'L 88' on cap and '150' on body imprinted with white ink.

Blister pack:

Plain, silver coloured, 25 µ aluminium foil/ 6-8 gsm HSL as the lidding material and clear, transparent PVC/PE/PVdC, 250 µ/25 µ/90 gsm, as the forming material, packed in a pre-printed unit carton with 10, 28 or 30 capsules.

HDPE container pack:

Capsules are packed in white, opaque, round 40 ml or 60 ml HDPE container for MACLAFAX XR 75 mg and 60 ml HDPE container for MACLAFAX XR 150 mg with 33 mm neck finish closed with 33 mm white polypropylene closure with wad having induction sealing liner. Each container contains 28 or 30 capsules with a silica gel. The containers are placed in a pre-printed outer carton with a package insert.

Holder of Certificate of Registration and Manufacturer
MACLEODS PHARMACEUTICALS SA (PTY) LTD
Office block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext. 12,
Alberton, South Africa.

This leaflet was last revised in
20 April 2021

Registration number
MACLAFAX XR 75 mg (Extended release capsules): 51/1.2/0061.057
MACLAFAX XR 150 mg (Extended release capsules): 51/1.2/0062.058

Access to the corresponding Professional Information

The corresponding professional information can be accessed at https://www.macleodspharma.com/or email macleodsrsa@macleodspharma.com or contact 011 682 1169.

PASIËNTINLIGTINGSBLAD

SKEDULERINGSTATUS: S5

MACLAFAX XR 75 mg (Verlengde-vrystellings kapsules)
Venlafaksienhidrochloried 75 mg
Suikervry

MACLAFAX XR 150 mg (Verlengde-vrystellings kapsules)
Venlafaksienhidrochloried 150 mg
Suikervry

Lees hierdie hele inligtingsblad aandagtig deur, voordat jy MACLAFAX XR begin gebruik

- Hou hierdie inligtingsblad. Dit mag wees dat jy dit weer wil lees.
- Indien jy verdere vrae het, vra asseblief jou dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer.
- MACLAFAX XR is vir jou persoonlik voorgeskryf en jy behoort nie jou medisyne met ander mense te deel nie. Selfs al het hulle dieselfde simptome as jy, kan dit vir hulle skadelik wees.

Wat in hierdie inligtingsblad is

1. Wat MACLAFAX XR is en waarvoor dit gebruik word.
2. Wat jy behoort te weet voordat jy MACLAFAX XR gebruik.
3. Hoe om MACLAFAX XR te gebruik
4. Moontlike newe-effekte
5. Hoe om MACLAFAX XR te berg
6. Inhoud van die pak en ander inligting

1. Wat MACLAFAX XR is en waarvoor dit gebruik word

MACLAFAX XR bevat die aktiewe bestanddeel venlafaksien.
MACLAFAX XR is 'n antidepressant wat behoort tot 'n groep medisyne genaamd serotonien- en norepinefrienheropname inhibeerders (SNHI's). MACLAFAX XR word in volwassenes gebruik vir die behandeling van:

- depressie, insluitend depressie met geassosieerde angstigheid
- en die volgende angsversteurings: algemene angsversteuring en sosiale angsversteuring (vrees of vermyding van sosiale situasies).

2. Wat jy behoort te weet voordat jy MACLAFAX XR neem

Moet nie MACLAFAX XR neem:

- Indien jy allergies (hipersensitief) vir venlafaksien of enige van die ander bestanddele van MACLAFAX XR soos gelys in afdeling 6, is nie.
- Indien jy ook enige medisyne bekend as onomkeerbare monoamienoksidase-inhibeerders (MAOIs) gebruik, of gebruik het, binne die laaste 14 dae, om depressie of Parkinson se siekte te behandel. Indien jy 'n onomkeerbare MAOI saam met MACLAFAX XR neem, kan dit newe-effekte veroorsaak, soos naarheid, braking, duiseligheid, bewing, blosing, spiertrekkings, verhoogde liggaamstemperatuur, oorvloedige sweet, aanvalle of selfs lewensbedreigende newe-effekte. Jy moet ook ten minste 7 dae wag nadat jy opgehou het met die gebruik van MACLAFAX XR voordat jy enige MAOI neem.
- Indien jy swanger is of borsvoed nie.
- Indien jy jonger as 18 jaar oud is nie.

Waarskuwings en voorsorgmaatreëls

Neem spesiale sorg met MACLAFAX XR:

- indien jy ander medisyne neem om depressie te behandel.
- Indien jy aanvalle (stuiptrekkings) gehad het.
- as jy voorheen geestesongesteldheid (manie) gehad het of as jy of 'n familielid 'n geskiedenis van bipolêre versteuring het, aangesien MACLAFAX XR buierigheid kan veroorsaak (bui van opgewondenheid, ooraktiwiteit en ongeremde gedrag).
- as jy oogprobleme het, soos sekere soorte gloukoom (verhoogde druk in die oog).
- indien jy hoë bloedsuiker het (diabetes).
- as jy depressief is en/of angsversteurings het, kan jy soms daaraan dink om jouself leed aan te doen of om selfmoord te pleeg. Hierdie gedagtes kan toeneem wanneer jy vir die eerste keer antidepressante begin gebruik of wanneer jou dokter die dosering verander. Indien jy op enige tydstip daaraan dink om jouself leed aan te doen, of om selfmoord te pleeg, moet jy jou dokter kontak of onmiddellik na 'n hospitaal gaan. Jy mag dit moontlik nuttig vind om 'n familielid of hegte vriend te vertel dat jy depressief is en hulle te vra om hierdie inligtingsblad te lees. Jy kan hulle moontlik vra om jou te vertel indien hulle dink dat jou depressie of angstigheid vererger, of as hulle bekommerd is oor veranderinge in jou gedrag.
- indien jy 'n bestaande harttoestand of -siekte het wat jou bloeddruk kan beïnvloed. MACLAFAX XR kan veroorsaak dat jou bloeddruk styg en in sommige gevalle onmiddellike behandeling vereis om jou bloeddruk te verlaag. Jou dokter sal jou bloeddruk toets voordat behandeling begin, na 'n dosisverhoging en gereeld daarna.
- as jy aan bloedingsneigings ly, of indien jy medisyne neem naamlik antistollingsmiddels (bv. warfarien) of plaatjie-inhibeerders (bv. aspirien), aangesien die risiko van bloeding van die vel en slymvlies, insluitend bloeding van die maagwand, kan verhoog word in pasiënte wat MACLAFAX XR neem.
- indien jy medisyne gebruik om gewig te verloor (bv. fentermien). MACLAFAX XR, alleen of in kombinasie met ander produkte, word nie aangedui vir gewigsverlies nie.
- Daar was 'n verband tussen 'n groep medisyne genaamd SSHI en SNHI en swaar bloeding na geboorte. MACLAFAX XR behoort tot die groep medisyne genaamd SSHI's. Indien jy bloedingsversteurings het of swanger is, sal jou dokter jou behandeling moet verander na 'n alternatiewe groep medisyne.

Terwyl MACLAFAX XR geneem word:

- Kontak jou dokter onmiddellik indien jy 'n allergiese reaksie op MACLAFAX XR ervaar met simptome soos swelling van die gesig, lippe, tong en keel, asemhalingsprobleme sowel as 'n verspreide veluitslag.
- Vertel jou dokter indien jy die volgende veranderinge in gedrag agterkom terwyl MACLAFAX XR geneem word: angs, rusteloosheid, paniekaanvalle, slapeloosheid, geïrriteerdheid, vyandig en aggressief raak, impulsief, voel onrustig en kan nie stilstaan of -sit nie of ly aan geestesongesteldheid. Jou dokter kan dit oorweeg om behandeling met MACLAFAX XR te staak, indien jy nie hierdie simptome gehad het voordat jy met MACLAFAX XR behandeling begin het nie. Jou dosering sal geleidelik verminder word indien jou dokter besluit om jou behandeling met MACLAFAX XR te staak.
- Serotoniensindroom, 'n potensieel lewensbedreigende toestand, kan voorkom met MACLAFAX XR behandeling, veral as dit saam met ander medisyne geneem word. Voorbeelde van hierdie medisyne sluit in:
  - Triptane (gebruik vir migraine)
  - Ander medisyne om depressie te behandel, byvoorbeeld SNHI's, SSHI's, trisikliese middels, of medisyne wat litium bevat.
  - Medisyne wat amfetamiene bevat (gebruik om aandagtekort hiperaktiwiteit versteuring (ADHD), narkolepsie en vetsug te behandel.
  - Medisyne wat linesolied bevat, 'n antibiotikum (gebruik om infeksies te behandel)
  - Medisyne wat moklobemied bevat, 'n MAOI (gebruik om depressie te behandel)
  - Medisyne wat sibutramien bevat (gebruik vir gewigsverlies)
  - Medisyne wat tramadol, fentaniel, tapentadol, petidien, of pentasokien bevat (gebruik om erge pyn te behandel)
  - Medisyne wat dekstrometorfaan bevat (gebruik vir die behandeling van hoes)
  - Medisyne wat metadoon bevat (gebruik om opioïedmiddel afhanklikheid of erge pyn te behandel)
  - Medisyne wat metileenblou bevat (wat gebruik word om hoë vlakke van methemoglobien in die bloed te behandel)
  - Produkte wat Sint-Janskruid bevat (ook genoem *Hypericum perforatum*, 'n natuurlike- of kruiemiddel wat gebruik word vir die behandeling van ligte depressie)
  - Produkte wat triptofaan bevat (gebruik vir probleme soos slaap en depressie)
  - Antipsigotika (gebruik om 'n siekte te behandel met simptome soos om dinge wat nie daar is nie te hoor, te sien of ware te neem, verkeerde oortuigings, ongewone agterdog, onduidelike redenasie en teruggetrokke raak)

Stel jou dokter in kennis of gaan na die naaste hospitaal as jy 'n kombinasie van die volgende waarneem: rusteloosheid, hallusinasies, verlies aan koördinasie, vinnige hartklop, verhoogde liggaamstemperatuur, verandering in bloeddruk, ooraktiewe reflekse, diaree, koma, naarheid en braking.

- MACLAFAX XR kan oogprobleme veroorsaak soos verwyde pupille, verhoogde druk en gloukoom. Stel jou dokter in kennis indien jy enige veranderinge in jou oë opmerk.
- Vertel jou dokter indien daar aan jou gesê is dat jy 'n abnormale hartritme het, aangesien MACLAFAX XR 'n toename in hartklop kan veroorsaak, veral by hoë dosisse.
- As jy tydens die behandeling hartkloppings of onreëlmatige hartslag of floutes ervaar, moet jy dadelik jou dokter inlig.
- Stel jou dokter in kennis as jy aggressiewe gedrag ervaar tydens behandeling met MACLAFAX XR, veral met die aanvang, dosisverlaging of staking van die behandeling.
- MACLAFAX XR kan lae vlakke van natrium in die bloed en/of die sindroom van onvanpaste antidiuretiese hormoonafskeiding (SOADH) veroorsaak; 'n toestand wat veroorsaak dat jou liggaam te veel antidiuretiese hormoon (ADH) maak. ADH is 'n chemikalie wat help om die regte balans van vloeistowwe in jou liggaam te hou. Verhoogde ADH kan veroorsaak dat te veel water in jou liggaam oorbly en chemikalieë in jou bloed, soos sout, kan afneem. Dit kan verhoed dat jou organe reg werk. Hierdie newe-effek kan voorkom veral as jy bejaard is, diuretika gebruik (waterpille) of gedehidreer is.
- Jou dokter sal jou cholesterolvlakke gereeld monitor, aangesien MACLAFAX XR die cholesterolvlakke in jou bloed kan verhoog.
- Indien jou dokter dink dat jy nie meer MACLAFAX XR nodig het nie, kan hy/sy jou vra om jou dosering stadig te verminder voordat jy heeltemal ophou. Dit is bekend dat newe-effekte voorkom wanneer mense ophou met die gebruik van MACLAFAX XR, veral as MACLAFAX XR skielik gestaak word of die dosering te vinnig verminder word (sien MOONTLIKE NEWE-EFFEKTE).
- MACLAFAX XR kan simptome van seksuele disfunksie veroorsaak. In sommige gevalle het hierdie simptome voortgeduur nadat behandeling gestaak is.
- MACLAFAX XR kan 'n gevoel van onrustigheid of 'n onvermoë veroorsaak om stil te sit of stil te staan gedurende die eerste paar weke van die behandeling. Jy moet jou dokter vertel indien dit met jou gebeur.
- MACLAFAX XR kan 'n droë mond veroorsaak. Neem spesiale sorg met jou tandhigiëne, aangesien 'n droë mond die risiko van tandbederf kan verhoog.
- Jou bloedglukosevlakke kan verander as gevolg van MACLAFAX XR. Daarom moet die dosis van jou diabetes medisyne aangepas word.
- Dit is onwaarskynlik dat jy verdraagsaamheid sal ontwikkel of verslaaf sal raak aan MACLAFAX XR indien jy dit oor 'n lang tydperk neem, maar jou dokter sal egter jou behandeling monitor vir tekens van verdraagsaamheid of verslawing.
- MACLAFAX XR kan met veiligheid gebruik word in gesonde bejaarde pasiënte.

Kinders en adolessente

- MACLAFAX XR moet nie aan kinders jonger as 18 jaar oud gegee word nie, aangesien daar nie bewys is dat dit veilig en effektief in hierdie ouderdomsgroep is nie.

Ander medisyne en MACLAFAX XR

Vertel altyd jou gesondheidsorgverskaffer indien jy enige ander medisyne neem. (Dit sluit alle komplementêre of tradisionele medisyne in.)
Neem slegs ander medisyne, terwyl jy MACLAFAX XR gebruik, indien jou dokter sê dat jy kan.
Jy moet jou dokter vertel indien jy die volgende medisyne gebruik:

- Monoamienoksidase-inhibeerders (MAOIs) soos moklobemied ('n antidepressant) en linesolied ('n antibiotikum).
- Medisyne om depressie te behandel, byvoorbeeld medisyne bekend as SNHI's of SSHI's en medisyne wat litium bevat.
- Medisyne wat die vlak van serotonien verhoog: Triptane, tramadol, triptofaan, SSHI's (soos paroksetien en fluoksetien), SNHI's (soos venlafaksien), trisikliese antidepressante (soos klomipramien, amitriptIlien), petidien, Sint-Janskruid (kruiemedisyne vir depressie) en MAOIs (soos moklobemied en linesolied). Hierdie medisyne verhoog die risiko van newe-effekte; indien jy ongewone simptome ervaar terwyl jy enige van hierdie medisyne saam met MACLAFAX XR inneem, moet jy jou dokter besoek.
- Aanvullings wat triptofaan bevat (word gebruik vir probleme soos slaap en depressie).
- Indinavir (vir MIV behandeling)
- Desipramien (vir depressie)
- Sibutramien (gebruik vir gewigsverlies).
- Ketokonasool ('n antifungusmiddel).
- Haloperidol of risperidoon (om psigiatriese kondisies te behandel)
- Metoprolol ('n betablokker vir die behandeling van hoë bloeddruk en hartprobleme)
- Medisyne wat jou hartritme kan beïnvloed. Voorbeelde van hierdie medisyne sluit in:
  - Antidisritmiese middels soos kinidien, amiodaroon, sotalol of dofetilied (word gebruik om abnormale hartritme te behandel)
  - Antipsigotika soos tioridasien (sien ook Serotonien-sindroom hierbo)
  - Antibiotika soos eritromisien of moksifloksasien (gebruik vir die behandeling van bakteriële infeksies)
  - Antihistamiene (word gebruik om allergieë te behandel).

Stel jou dokter in kennis dat jy MACLAFAX XR neem wanneer bloedtoetse benodig word om te toets vir fensiklidien (PCP) of amfetamien.

MACLAFAX XR met voedsel en drankies en alkohol

Alkohol moet vermy word tydens behandeling met MACLAFAX XR.

Swangerskap, borsvoeding en fertiliteit

Indien jy swanger is of jou baba borsvoed, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgwerker vir advies voordat jy MACLAFAX XR neem.

- Vertel jou dokter as jy swanger raak, of as jy probeer om swanger te raak, terwyl jy MACLAFAX XR gebruik. Jy moet nie MACLAFAX XR neem as jy swanger is nie.
- Indien jy MACLAFAX XR teen die einde van jou swangerskap neem, kan jou baba sommige simptome hê wanneer hy gebore word. Dit begin gewoonlik met die geboorte of binne 'n paar dae nadat jou baba gebore is. Hierdie simptome kan nie behoorlike voeding, probleme met asemhaling en langdurige hospitalisasie insluit.
- Vertel jou dokter as jy borsvoed. Jy moet nie MACLAFAX XR neem tydens borsvoeding nie.

Bestuur en gebruik van masjinerie

MACLAFAX XR kan inkorting van oordeel, denke of spierbeheer veroorsaak. Dit is nie altyd moontlik om te voorspel tot watter mate MACLAFAX XR jou daaglikse aktiwiteite kan beïnvloed nie. Jy moet nie aan bogenoemde aktiwiteite deelneem nie, totdat jy bewus is van die mate waarin MACLAFAX XR jou beïnvloed.

3. Hoe om MACLAFAX XR te neem

- Moet nie medisyne wat vir jou voorgeskryf is, met enige ander persoon deel nie.
- Neem altyd MACLAFAX XR presies soos jou dokter of apteker jou vertel het. Vra jou dokter of apteker indien jy onseker is.
- Jou dokter sal jou presies vertel hoe lank jou behandeling met MACLAFAX XR sal duur. Moet nie die behandeling vroeër stop nie.
- Indien jy onder die indruk is dat die effek van MACLAFAX XR te sterk of te swak is, praat dan met jou dokter of apteker.
- Bly onder die sorg van 'n gesondheidsorgverskaffer wanneer jy MACLAFAX XR gebruik. Moet nie jou behandeling verander of stop sonder om eers met jou gesondheidsorgverskaffer te praat nie.

Aanbevole MACLAFAX XR dosis:

- MACLAFAX XR kapsules is vir mondelinge gebruik.
- Jou dokter sal jou vertel hoeveel MACLAFAX XR om te neem en vir hoe lank jy moet aanhou om dit te neem.
- Die normale aanbevole aanvangsdosis vir behandeling van depressie, algemene angsversteuring en sosiale angsversteuring is 75 mg per dag. Die dosering kan geleidelik deur jou dokter verhoog word, en indien nodig, selfs tot 'n maksimum dosis van 375 mg per dag vir depressie. Die maksimum dosering vir algemene angsversteuring en sosiale angsversteuring is 225 mg/dag.
- Neem MACLAFAX XR elke dag op ongeveer dieselfde tyd, hetsy soggens of saans. Kapsules moet heel met vloeistof ingesluk word en nie oopgemaak, fyngedruk, gekou of opgelos word nie. MACLAFAX XR moet saam met voedsel geneem word.
- As jy lewer- of nierprobleme het, sal jou dokter jou MACLAFAX XR dosis aanpas.
- Moet nie bekommerd wees indien jy klein wit korreltjies of deeltjies in jou stoelgang sien nadat jy MACLAFAX XR geneem het nie. MACLAFAX XR formule bevat sferoïede wat die medisyne stadig in die spysverteringskanaal vrystel. Die onoplosbare gedeelte van hierdie sferoïede word uitgeskakel en kan in ontlasting gesien word.

As jy meer MACLAFAX XR neem as wat jy moet

In die geval van oordosering, raadpleeg jou dokter of apteker. Indien nie een beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.
Die simptome van 'n moontlike oordosering kan vinnige hartklop, veranderinge in die vlak van waaksaamheid (wat wissel van slaperigheid tot koma), dowwe sig, aanvalle of stuiptrekkings, en braking insluit.

Indien jy vergeet om MACLAFAX XR te neem

Indien jy vergeet om 'n dosis te neem, neem dit sodra jy daarvan onthou, en gaan dan aan soos voorheen. Moet nie 'n dubbele dosis neem om vir die vergete individuele dosisse op te maak nie.

As jy ophou om MACLAFAX XR te neem

Moet nie ophou om jou kapsules te neem net omdat jy beter voel nie. Dit is belangrik dat jy aanhou om MACLAFAX XR te neem vir so lank as wat jou dokter jou sê.
Indien jou dokter dink dat jy nie meer MACLAFAX XR nodig het nie, kan hy/sy jou vra om jou dosering stadig te verminder voordat jy heeltemal daarmee ophou. Nadat jy lang- en kort termyn behandeling met MACLAFAX XR gestaak het, moet jy weet dat jy sekere newe-effekte kan ervaar. Sommige pasiënte kan simptome ervaar soos buierigheid, angs, rusteloosheid, senuweeagtigheid, verwarring, slapeloosheid of ander slaapsteurnisse, moegheid, slaperigheid, tinteling, duiseligheid, aanvalle, draai sensasie (vertigo), hoofpyn, griepagtige simptome, suis in die ore (tinnitus), ingekorte koördinasie en balans, bewing, sweet, droë mond, verlies aan eetlus, diaree, naarheid en braking.
Jou dokter sal jou adviseer oor hoe jy die behandeling met MACLAFAX XR geleidelik moet staak. Vra jou dokter vir verdere advies as jy enige van hierdie of ander simptome ervaar wat jou pla.

4. Moontlike newe-effekte

MACLAFAX XR kan newe-effekte hê.
Nie alle newe-effkete wat vir MACLAFAX XR aangemeld is, is in hierdie inligtingsblad ingesluit nie. Indien jou algemene gesondheid versleg of indien jy enige ongunstige effekte ervaar terwyl jy MACLAFAX XR neem, kontak asseblief jou dokter, apteker of ander gesondheidsorgverskaffer vir advies.
Indien enige van die volgende gebeur, hou op om MACLAFAX XR te neem, en kontak jou dokter onmiddellik of gaan na die ongevalle afdeling van jou naaste hospitaal:
Vra nood mediese hulp as jy enige van die hierdie **tekens van 'n allergiese reaksie het**:

- Galbulte; kortasem of asemhalingsprobleme; swelling van jou gesig, lippe, tong of keel.

Hierdie is almal baie ernstige newe-effekte. As jy dit het, het jy moontlik 'n ernstige allergiese reaksie op MACLAFAX XR gehad. Jy benodig moontlik dringende mediese hulp of hospitalisasie.

Vertel dadelik jou dokter of gaan na die ongevalle afdeling van jou naaste hospitaal indien jy enige van die volgende opmerk:

- Voel gedehidreerd, het lae vlakke natrium in die bloed (meestal in bejaardes; die simptome kan insluit dat jy duiselig, swak, verward, slaperig of baie moeg, of siek voel, ernstiger simptome is flou word, aanvalle of valle) , waterretensie deur die liggaam (sindroom van onvanpaste afskeiding van antidiuretiese hormoon (SOADH)).
- Indien jy aanvalle het (stuiptrekkings).
- Gedagtes van selfmoord en selfbeskadiging.
- Serotoniensindroom, 'n potensieel lewensbedreigende toestand kan voorkom met MACLAFAX XR behandeling. Stel jou dokter in kennis of gaan na die naaste hospitaal as jy 'n kombinasie van die volgende waarneem: rusteloosheid, hallusinasies, verlies aan koördinasie, vinnige hartklop, verhoogde liggaamstemperatuur, verandering in bloeddruk, ooraktiewe reflekse, diaree, naarheid, braking en koma.
- In sy ernstigste vorm kan serotoniensindroom lyk soos Neuroleptiese Maligne Sindroom (NMS). Tekens en simptome van NMS kan insluit 'n kombinasie van koors, vinnige hartklop, sweet, ernstige spierstyfheid, verwarring, verhoogde spierensieme (bepaal deur 'n bloedtoets).
- Simptome van rabdomiolise (afbreek van spierweefsel): donker, rooi of kola kleurige uriene, verminderde urienuitset, algemene swakheid, spierstyfheid of pyn, spierteerheid, swakheid van die aangetaste spiere.
- Vinnige en/of onreëlmatige hartklop of abnormale vinnige hartklop, veranderinge op die EKG verwys na 'n verlenging van die QT-interval, d.w.s., vertraagde geleiding van elektriese seine.
- Hoes, asemgefluit, kortasem en 'n hoë temperatuur, wat simptome is van inflammasie in die longe wat gepaard gaan met die toename in witbloedselle (pulmonale eosinofilie).
- Braking van bloed, of swart teeragtige stoelgang (ontlasting).
- Ontsteking van die pankreas met simptome, insluitend boonste buikpyn, naarheid en braking.
- Inflammasie van die lewer of lewerversaking wat buikpyn en vergeling van die vel of wit van die oë (geelsug) kan veroorsaak.
- Stevens-Johnson-sindroom (ernstige siekte met blase wat vorm op die vel, mond, oë en geslagsdele).
- Erge veluitslag, jeuk of netelroos (verhewe kolle van rooi- of bleek vel wat dikwels jeuk)
- Langdurige bloeding - as jy jouself sny of beseer, kan dit langer neem as gewoonlik voordat bloeding stop.
- Sametrekking van die kaakspier (kaakklem).

Hierdie is almal baie ernstige newe-effekte. Jy benodig moontlik dringende mediese aandag.

Vertel jou dokter indien jy enige van die volgende opmerk:
Algemene newe-effekte:

- ongewone drome, verminderde seksdrang, slaapprobleme, senuweeagtigheid
- duiseligheid, droë mond, traagheid, gevoelloosheid, insluitend gevoelloosheid, prikkelende of tintelende vel, voel slaperig, bewing, veranderde of ingekorte smaaksensasie.
- oogprobleme soos dowwe sig, verwyde pupille, onvermoë van die oog om outomaties fokus te verander vanaf ver na naby voorwerpe,
- tinnitus (geluid in die oor as daar geen eksterne geluid is nie)
- verhoogde bloeddruk, blosing
- gaap meer, probleme met asemhaling
- verminderde eetlus, siek gevoel (naarheid), hardlywigheid, siek wees (braking)
- probleme met urinering
- probleme om 'n ereksie te kry, veranderinge in ejakulasie/orgasme in mans
- swakheid, moegheid, pyn, maagpyn, rugpyn, borskaspyn.

Minder algemene newe-effekte:

- kneusing van die vel
- voel onverskillig, hallusinasies, psigiatriese probleme, soos hiperaktiwiteit en voel ongewoon meer as opgewonde
- skielike onwillekeurige rukke of trekke van die spiere
- probleme met slaap, voel gedisoriënteerd, gebrek aan motivering
- flou word, lighoofdigheid of floute wanneer opstaan
- ontsteking van die dikderm (wat lei tot diaree), winde opbreek, sukkel om te sluk, ontsteking van die mond, slegte asem
- veluitslag, sensitiwiteit vir sonlig
- probleme met, of onvermoë om te kan urineer
- abnormale orgasme in vrouens
- voel koud of warm, dors, sidder, voel sleg, abnormale stap
- gewig optel
- veranderinge in bloedtoetsresultate (vermindering in natrium in die bloed, afname in die aantal witbloedselle, verhoogde bloedsuiker, vermindering van aantal bloedplaatjies, gewigstoename, gewigsvermindering, lewerensieme verhoog.

Newe-effekte waarvan die frekwensie nie bekend is nie:

- bloeiende tandvleise
- verminderde aantal bloedplaatjies in jou bloed, wat lei tot 'n verhoogde risiko vir kneusing of bloeding
- tekens van infeksie, soos hoë temperatuur, kouekoors, rilling, hoofpyne, sweet, griepagtige simptome. Dit kan die gevolg wees van 'n bloedversteuring (vermindering van sekere witbloedselle) wat lei tot 'n verhoogde risiko vir infeksie.
- verhoogde prolaktienvlakke in die bloed (abnormale produksie van borsmelk)
- verwarring; voel geskei, (of losstaande) van jouself, rusteloosheid, disoriëntasie en verwarring dikwels gepaard met hallusinasie (delirium), aggressie, geheueverlies, angs, depressie, gebrek aan gevoel of emosie; abnormale denke, onvanpaste gedrag
- hoofpyn, probleme om beweging te beheer bv. gebrek aan koördinasie of onwillekeurige bewegings van die spiere, spierstyfheid, gevoel van rusteloosheid of 'n onvermoë om stil te sit of stil te staan, herhalende, onwillekeurige bewegings soos mondtrekkings en oogknip, gevoelloosheid of 'n verminderde gevoel van aanraking, swak slaapkwaliteit
- verhoogde druk in die oë (gloukoom)
- vertigo (draai sensasie)
- voel hoe die hart in die borskas pomp.
- lae bloeddruk
- seerkeel, loop- of toe neus
- die tande slyp of kners, verhoogde eetlus, diaree, sooibrand of slegte spysvertering, winde opbreek, winde laat
- spierpyn, spierspasma
- sweet (insluitend nagsweet), netelroos, jeukerige veluitslag, abnormale haarverlies
- nodig om meer te urineer as normaal
- menstruele afwykings wat verband hou met verhoogde bloeding of verhoogde ongereelde bloeding, bloeding (swaar bloeding) nadat geboorte gegee is.

Indien jy enige newe-effekte opmerk wat nie in hierdie inligtingsblad genoem word nie, moet jy jou dokter of apteker daarvan in kennis stel.

Aanmelding van newe-effekte

Indien jy newe-effekte kry, praat met jou dokter of apteker of verpleegkundige. Dit sluit enige moontlike newe-effekte in, wat nie in hierdie inligtingsblad gelys is nie. Jy kan ook newe-effekte aanmeld by SAHPRA via die "**6.04 Adverse Drug Reaction Reporting Form**", wat aanlyn gevind kan word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8.
Deur newe-effekte aan te meld, kan jy help om meer inligting oor die veiligheid van MACLAFAX XR te voorsien.

5. Hoe om MACLAFAX XR **te berg**

Bewaar by of benede 25°C.
Beskerm teen lig en vog.
Bewaar die stulpstrook in die karton totdat dit benodig word vir gebruik.
Hou die HDPE houers dig gesluit.
HOU BUITE BEREIK VAN KINDERS.
Moet nie in 'n badkamer bêre nie.
Moet nie na die vervaldatum wat aangebring is op die etiket/karton/bottel gebruik nie.
Neem alle ongebruikte medisyne terug na jou apteker.
Moet nie ongebruikte medisyne in die riool of rioolstelsel (bv. toilette) gooi nie.

6. Inhoud van die pak en ander inligting

Wat MACLAFAX XR bevat

- Die aktiewe bestanddeel is venlafaksienhidrochloried 75 mg/150 mg.
- Die ander bestanddele is lae gesubstitueerde hidroksiepropielsellulose, mieliestysel, mikrokristallyne sellulose, etielsellulose, hidroksipropielmetielsellulose, gesuiwerde talkpoeier, harde gelatien kapsules wat titaandioksied bevat, rooi ysteroksied, gelatien en natriumlaurielsulfaat. Daarbenewens bevat MACLAFAX XR 75 mg geel ysteroksied.

Hoe MACLAFAX XR lyk en die inhoud van die pak

MACLAFAX XR 75 mg (Verlengde-vrystellings kapsules)
Wit tot afwit verlengde-vrystelling krale, gevul in grootte '1' kapsules met 'n perske doppie/perske liggaam, met 'L 87' op doppie en '75' op liggaam gedruk met rooi ink.
MACLAFAX XR 150 mg (Verlengde-vrystellings kapsules)
Wit tot afwit verlengde-vrystellings krale, gevul in grootte '0el' kapsules met donker oranje doppie/donker oranje liggaam, met 'L 88' op doppie en '150' op liggaam gedruk met wit ink.

Stulpverpakking:

Gewone, silwergekleurde, 25 µ aluminium foelie/ 6-8 gsm HSL as die dekmateriaal en helder, deursigtige PVC/PE/PVdC, 250 µ/25 µ/90 gsm, as die vormingsmateriaal, verpak in 'n voorafgedrukte eenheidskarton met 10, 28 of 30 kapsules.

HDPE houer verpakking:

Kapsules is verpak in 'n wit, ondeursigtige, ronde 40 ml of 60 ml HDPE houer vir MACLAFAX XR 75 mg en 60 ml HDPE houer vir MACLAFAX XR 150 mg met 33 mm nekafwerking, gesluit met 33 mm wit polipropileen sluiting met waad en induksie-sluitingvoering. Elke houer bevat 28 of 30 kapsules met 'n silika gel. Die houers word geplaas in 'n voorafgedrukte buitenste karton met 'n inligtingsblad.

Houer van die Sertifikaat van Registrasie en Vervaardiger
MACLEODS PHARMACEUTICALS SA (Edms) Bpk
Kantoorblok 1, Bassonia Estate Kantoorpark (Oos),
Cussonia Rylaan 1, Bassonia Rock, Uitbreiding 12,
Alberton, Suid Afrika

Hierdie inligtingsblad is laas hersien in:
20 April 2021

Registrasienommer
MACLAFAX XR 75 mg (Verlengde-vrystellings kapsules): 51/1.2/0061.057
MACLAFAX XR 150 mg (Verlengde-vrystellings kapsules): 51/1.2/0062.058

Toegang tot die ooreenstemmende Professionele Inligting

Die ooreenstemmende professionele inligting kan verkry word by https://www.macleodspharma.com of e-pos macleodsrsa@macleodspharma.com of kontak 011 682 1169.

PACKAGING RESEARCH & DEVELOPMENT

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

1. Product: Maclafax XR (Venlafaxine hydrochloride capsule)					
2. Country: South Africa		**3. Packaging component: Patient Information**			
4. No. of Colours: 1 Colour		**5. Pantone Shade No.: Black**			
6. Specification: 40 gsm bible paper					
7. Machine Layout No.: NA		**8. Dimensions: 535 x 400 mm**			
9. Design / Style: NA		**10. Item code No.: PM03626301**			
11. Artwork has been made: Actual Size		**12. Pharma code No.: 27530 mini**			
13. Barcode/NDC no: NA		**14. Supersedes Item code No: NA**			
15. Revision no: 00		**16. A/W File name: E:\ANDA Regulatory\South Africa\Venlafaxin\Maclafax XR PI & PIL-PM03626301.cdr**			
Approved By:		**17. Location: Baddi**			
PRD	**M.A. HOLDER**	**RAD**	**QC**	**PRODN**	**QA**
	Vanita Rajool				

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	**Item code**	**Artwork Release Date**	**Artwork Implementation Date**
1) New Artwork for South Africa	**PM03626301**		