1.3.1.1 Professional Information for Medicines for Human Use approved

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DEPRETA 30 (capsule)

DEPRETA 60 (capsule)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPRETA 30 :

Each capsule contains 30 mg of duloxetine as duloxetine hydrochloride. Contains sugar: sucrose 78 mg.

DEPRETA 60:

Each capsule contains 60 mg of duloxetine as duloxetine hydrochloride. Contains sugar: sucrose 156 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DEPRETA 30:

Blue opaque / white opaque, size '3' hard gelatin capsule filled with white to off white pellets and imprinted with 'DLX' on blue opaque cap and '30' on white opaque body with black ink.

DEPRETA 60:

Blue opaque / green opaque, size '1' hard gelatin capsule filled with white to off white pellets and imprinted with 'DLX' on blue opaque cap and '60' on green opaque body with black ink.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DEPRETA is indicated for the treatment of depression (as defined by DSM-IV criteria).

DEPRETA is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).

4.2. Posology and method of administration

Posology

Depression: DEPRETA should be initiated and maintained at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used the efficacy of the 120 mg dose was not statistically different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Diabetic peripheral neuropathic pain: DEPRETA should be administered at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used the efficacy of the 120 mg dose was not statistically significantly different from that of the 60 mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Discontinuation of treatment:

Abrupt discontinuation of DEPRETA should be avoided.

When stopping treatment with DEPRETA the dose should be gradually reduced over a period of at least two weeks to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the doctor may continue decreasing the dose, but at a more gradual rate.

Special populations:

Renal impairment: Initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function. (See sections 4.4, 5.2 and 4.3).

Hepatic impairment: Initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function.

(See sections 4.4, 5.2 and 4.3).

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

Pediatric population: Safety and efficacy have not been established in patients under the age of 18 years (see section 4.3).

Method of administration

For oral use

4.3. Contraindications

DEPRETA is contra-indicated in patients:

- with a known hypersensitivity to duloxetine or to any of the excipients
- who are pregnancy and/or breastfeeding
- have severe impairment of hepatic function
- have advanced renal impairment (creatinine clearance <30 mL/min)
- where there is concomitant use of monoamine oxidase inhibitors (MAOIs). (See also section 4.4)
- Children under 18 years as the safety in children has not been established (see section 4.4).

4.4. Special warnings and precautions for use

Suicide

Major Depressive Disorder:

Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during therapy or early after treatment discontinuation (see sections 4.5 and 4.8).

Close supervision of patients, and in particular those at high risk should accompany medicinal product therapy, especially in early treatment and following dose changes.
Patients with major depressive disorder, both adults and children, may experience worsening of their depression. This risk may persist until significant remission occurs. A casual role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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

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 DEPRETA, 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, DEPRETA should be tapered (see below and section 4.2).

Suicidal behaviour

As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during DEPRETA therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Medical practitioners should encourage patients to report any distressing thoughts or feelings at any time.

Use in Children and Adolescents Under 18 Years of Age

DEPRETA should not be used in the treatment of children and adolescents under the age of 18 years as safety and efficacy has not been established (see section 4.3). Suicide-related behaviours (suicide attempts and suicidal thoughts), self-harm and hostility (predominantly aggression, oppositional behaviour, and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms (see section 5.2). In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking (see section 4.8).

Mania and Seizures

DEPRETA should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Mydriasis

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing DEPRETA to patients with increased intra-ocular pressure or those at risk of acute narrow-angle glaucoma.

Blood Pressure and Heart Rate

DEPRETA has been associated with an increase in blood pressure, and clinically significant hypertension in some patients.

This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with DEPRETA, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. DEPRETA should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when DEPRETA is used with medicinal products that may impair its metabolism (see section 4.5).For patients who experience a sustained increase in blood pressure while receiving DEPRETA, either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension, DEPRETA should not be initiated.

Renal Impairment

Increased plasma concentrations of DEPRETA occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 mL/min). For patients with severe renal impairment, see section 4.3 and 4.2 for information on patients with mild or moderate renal dysfunction.

Hepatic impairment:

Increased plasma concentrations of duloxetine occur in patients with hepatic impairment. (See sections 4.2 and 4.3).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with DEPRETA treatment, particularly with concomitant use of other serotonergic medicines (including SSRIs, SNRIs tricyclic antidepressants or triptans), with medicines that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (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).

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

St John's Wort

Adverse reactions may be more common during concomitant use of “Interactions with other medicinal products and other forms of interactions”) and herbal preparations containing St John's Wort (Hypericum perforatum).

Haemorrhage

There have been reports of bleeding abnormalities, such as ecchymoses, purpura, and gastrointestinal haemorrhage, with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including DEPRETA. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia

Hyponatraemia has been reported when administering DEPRETA, including cases with serum sodium lower than 110 mmol/L. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients, or patients treated with diuretics.

Discontinuation of Treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with DEPRETA and 23% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur

within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that DEPRETA should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Elderly

Data on the use of DEPRETA 120 mg in elderly patients with major depressive disorder is limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage (see sections 4.2 and 5.2).

Akathisia/Psychomotor Restlessness

The use of DEPRETA 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.

Medicinal Products Containing Duloxetine

Duloxetine is used under different proprietary names in several indications. The use of more than one of these products concomitantly should be avoided.

Hepatitis/Increased Liver Enzymes

Cases of liver injury, including severe elevations of liver enzymes (>10-times upper limit of normal), hepatitis, and jaundice have been reported with DEPRETA (see section 4.8). Some cases were associated with excessive alcohol use. Most of them occurred during the first

months of treatment. The pattern of liver damage was predominantly hepatocellular.

DEPRETA should be used with caution in patients treated with other medicinal products associated with hepatic injury. DEPRETA should also be used with caution in patients with substantial alcohol use.

Sexual dysfunction

DEPRETA may cause symptoms of sexual dysfunction (see section 4.8). These may continue despite discontinuation of DEPRETA.

Sucrose

DEPRETA contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Monoamine Oxidase Inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with monoamine oxidase inhibitors (MAOIs) or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping DEPRETA before starting an MAOI (see section 4.3).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{0-t} 6-fold. Caution is

advised if administering DEPRETA with inhibitors of CYP1A2 and a lower DEPRETA dose should be used.

CNS Medicinal Products: The risk of using DEPRETA in combination with other CNS-active medicinal products has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when DEPRETA is taken in combination with other centrally-acting medicinal products or substances, including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbitone, sedative antihistamines).

Serotonergic medicines: In rare cases, serotonin syndrome has been reported in patients using SSRIs/ SNRIs concomitantly with serotonergic medicines. Caution is advisable if DEPRETA is used concomitantly with serotonergic agents like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, St John's Wort (Hypericum perforatum) or triptans, tramadol, pethidine, and tryptophan (see section 4.4). Concomitant use with MOAI's, including moclobemide or linezolid, is contraindicated (see above and section 4.3)

Effect of duloxetine on other medicinal products

Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with DEPRETA (60 mg twice daily).

Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When DEPRETA was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady-state AUC of tolterodine (2

mg twice daily) by 71%, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if DEPRETA is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), particularly if they have a narrow therapeutic index (such as flecainide, propafenone, and metoprolol).

Oral contraceptives and other steroidal medicines: Results of in vitro studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific in vivo drug interaction studies have not been performed.

Anticoagulants and antiplatelet medicines: Caution should be exercised when DEPRETA is combined with oral anticoagulants or antiplatelet medicines due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when DEPRETA was co-administered to patients treated with warfarin. However, concomitant administration of DEPRETA with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Inhibitors of CYP2D6: Because CYP2D6 is involved in DEPRETA metabolism, concomitant use of DEPRETA with inhibitors of CYP2D6 may result in higher concentrations of DEPRETA. Paroxetine (20 mg once daily) decreased the apparent plasma clearance of DEPRETA by about 37 %. Caution is advised if administering DEPRETA with inhibitors of CYP2D6 (e.g. SSRIs).

Effects of other medicinal products on duloxetine

Antacids and H2 antagonists: Co-administration of DEPRETA with aluminium- and magnesium-containing antacids, or DEPRETA with famotidine, had no significant effect on the rate or extent of DEPRETA absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of DEPRETA compared with non-smokers.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of DEPRETA in pregnancy has not been established (see section 4.3).
Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of DEPRETA lower than the maximum clinical exposure.

The potential risk for humans is unknown.

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

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal DEPRETA use near term. Discontinuation symptoms seen with DEPRETA may include hypotonia, tremor, and jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Breastfeeding

DEPRETA is excreted into human milk. The use of DEPRETA while breastfeeding is contraindicated (see section 4.3).

Fertility

In animal studies, DEPRETA had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. DEPRETA may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions in patients treated with **DEPRETA** were nausea, headache, dry mouth, somnolence and dizziness. However, the majority of common adverse reactions were mild to moderate; they usually started early in therapy, and most tended to subside even as therapy was continued.

Hostility, suicidal ideation and self-harm have been reported in children treated with SSRIs or SNRIs like DEPRETA.

b. Tabulated summary of adverse reactions

Frequent	**Less frequent**	**Frequency unknown**
Infections and Infestations		
	Laryngitis	
Immune System Disorders		

	Anaphylactic reaction Hyper-sensitivity disorder Angioedema		
Endocrine Disorders			
	Hypo-thyroidism		
Metabolism and Nutrition Disorders			
Decreased appetite	Hyperglycaemia (reported especially in diabetic patients) Dehydration Hyponatraemia SIADH		
Psychiatric Disorders			
Insomnia Agitation Libido decreased, Anxiety Orgasm abnormal Abnormal dreams	Suicidal ideation Sleep disorder Bruxism Disorientation Apathy Suicidal behaviour Mania Hallucinations Aggression and anger		
Nervous System Disorders			
Headache Somnolence Dizziness Lethargy Tremor Paraesthesia	Myoclonus Akathisia Nervousness Disturbance in attention Dysgeusia		

	Dyskinesia Restless legs syndrome Poor quality sleep Serotonin syndrome Convulsions Psychomotor restlessness Extra-pyramidal symptoms[6]		
Eye Disorders			
Blurred vision	Mydriasis Visual impairment Glaucoma		
Ear and Labyrinth Disorders			
Tinnitus	Vertigo Ear pain		
Cardiac Disorders			
Palpitations	Tachycardia Supra-ventricular Dysrhythmia, mainly atrial fibrillation		
Vascular Disorders			
Blood pressure increase Flushing Hot flush	Syncope Hypertension Orthostatic hypotension Peripheral coldness Hypertensive crisis		

Respiratory, Thoracic and Mediastinal Disorders			
Yawning	Throat tightness Epistaxis Interstitial lung disease Eosinophilic pneumonia		
Gastrointestinal Disorders			
Nausea Dry mouth Constipation Diarrhoea Abdominal pain Vomiting Dyspepsia Flatulence	Gastrointestinal haemorrhage Gastroenteritis Eructation Gastritis Dysphagia Stomatitis Haematochezia Breath odour Microscopic colitis		
Hepato-biliary Disorders			
	Hepatitis Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury Hepatic failure Jaundice		
Skin and Subcutaneous Tissue Disorders			
Sweating increased Rash	Night sweats Urticaria Dermatitis contact Cold sweat	Cutaneous vasculitis	

	Photo-sensitivity reactions Increased tendency to bruise Stevens-Johnson Syndrome		
Musculoskeletal and Connective Tissue Disorders			
Musculo-skeletal pain Muscle spasm	Muscle tightness Muscle twitching Trismus		
Renal and Urinary Disorders			
Dysuria Pollakiuria	Urinary retention Urinary hesitation Nocturia Polyuria Urine flow decreased urine odour abnormal		
Reproductive System and Breast Disorders			
Erectile dysfunction Ejaculation disorder Ejaculation delayed	Gynaecological haemorrhage Menstrual disorder Sexual dysfunction Testicular pain Menopausal symptoms Galactorrhoea Hyper-prolactinaemia		
General Disorders and Administration Site Conditions			

Falls[8] Fatigue	Chest pain Feeling abnormal Feeling cold Thirst Chills Malaise Feeling hot Gait disturbance Increased blood pressure Hepatic lab findings		
Investigations			
Weight decrease	Weight increase Blood creatine phosphokinase increased Blood potassium increased Blood cholesterol increased		

c. Description of selected adverse reactions

Discontinuation of DEPRETA (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when DEPRETA treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and 4.4).

In the 12-week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients, while those laboratory tests showed a slight decrease in the routine care group.

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Medicine Reactions Reporting Form**", found online under SAHPRA's publications: https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA

4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed

overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for duloxetine, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Category and Class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action

Duloxetine is a combined serotonin (5-hydroxytrptamine 5-HT) and noradrenaline (NA) (norepinephrine) reuptake inhibitor. It weakly inhibits dopamine reuptake, with no significant affinity for histaminergic, dopaminergic, cholinergic, and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline (norepinephrine) in various brain areas of animals.

Neurochemical and behavioural studies in laboratory animals showed an enhancement of both serotonin and noradrenaline (norepinephrine) neurotransmission in the central nervous system (CNS).

The presumed mechanism of action of duloxetine in the treatment of depression is thought to be due to its inhibition of neuronal uptake of serotonin and norepinephrine and a resultant increase in serotonergic and noradrenergic neurotransmission in the CNS.

The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status, and CYP2D6 metaboliser status.

Absorption: Duloxetine is well absorbed after oral administration, with a C_{max} occurring 6 hours post-dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). These changes do not have any clinical significance. Steady-state plasma concentrations are achieved after 3 days of dosing.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha1-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites, glucuronide conjugate of 4-hydroxy duloxetine and sulfate conjugate of 5-

hydroxy, 6-methoxy duloxetine. Based upon in vitro studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special Populations

Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: Pharmacokinetic differences have been identified between younger and elderly females (≥ 65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child-Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3-times longer, and the AUC was 3.7-times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Breastfeeding mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice-daily dosing. Lactation did not influence duloxetine pharmacokinetics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of DEPRETA are sugar spheres, hypromellose, hydroxy propyl cellulose, crospovidone, talc, triethylcitrate and titanium dioxide.

DEPRETA: The capsule shell contains gelatin, sodium laury sulphate, FD & C Blue 2 (C.I. No: 73015), titanium dioxide (C.I. No: 77891).

DEPRETA: The black ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide (C.I. No: 77499) and potassium hydroxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

To be allocated. 3 years shelf life has been proposed.

6.4 Special precautions for storage

Store at or below 25°C.

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

DEPRETA 30:

1) **Blister Pack:**

Capsules are packed in 60 micron PVC film /25 micron polyamide/ 60 micron aluminium foil/ 60 micron PVC film as the forming material and 25 µm aluminum foil with 7 gsm heat seal lacquer as the lidding material.

Pack size: 30's – Each carton contains 3 blisters of 10 capsules each.

2) HDPE Pack:

White opaque round 40 mL HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner containing 1 no of 1 g silica gel sachet.

Pack size: 30's – One HDPE container contains 30 Capsules.

DEPRETA 60 mg CAPSULES:

1) Blister Pack:

Capsules are packed in 60 micron PVC film /25 micron polyamide/ 60 micron aluminium foil/ 60 micron PVC film as the forming material and 25 µm aluminum foil with 7 gsm heat seal lacquer as the lidding material.

Pack size: 30's – Each carton contains 3 blisters of 10 capsules each.

2) HDPE Pack:

White opaque round 40 mL HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner containing 1 no of 1 g silica gel sachet.

Pack size: 30's – One HDPE container contains 30 capsules.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8 REGISTRATION NUMBER(S)

DEPRETA 30: 47/1.2/0097

DEPRETA 60: 47/1.2/0098

9 DATE OF FIRST AUTHORISATION

13 APRIL 2021

10 DATE OF REVISION OF TEXT