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DEPRETA
P1527346

DEPRETA
P1527346

PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE
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.

Paediatric 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 listed in section 6.1
- who are pregnant and/or breastfeeding
- who have severe impairment of hepatic function
- who 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 St John's Wort 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 to 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, Anger	
Nervous System Disorders		
Headache, Somnolence, Dizziness, Lethargy, Tremor	Myoclonus, Akathisia, Nervousness, Disturbance in attention, Dysgeusia, Dyskinesia, Restless legs, Myoclonus, Akathisia, Nervousness, Disturbance in attention, Dysgeusia, Dyskinesia, Restless legs syndrome, Poor quality sleep, Serotonin syndrome, Convulsions, Psychomotor restlessness, Extra-pyramidal symptoms	
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 sweats, Photo-sensitivity reactions, Increased tendency to bruise, Stevens-Johnson Syndrome	Cutaneous vasculitis
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, 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 Cmax 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 alpha-1acid 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 lauryl sulphate, FD & C Blue 2 (C.I. No: 73015), titanium dioxide (C.I. No: 77891).
DEPRETA: The edible 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
36 months

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:
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
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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

DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET

S5

DEPRETA 30 (capsule)
DEPRETA 60 (capsule)
Duloxetine hydrochloride.
Contains sugar: 78 mg and 156 mg of sucrose respectively.

Read all of this leaflet carefully before you start taking DEPRETA.
- 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.
- **DEPRETA** 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 **DEPRETA** is and what it is used for
2. What you need to know before you use **DEPRETA**
3. How to use **DEPRETA**
4. Possible side effects
5. How to store **DEPRETA**
6. Contents of the pack and other information

1. What DEPRETA is and what it is used for
DEPRETA contains the active substance duloxetine. Duloxetine increases the levels of serotonin and noradrenaline in the nervous system.
DEPRETA is used to treat:
- depression
- diabetic neuropathic pain (often described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain).

2. What you need to know before you take DEPRETA
Do not take DEPRETA if you:
- are allergic to duloxetine or any of the other ingredients of this medicine (listed in section 6)
- are pregnant or breastfeeding
- have liver disease
- have severe kidney disease
- are taking or have recently taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor (MAOI)
- **DEPRETA** should not be used in children under 18 years of age as safety has not been established.

Warnings and precautions
Take special care with DEPRETA if you:
- are taking other medicines to treat depression
- are taking St. John's Wort, a herbal treatment (Hypericum perforatum)
- have kidney disease
- have had seizures (fits)
- suffer from bipolar disorder
- have eye problems, such as certain kinds of glaucoma (increased pressure in the eye)
- have a history of bleeding disorders (tendency to develop bruises)
- are at risk of low sodium levels (for example if you are taking diuretics, especially if you are elderly)
- if you have high blood pressure
- are currently being treated with another medicine which may cause liver damage or if you use alcohol in substantial amounts
- **DEPRETA** may cause a sensation of restlessness or an inability to sit or stand still.
- If you are depressed, you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

Other medicines and DEPRETA:
Always tell your healthcare professional if you are taking any other medicine. (This includes all complementary or traditional medicines).
DEPRETA may have an effect on other medicines or other medicines may have an effect on **DEPRETA**.
- Monoamine Oxidase Inhibitors (MAOIs): You should not take **DEPRETA** if you are taking, or have recently taken (within the last 14 days) another antidepressant medicine called a monoamine oxidase inhibitor (MAOI). Examples of MAOIs include moclobemide (an antidepressant) and linezolid (an antibiotic). Taking a MAOI together with many prescription medicines, including **DEPRETA**, can cause serious or even life-threatening side effects. You must wait at least 14 days after you have stopped taking an MAOI before you can take **DEPRETA**. Also, you need to wait at least 5 days after you stop taking **DEPRETA** before you take a MAOI.
- Medicines that cause sleepiness: These include medicines prescribed by your doctor including benzodiazepines, strong painkillers, antipsychotics, phenobarbitone, antihistamines.
- 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. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with **DEPRETA**, you should see your doctor.
- Oral anticoagulants or antiplatelet medicines:
  Medicines which thin the blood or prevent the blood from clotting. These medicines might increase the risk of bleeding.

The main ingredient of **DEPRETA**, duloxetine, is also used in other medicines for other conditions. You should not take one of these medicines at the same time as **DEPRETA**. Check with your doctor if you are already taking other medicines containing duloxetine.

DEPRETA with food and drink
DEPRETA may be taken with or without food.

Pregnancy, breastfeeding and fertility
You should not take **DEPRETA** if you are pregnant (see 'Do not take **DEPRETA**').

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

Tell your doctor if you are breastfeeding. The use of **DEPRETA** while breastfeeding is contraindicated (see Do not take **DEPRETA**).

Driving and using machines
DEPRETA may make you feel sleepy or dizzy. Do not drive or use any tools or machines until you know how **DEPRETA** affects you.

DEPRETA contains sucrose:
DEPRETA contains sucrose, which is a type of sugar.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take DEPRETA
Do not share medicines prescribed for you with any other person.
DEPRETA is for oral use. You should swallow your capsule whole with a drink of water.
For depression and diabetic neuropathic pain:
The usual dose of **DEPRETA** is one capsule (60 mg duloxetine) once a day, but your doctor will prescribe the dose that is right for you.

Always take **DEPRETA** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. Your doctor will tell you how long your treatment with **DEPRETA** will last. Do not stop taking your treatment without consulting your doctor. If you have the impression that the effect of **DEPRETA** is too strong or too weak, talk to your doctor or pharmacist.

If you take more DEPRETA than you should
In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison center.

If you take more than required dose you may experience symptoms that include sleepiness, coma, serotonin syndrome (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles) fits, vomiting and fast heart rate.

If you forget to take DEPRETA
If you forgot to take a dose, take it as soon as you remember unless it is nearly time for your next dose. Do not take a double dose to make up for forgotten individual doses

4. Possible side effects
DEPRETA can have side effects.
Not all side effects reported for **DEPRETA** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **DEPRETA**, please consult your healthcare provider for advice.

If any of the following happens, stop taking **DEPRETA** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Difficulty in breathing or dizziness with swollen tongue or lips

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

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- suicidal thoughts,
- suicidal behaviour, self-harm, mania (over activity, racing thoughts and decreased need for sleep), hallucinations, aggression and anger,

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

Tell your doctor if you notice any of the following:
The following side effects occur frequently:
- headache, feeling sleepy
- feeling sick (nausea), dry mouth
- lack of appetite
- anxiety, reduced sex drive, difficulty or failure to experience orgasm, unusual dreams
- dizziness, feeling sluggish, tremor, numbness, including numbness, pricking or tingling of the skin
- blurred eyesight
- tinnitus (hearing sound in the ear when there is no external sound)
- feeling the heart pumping in the chest
- increased blood pressure, flushing
- increased yawning
- constipation, diarrhoea, stomach pain, being sick (vomiting), heartburn or indigestion, breaking wind
- increased sweating,(itchy) rash
- muscle pain, muscle spasm
- painful urination, frequent urination
- problems getting an erection ,changes in ejaculation
- falls (mostly in elderly people), fatigue
- weight loss

The following side effects occur less frequently:
- throat inflammation that causes a hoarse voice
- grinding or clenching the teeth, feeling disorientated, lack of motivation
- sudden involuntary jerks or twitches of the muscles, sensation of restlessness or an inability to sit or stand still, feeling nervous,
- difficulty concentrating, changes in sense of taste,
- difficulty controlling movement e.g. lack of coordination or involuntary movements of the muscles, restless legs syndrome
- large pupils (the dark centre of the eye), problems with eyesight
- feeling of dizziness or "spinning" (vertigo), ear pain
- fast and/or irregular heart beat
- fainting, dizziness, lightheadedness or fainting on standing up, cold fingers and/or toes
- throat tightness, nose bleeds
- vomiting blood, or black tarry stools (faeces),
- gastroenteritis, burping, difficulty swallowing
- inflammation of the liver that may cause abdominal pain and yellowing of the skin or whites of the eyes
- night sweats, hives, cold sweats, sensitivity to sunlight, increased tendency to bruise
- muscle tightness, muscle twitching
- difficulty or inability to pass urine, difficulty to start urinating, needing to pass urine during the night, needing to pass more urine than normal, having a decreased urine flow
- abnormal vaginal bleeding, abnormal periods, including heavy, painful, irregular or prolonged periods, unusually light or missed periods, pain in the testicles or scrotum
- chest pain, feeling cold, thirst, shivering, feeling hot
- abnormal gait
- weight gain

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

Reporting of side effects
If you get any 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://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA. By reporting side effects, you can help provide more information on the safety of **DEPRETA**.

5. How to store DEPRETA
Store at or below 25 °C.
Keep the blisters in the carton until required for use.
Keep HDPE containers tightly closed.
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information
What DEPRETA contains
The other ingredients of **DEPRETA** are hypromellose, hydroxy propyl cellulose, crospovidone, talc, triethylcitrate and titanium dioxide.
DEPRETA: The capsule shell contains gelatin, sodium lauryl sulphate, FD & C Blue 2 (C.I. No: 73015), titanium dioxide (C.I. No: 77891).
DEPRETA: The edible 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.

What DEPRETA looks like and contents of the pack
DEPRETA 30:
Blue opaque / white opaque, size '3' hard gelatin capsule filled with white to off white pellets and imprinted with 'DLX' on the blue opaque cap and '30' on the 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 the blue opaque cap and '60' on the green opaque body with black ink.

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 aluminium foil with 7 gsm heat seal lacquer as the lidding material.
Pack size: 30's – Each carton contains 3 blisters of 10 capsules each.

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

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South Africa

Registration number
DEPRETA 30: 47/1.2/0097
DEPRETA 60: 47/1.2/0098
This leaflet was last revised in:
13 April 2021

A/s: 420 x 740 mm ■ Black

AUROBINDO Packaging Development	Product Name	Component	Item Code	Date & Time
	Depreta Capsules	Leaflet	P1527346	06.08.2021 & 06.15 pm
	Country	Version No.	Reason Of Issue	Reviewed / Approved by
	South Africa_U7	05	Submission	
Team Leader: Kiran K	Dimensions (mm)	Colours: 01		
Initiator: Bhogi	A/s: 420 x 740 mm	26508		
Artist: Sree Designers	Pharma Code: 27346			
Additional Information:				

PROFESSIONELE INLIGTING OOR MEDISYNE VIR MENSLIKE GEBRUIK

SKEDULERINGSTATUS:

S5

1. NAAM VAN DIE MEDISYNE

DEPRETA 30 (kapsule)
DEPRETA 60 (kapsule)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

DEPRETA 30:
Elke kapsule bevat 30 mg duloksetien as duloksetienhidrochloried. Bevat suiker: 78 mg sukrose

DEPRETA 60:
Elke kapsule bevat 60 mg duloksetien as duloksetienhidrochloried. Bevat suiker: 156 mg sukrose
Raadpleeg afdeling 6.1 vir die volledige lys van hulpstowwe.

3. FARMASEUTIESE VORM

DEPRETA 30:
Ondeursigtige blou/ondeursigtige wit grootte 3 hardegelatienkapsule wat wit tot afwit korrels bevat met "DLX" in swart ink op die ondeursigtige blou doppie en "30" op die ondeursigtige wit romp gedruk.

DEPRETA 60:
Ondeursigtige blou/ondeursigtige groen grootte 1 hardegelatienkapsule wat wit tot afwit korrels bevat met "DLX" in swart ink op die ondeursigtige blou doppie en "60" op die ondeursigtige groen romp gedruk.

4. KLINIESE BESONDERHEDE

4.1. Terapeutiese indikasies

DEPRETA is aangedui vir die behandeling van depressie (soos gedefinieer deur DSM-IV-kriteria).
DEPRETA is aangedui vir die behandeling van perifere neuropatiese pyn in diabete (PNPD).

4.2. Dosis en metode van toediening

Dosering

Depressie: DEPRETA moet sonder inagneming van maaltye teen 'n dosis van 60 mg een keer per dag begin en volgehou word. Alhoewel dosisse tot 120 mg per dag gebruik is, was die doeltreffendheid van die dosis van 120 mg nie statisties anders as dié van die dosis van 60 mg een keer per dag nie, en die voorkoms van newe-effekte was hoër met die dosis van 120 mg.

Perifere neuropatiese pyn in diabete: DEPRETA moet sonder inagneming van maaltye teen 'n dosis van 60 mg een keer per dag toegedien word. Alhoewel dosisse tot 120 mg per dag gebruik is, was die doeltreffendheid van die dosis van 120 mg nie statisties anders as dié van die dosis van 60 mg een keer per dag nie, en die voorkoms van newe-effekte was hoër met die dosis van 120 mg.

Staking van behandeling:
Skielike staking van **DEPRETA** moet vermy word.
Wanneer die behandeling met **DEPRETA** gestaak word, moet die dosis oor 'n periode van ten minste twee weke geleidelik verminder word om die risiko vir onttrekkingsreaksies te verlaag (kyk afdelings 4.4 en 4.8). As ondraaglike simptome ná 'n verlaging in die dosis of na staking van behandeling voorkom, kan hervatting met die voorheen voorgeskrewe dosis oorweeg word. Daarna kan die dokter voortgaan om die dosis te verlaag, maar teen *'n* meer geleidelike tempo.

__Spesiale populasies:__
Swak nierfunksie: Die aanvangsdosis moet 30 mg een keer per dag wees vir pasiënte met ligte tot matige swak nierfunksie (kyk afdelings 4.4, 5.2 en 4.3).
Swak lewerfunksie: Die aanvangsdosis moet laer of minder dikwels wees vir pasiënte met ligte tot matige swak lewerfunksie (kyk afdelings 4.4, 5.2 en 4.3).
Bejaarde bevolking: Geen dosisaanpassing word vir bejaardes op grond van ouderdom aanbeveel nie.
Pediatriese populasie: Die veiligheid en effektiwiteit vir pasiënte jonger as 18 jaar is nie bepaal nie (kyk afdeling 4.3).

Metode van toediening
Slegs vir orale gebruik

4.3. Kontra-indikasies

DEPRETA is teenaangedui vir pasiënte:
- met bekende hipersensitiwiteit vir duloksetien of enige van die hulpstowwe in afdeling 6.1 gelys.
- wat swanger is en/of borsvoed
- met erge swak lewerfunksie
- met gevorderde nierversaking (kreatinienopruiming < 30 mL/min)
- wat terselfdertyd monoamienoksidaseremmers (MAO-remmers) gebruik (kyk ook afdeling 4.4)
- kinders jonger as 18 jaar, aangesien die veiligheid in kinders nog nie vasgestel is nie (kyk afdeling 4.4).

4.4. Spesiale waarskuwings en voorsorgmaatreëls tydens gebruik

Selfdood

Major depressiewe versteuring:
Depressie gaan gepaard met 'n hoë risiko vir selfdoodgedagtes, selfbesering en selfdood (pogings tot selfdood). Hierdie risiko duur voort totdat beduidende remissie voorkom. Aangesien 'n verbetering dalk nie binne die eerste paar weke van behandeling sal intree nie, moet pasiënte noukeurig gemonitor word totdat daar 'n verbetering is. Dit is algemene kliniese ervaring dat die risiko vir selfdood in die vroeë stadium van herstel hoër kan wees.

Pasiënte met 'n geskiedenis van selfdoodpogings of dié wat voor aanvang van behandeling 'n beduidende mate van idealisering van selfdood gehad het, het 'n groter risiko vir selfdoodgedagtes of selfdoodpogings en moet tydens behandeling noukeurig gemonitor word. 'n Meta-analise van die placebogekontroleerde kliniese proewe van antidepressante in volwasse pasiënte met psigiatriese versteurings het 'n hoër risiko vir selfdoodgedrag met antidepressante in pasiënte jonger as 25 jaar oud vertoon in vergelyking met placebo.

Gevalle van selfdoodgedagtes en selfdoodgedrag is tydens die behandeling of vroeg na die staking van die behandeling aangemeld (kyk afdelings 4.5 en 4.8).
Pasiënte, en veral diegene met 'n hoë risiko, moet tydens behandeling met medisyne noukeurig dopgehou word, en veral aan die begin van behandeling en nadat die dosis verander is.

Depressie van pasiënte met major depressiewe versteuring, sowel volwassenes as kinders, kan erger word. Hierdie risiko kan voortduur totdat beduidende remissie voorkom. 'n Oorsakende rol van antidepressante vir sulke gedrag is egter nie bepaal nie.

Pasiënte (en versorgers van pasiënte) moet gewys word op die noodsaak om uit te kyk vir enige kliniese agteruitgang, selfdoodgedrag of -gedagtes, ongewone veranderings in gedrag en om onmiddellik mediese hulp te kry as hierdie simptome voorkom.

Omdat major depressiewe versteurings en ander psigiatriese en nie-psigiatriese versteurings selfdoodneigings kan versterk, moet dieselfde voorsorgmaatreëls getref word wanneer pasiënte met major depressiewe versteuring behandel word as wanneer pasiënte met ander psigiatriese en nie-psigiatriese versteurings behandel word.

Die volgende simptome is aangemeld in pasiënte wat met antidepressante vir major depressiewe versteurings asook vir ander indikasies, psigiatries sowel as niepsigiatries, behandel is: angs, agitasie, paniekaanvalle, slaaploosheid, geïrriteerdheid, vyandigheid, aggressiwiteit, impulsiwiteit, akatisie, hipomanie en manie.
Hoewel die oorsakende verband met die ontstaan van selfdoodneigings nie bepaal is nie, moet oorweeg word om die terapeutiese regimen te verander, waaronder moontlike staking van **DEPRETA**, vir pasiënte wie se simptome erg is, skielik ontstaan of waar dit nie deel van die pasiënt se aanvanklike simptome was nie. As besluit word om behandeling te staak, moet **DEPRETA** geleidelik onttrek word (kyk hier onder en afdeling 4.2).

Selfdoodgedrag
Soos met ander medisyne met 'n soortgelyke farmakologiese werking (antidepressante), is geïsoleerde gevalle van selfdoodgedagtes en selfdoodgedrag tydens behandeling met **DEPRETA** of vroeg na die staking van die behandeling aangemeld. Kyk hier bo vir risikofaktore vir selfdood tydens depressie. Mediese praktisyns moet pasiënte aanmoedig om kommerwekkende gedagtes of gevoelens te eniger tyd aan te meld.

Gebruik deur kinders en adolessente jonger as 18 jaar
DEPRETA moet nie gebruik word vir die behandeling van kinders en adolessente onder die ouderdom van 18 jaar nie, aangesien veiligheid en doeltreffendheid nie bepaal is nie (kyk afdeling 4.3). Selfdoodverwante gedrag (selfdoodpogings en selfdoodgedagtes), selfbesering en vyandigheid (hoofsaaklik aggressie, opponerende gedrag en woede) is in kliniese proewe meer dikwels waargeneem in kinders en adolessente wat met antidepressante behandel is in vergelyking met diegene wat met placebo behandel is. As daar tog op grond van kliniese behoefte 'n besluit geneem word om te behandel, moet die pasiënt noukeurig gemonitor word vir die voorkoms van selfdoodsimptome (kyk afdeling 5.2). Daarbenewens is daar geen langtermyndata oor die veiligheid van kinders en tieners met betrekking tot groei, volwassewording en kognitiewe ontwikkeling en gedrag nie (kyk afdeling 4.8).

Manie en toevalle
DEPRETA moet versigtig gebruik deur pasiënte met 'n geskiedenis van manie of 'n diagnose van bipolêre versteuring, en/of toevalle.

Midriase
Midriase is tydens gebruik van duloksetien aangemeld en daarom moet **DEPRETA** versigtig voorgeskryf word aan pasiënte met hoë intra-okulêre druk of diegene met 'n risiko vir akute nouhoekgloukoom.

Bloeddruk en polsslag
DEPRETA het in sommige pasiënte met 'n styging in bloeddruk en klinies beduidende hipertensie gepaardgegaan.
Dit kan vanweë die noradrenergiese effek van duloksetien wees. Gevalle van 'n hipertensiewe krisis is met **DEPRETA** aangemeld, veral in pasiënte met bestaande hipertensie. Daarom word monitering van bloeddruk van pasiënte met bekende hipertensie en/of ander hartsiektes aanbeveel, veral gedurende die eerste maand van behandeling. **DEPRETA** moet versigtig gebruik word deur pasiënte wie se toestande deur 'n vinniger hartklop of deur 'n styging in bloeddruk benadeel kan word. Wees ook versigtig wanneer **DEPRETA** saam met medisyne gebruik word wat die metabolisme daarvan kan beïnvloed (kyk afdeling 4.5). Vir pasiënte wat 'n aanhoudende styging in bloeddruk ervaar terwyl hulle **DEPRETA** ontvang, moet verlaging van die dosis of geleidelike staking oorweeg word (kyk afdeling 4.8)).
Behandeling met **DEPRETA** moet nie begin word vir pasiënte met ongekontroleerde hipertensie nie.

Swak nierfunksie
Hoër plasmakonsentrasies van **DEPRETA** kom voor in pasiënte met erge swak nierfunksie (kreatinienopruiming < 30 mL/min) wat hemodialise kry. Lees afdeling 4.3 vir pasiënte met erge swak nierfunksie, en 4.2 vir inligting oor pasiënte met ligte of matige swak nierfunksie.

Swak lewerfunksie:
Hoër plasmakonsentrasies van duloksetien kom voor in pasiënte met swak lewerfunksie (kyk afdelings 4.2 en 4.3).

Serotoniensindroom
Die serotoniensindroom, 'n potensieel lewensbedreigende toestand, kan met behandeling met **DEPRETA** voorkom en veral met gelyktydige gebruik van ander serotonergiese medisyne (waaronder SSHR's, SNHR's, trisikliese antidepressante of triptane), of met medisyne wat die metabolisme van serotonien vertraag, soos MAO-remmers, of met antipsigotika of ander dopamienantagoniste wat die serotonerge neuro-oordragstelsels kan beïnvloed (kyk afdelings 4.3 en 4.5).

Simptome van die serotoniensindroom kan onder meer veranderings in verstandelike toestand (bv. agitasie, hallusinasies, koma), outonome onstabiliteit (bv. tagikardie, labiele bloeddruk, hipertermie), neuromuskulêre aberrasie (bv. hiperrefleksie, inkoördinasie) en/of gastro-intestinale simptome (bv. naarheid, braking, diarree) wees.

As behandeling met **DEPRETA** saam met serotonerge medisyne wat die serotonergiese of dopaminerge neurotransmitterstelsels kan beïnvloed klinies aangedui is, moet die pasiënt veral tydens aanvang van behandeling en met verhoging van die dosis noukeurig dopgehou word.

Die Sint Janskruid ("St. John's Wort")
Ongewenste reaksies kan meer voorkom tydens die gebruik van **DEPRETA** en kruiepreparate wat Sint Janskruid bevat *(Hypericum perforatum)*.

Bloeding
Daar was verslae van bloedingsafwykings, soos ekgimose, purpura en gastro-intestinale bloeding, met selektiewe serotonienheropnameremmers (SSHR's) en serotonien/noradrenalienheropnameremmers (SNHR's), waaronder **DEPRETA.** Wees versigtig met pasiënte wat antistolmiddels en/of medisyne gebruik wat die bloedplaatjiefunksie beïnvloed [bv. NSAIM's of asetielsalisielsuur (ASA)], en met pasiënte met bekende neiging tot bloeding.

Hiponatremie
Hiponatremie is tydens toediening van **DEPRETA** aangemeld, waaronder gevalle met natriumvlakke laer as 110 mmol/L in die serum. Hiponatremie kan voorkom vanweë die sindroom van ontoepaslike afskeiding van anti-diuretiese hormoon (SOADH). Die meerderheid gevalle van hiponatremie is in bejaardes gerapporteer, veral as dit gekoppel is aan 'n onlangse geskiedenis van of veranderings aan die veranderde vloeistofbalans. Wees versigtig met pasiënte met 'n hoër risiko vir hiponatremie, soos bejaardes, sirrotiese of gedehidreerde pasiënte, of pasiënte wat met diuretika behandel word.

Staking van behandeling
Onttrekkingsimptome is algemeen as behandeling gestaak word en veral as dit skielik gedoen word (kyk afdeling 4.8). In kliniese toetse is ongewensde voorvalle na skielike staking van die behandeling gesien in ongeveer 45 % van die pasiënte wat met **DEPRETA** behandel is en in 23 % van die pasiënte wat placebo gekry het. Die risiko vir onttrekkingsimptome wat met SSHR's en SNHR's gesien is, kan van verskeie faktore afhang, waaronder die duur en die dosis van behandeling en tempo van verlaging van die dosis. Die mees algemene reaksies word in afdeling 4.8 gelys. Oor die algemeen is hierdie simptome is lig tot matig, maar in party pasiënte kan dit ernstig wees. Hulle kom gewoonlik binne die eerste paar dae na staking van behandeling voor, maar daar was uiters min verslae van sulke simptome in pasiënte wat per ongeluk dosis oorgeslaan het. Oor die algemeen is hierdie simptome selfbeperkend en klaar gewoonlik binne 2 weke op, maar in sommige individue kan hulle langer voortduur (2 tot 3 maande of meer). Dit word dus aanbeveel dat **DEPRETA** geleidelik oor tydperk van nie minder nie as 2 weke, volgens die pasiënt se behoeftes afgeskaal moet word wanneer behandeling gestaak word (kyk afdeling 4.2).

Bejaardes
Data oor die gebruik van 120 mg **DEPRETA** vir bejaarde pasiënte met ernstige depressie is beperk. Wees daarom versigtig wanneer bejaardes met die maksimum dosis behandel word (kyk afdelings 4.2 en 5.2).

Akatisie/psigomotoriese rusteloosheid
Die gebruik van **DEPRETA** gaan gepaard met die ontwikkeling van akatisie, wat gekenmerk word deur subjektief onaangename of ontstellende rusteloosheid en behoefte om aanhoudend te beweeg en dikwels saam met onvermoë om te stil sit of te staan. Dit gebeur meer dikwels in die eerste paar weke van behandeling. 'n Verhoging in die dosis kan nadelig wees vir pasiënte wat hierdie simptome ondervind.

Medisyne wat duloksetien bevat
Duloksetien word onder verskillende name vir verskillende aanduidings gebruik. Die gelyktydige gebruik van meer as een van hierdie produkte moet vermy word.

Hepatitis/hoë vlakke lewerensieme
Gevalle van lewerbesering, waaronder erge verhogings in vlakke van lewerensieme (> 10 keer die boonste limiet van normaal), hepatitis en geelsug is met **DEPRETA** aangemeld (kyk afdeling 4.8). Sommige gevalle hou verband met oormatige alkoholgebruik. Die meeste daarvan het in die eerste maande van behandeling voorgekom. Die patroon van lewerskade was hoofsaaklik hepatosellulêr. **DEPRETA** moet versigtig met pasiënte wat behandel word met ander medisyne wat met lewerbesering gepaardgaan. **DEPRETA** moet versigtig gebruik word deur pasiënte met verswakte kardiovaskulêre funksie.

Seksuele disfunksie
DEPRETA kan simptome van seksuele disfunksie veroorsaak (kyk afdeling 4.8). Dit kan ondanks die staking van **DEPRETA** voortgaan.

Sukrose
DEPRETA bevat sukrose. Pasiënte met die seldsame oorerflike probleme van onverdraagbaarheid van fruktose, glukose-galaktose-wanbsorpsie of sukrose-isomaltasegebrek moet nie hierdie medisyne gebruik nie.

4.5 Interaksies met ander medisyne en ander vorms van interaksie

Monoamienoksidaseremmers (MAOR's): As gevolg van die risiko van serotoniensindroom, moet duloksetien nie saam met monoamienoksidaseremmers (MAO-remmers) gebruik word nie of nie binne ten minste 14 dae nadat die behandeling met 'n MAOR gestaak is nie. Op grond van die halfleeftyd van duloksetien, moet minstens 5 dae toegelaat word nadat **DEPRETA** gestaak is voordat met 'n MAO-remmer begin word (kyk afdeling 4.3).

CYP1A2-remmers: Aangesien CYP1A2 betrokke is by metabolisme van duloksetien, sal gebruik van duloksetien saam met kragtige remmers van CYP1A2 waarskynlik hoër konsentrasies duloksetien tot gevolg hê. Fluvoksamien (100 mg een keer per dag), 'n kragtige remmer van CYP1A2, het die skynbare plasma-opruiming van duloksetien met ongeveer 77 % verlaag en AOK_{0-t} 6-voudig verhoog. Wees versigtig wanneer **DEPRETA** saam met CYP1A2-remmers toegedien word en 'n laer dosis **DEPRETA** moet gebruik word.

Medisinale produkte vir die SSS: Die risiko om **DEPRETA** in kombinasie met ander SSS-aktiewe medisyne te gebruik, is nie stelselmatig geëvalueer nie, behalwe in die gevalle wat in hierdie afdeling beskryf word. Wees dus versigtig wanneer **DEPRETA** in kombinasie met ander sentraalwerkende medisyne of stowwe, waaronder alkohol en kalmeermiddels (bv. bensodiasepiene, morfinomimetika, antipsigotika, fenobarbitoon, kalmerende antihistamiene) gebruik word.

Serotonerge medisyne: Die serotoniensindroom is in enkele gevalle gerapporteer in pasiënte wat SSHR's/SNHR's saam met serotonergiese medisyne gebruik het. Wees versigtig as **DEPRETA** gebruik word saam met serotonerge middels soos SSHR's, SNHR's, trisikliese antidepressante soos klomipramien of amitriptilien, Sint Janskruid (Hypericum perforatum) of triptane, tramadol, petidien en triptofaan (kyk afdeling 4.4). Gebruik saam met MAOR's, waaronder moklobemied of linesolied, is teenaangedui (kyk hier bo en afdeling 4.3)

Effekte van duloksetien op ander medisinale produkte
Medisyne wat deur CYP1A2 gemetaboliseer word: Die farmakokinetika van teofillien, 'n CYP1A2-substraat, word nie beduidend deur toediening met **DEPRETA** (60 mg twee keer per dag) beïnvloed nie.

Medisyne wat deur CYP2D6 gemetaboliseer word: Duloksetien is 'n matige remmer van CYP2D6. Toe **DEPRETA** twee keer per dag teen 'n dosis van 60 mg saam met 'n enkele dosis desipramien, 'n CYP2D6-substraat, toegedien is het die AOK van desipramien drievoudig toegeneem. Gelyktydige toediening van duloksetien (40 mg twee keer per dag) verhoog die AOK van tolterodien (2 mg twee keer per dag) by gelykvlakke met 71 %, maar beïnvloed nie die farmakokinetika van sy aktiewe 5-hidroksimetaboliet nie en geen dosisaanpassing word aanbeveel nie. Wees versigtig as **DEPRETA** gegee word saam met medisyne wat hoofsaaklik deur CYP2D6 gemetaboliseer word (risperidoon, trisikliese antidepressante [TAD's], soos nortriptilien, amitriptilien, en imipramien), veral as hulle 'n klein terapeutiese indeks het (soos flekaïnied, propafenone, en metoprolol).

Orale voorbehoedmiddels en ander steroïedmedisyne: Resultate van *in vitro*-studies toon aan dat duloksetien nie die katalitiese aktiwiteit van CYP3A induseer nie. Geen spesifieke *in vivo*-studies van die interaksies met geneesmiddels is gedoen nie.

Antistolmiddels en medisyne teen bloedplaatjies: Wees vanweë 'n groter risiko vir bloeding as gevolg van 'n farmakodinamiese interaksie versigtig wanneer **DEPRETA** met orale antistolmiddels of bloedplaatjiewerende medisyne gekombineer word. Verder is toenames in INR-waardes aangemeld toe **DEPRETA** gegee is aan pasiënte wat met warfarien behandel is. Toediening van **DEPRETA** saam met warfarien by bestendige toestande, aan gesonde vrywilligers, as deel van 'n kliniese farmakologiese studie, het egter nie 'n klinies beduidende verandering in INR vanaf die basislyn of in die farmakokinetika van R- of S-warfarien tot gevolg gehad nie.

Remmers van CYP2D6: Aangesien CYP2D6 betrokke is by metabolisme van **DEPRETA,** sal gebruik van duloksetien saam met kragtige remmers van CYP1A2 waarskynlik hoër konsentrasies van **DEPRETA** tot gevolg hê. Paroksetien (20 mg een keer per dag) het die skynbare opruiming van **DEPRETA** uit plasma met ongeveer 37 % verlaag. Wees versigtig wanneer **DEPRETA** saam met remmers van CYP2D6 (bv. SSHR's) toegedien word.

Effekte van ander medisinale produkte op duloksetien
Teensuurmiddels en H2-antagoniste: Toediening van **DEPRETA** saam met aluminium- en magnesiumbevattende teensuurmiddels, of van **DEPRETA** saam met famotidien, het geen beduidende effek gehad op die tempo of omvang van absorpsie van **DEPRETA** na toediening van 'n orale dosis van 40 mg nie.
Induseerders van CYP1A2: Ontledings van farmakokinetiese data van populasies het getoon dat rokers byna 50 % laer plasmakonsentrasies van **DEPRETA** het vergeleke met nie-rokers.

4.6 Fertiliteit, swangerskap en borsvoeding

Swangerskap
Die veiligheid van **DEPRETA** tydens swangerskap is nie bepaal nie (kyk afdeling 4.3).
Studies met diere het toksisiteit op voortplanting getoon teen sistemiese blootstellingsvlakke (AOK) van **DEPRETA** laer as die maksimum kliniese blootstelling.
Die moontlike risiko vir mense is onbekend.
Epidemiologiese data dui daarop dat die gebruik van SSHR's tydens swangerskap, veral laat in swangerskap, die risiko vir volgehoue pulmonale hipertensie van die pasgebore (VPHP) verhoog. Alhoewel geen studies die verband tussen VPHP en behandeling met 'n SNHR-ondersoek het nie, kan hierdie moontlike risiko met **DEPRETA** nie uitgesluit word nie, as die verwante werkingsmeganisme (remming van die heropname van serotonien) in ag geneem word.
Soos met ander serotonerge medisyne, kan onttrekkingsimptome in die pasgeborene voorkom na gebruik van **DEPRETA** deur die moeder aan die einde van die swangerskap. Stakingsimptome wat met **DEPRETA** gesien word, kan hipotonie, bewing en krieweling, voedingsprobleme, asemhalingsnood en toevalle insluit. Die meeste gevalle het tydens geboorte of binne enkele dae na geboorte voorgekom.

Borsvoeding
DEPRETA word in borsmelk uitgeskei. Die gebruik van **DEPRETA** tydens borsvoeding is teenaangedui (kyk afdeling 4.3).

Fertiliteit
In dierestudies het **DEPRETA** geen invloed op manlike vrugbaarheid gehad nie, en die effekte in vroue was slegs duidelik by dosisse wat moederlike toksisiteit veroorsaak het.

4.7 Effek op vermoë om 'n voertuig te bestuur en masjiene te gebruik

Geen studies van die effek op die vermoë om 'n voertuig te bestuur of masjiene te gebruik is gedoen nie. **DEPRETA** kan met kalmering en duiseligheid gepaardgaan. Pasiënte moet daarop gewys word dat as hulle sedasie of duiseligheid ervaar, hulle potensieel gevaarlike take soos motorbestuur of hantering van masjinerie moet vermy.

4.8 Ongewensde effekte

a. Opsomming van die veiligheidsprofiel
Die mees algemeenste aangemelde newe-reaksies in pasiënte wat met **DEPRETA** behandel is, was naarheid, hoofpyn, droë mond, slaperigheid en duiseligheid. Die meeste van die algemene reaksies was egter lig tot matig; hulle het gewoonlik vroeg in die terapie begin, en die meeste was geneig om te bedaar selfs al is die terapie voortgesit.
Vyandigheid, selfdoodgedagtes en selfbesering is aangemeld in kinders wat met SSHR's of SNHR's soos **DEPRETA** behandel is.

b. Getabuleerde opsomming van nadelige reaksies

Dikwels	**Minder dikwels**	**Frekwensie onbekend**
Infeksies en infestasies		
	Laringitis	
Versteurings van immuunstelsel		
	Anafilaktiese reaksie, Hipersensitiwiteitsversteuring, Angioedeem	
Versteurings van die endokrienstelsel		
	Hipotiroïdisme	
Versteurings in metabolisme en voeding		
Swakker eetlus	Hiperglisemie (veral deur diabetiese pasiënte aangemeld), Dehidrasie, Hiponatremie, SOADH	
Psigiatriese versteurings		
Slaaploosheid Agitasie Laer seksdrang, Angs, Abnormale orgasme, Abnormale drome	Selfdoodgedagtes, Slaapversteurings, Bruksisme, Disoriëntering, Apatie, Selfdoodgedrag, Manie, Hallusinasies, Aggressie en woede	
Versteurings van die senustelsel		
Hoofpyn, Lomerigheid, Duiseligheid, Letargie, Bewerasie, Parestesie	Mioklonus, Akatisie, Senuagtigheid, Versteuring in aandag, Smaakversteuring, Diskinesie, Rustelosebeensindroom, Swak gehalte slaap, Serotoniensindroom Konvulsies, Psigomotoriese onrustigheid, Ekstra-piramidale simptome	
Versteurings van die oë		
Dowwe visie	Midriase, Swak visie, Gloukoom	
Versteurings van die ore en labirint		
Tinnitus	Vertigo, Oorpyn	
Versteurings van die hart		
Palpitasies	Tagikardie, Supraventrikulêre disritmie, hoofsaaklik atriale fibrillasie	
Vaskulêre versteurings		
Hoë bloeddruk , Blosing Gloede	Sinkopee Hipertensie, Ortostatiese hipotensie, Perifere koudheid, Hipertensiewe krisis	
Respiratoriese, toragiese en mediastinale versteurings		
Gaap	Toe keel, Epistakse, Interstisiële longsiekte, Eosinofiele longontsteking	
Gastro-intestinale versteurings		
Naarheid, Droë mond, Hardlywigheid, Diarree, Buikpyn, Braking, Dispepsie, Winderigheid	Gastro-intestinale bloeding, Gastro-enteritis, Eruktasie, Gastritis, Disfagie Stomatitis, Hematochesie, Asemreuk, Mikroskopiese kolitis	
Hepatobiliêre versteurings		
	Hepatitis, Hoër vlakke lewerensieme (ALT, AST, alkaliese fosfatase) Lewerversaking , Geelsug	
Versteurings van die vel en subkutane weefsel		
Meer sweet, Veluitslag	Nagsweet, Urtikarie, Kontakdermatitis, Koue sweet, Fotosensitiwiteitsreaksies, Groter neiging om te kneus, Stevens-Johnsonsindroom	Kutane vaskulitis
Versteurings van muskuloskeletale stelsel en van die bindweefsel		
Muskuloskeletale pyn, Spierspasma	Stywe spiere, Spiertrekkings ,Trismus	
Versteurings van die niere en urien		
Disurie Pollakiurie	Urienretensie, Huiwerige urinering, Nokturie, Poliurie, Minder urienvloei, Urienreuk abnormaal	
Versteurings van die voortplantingstelsel en borste		
Ereksiedisfunksie, Ejakulasie-versteuring, Vertraagde ejakulasie	Ginekologiese bloeding, Menstruasie-afwykings, seksuele disfunksie, Testikelpyn, Menopousale simptome, Galaktorree, Hiperprolaktinemie	
Algemene versteurings en effekte by die plek van toediening		
Struikeling Moegheid	Pyn in die borskas, Voel abnormaal, Voel koud, Dors, Kouekoors, Ongesteldheid, Voel warm, Versteuring in gang, Hoë bloeddruk, Hepatiese laboratoriumbevindinge	
Laboratoriumtoetse		
Gewigsverlies	Toename in gewig, Hoër vlakke kreatienfosfokinase in die bloed, Hoër vlakke kalium in die bloed, Hoër vlakke cholesterol in die bloed	

c. Beskrywing van spesifieke nadelige reaksies
Staking van **DEPRETA** (veral as dit skielik is) lei gewoonlik tot onttrekkingsimptome. Duiseligheid, sensoriese versteurings (waaronder parestesie of elektriese skokagtige sensasies, veral in die kop), slaapstoornisse (waaronder slapeloosheid en intense drome), moegheid, slaperigheid, agitasie of angs, naarheid en/of braking, bewing, hoofpyn, mialgie, geïrriteerdheid, diarree, hiperhidrose en vertigo is die mees algemene reaksies.
Oor die algemeen is hierdie simptome, vir SSHR's en SNHR's, is lig tot matig en selfbeperkend, maar in party pasiënte kan hulle ernstig wees en/of lank duur. Dit word daarom aanbeveel dat as behandeling met **DEPRETA** nie meer nodig is nie 'n geleidelike staking deur afskaling van die dosis gedoen word (kyk afdelings 4.2 en 4.4).

In die 12-week-akute fase van drie kliniese toetse met duloksetien met pasiënte met diabetiese neuropatiese pyn, is klein maar statisties beduidende toenames in vastende bloedglukosevlakke waargeneem in pasiënte wat met duloksetien behandel is. HbA1c was stabiel in sowel pasiënte wat met duloksetien en placebo behandel is. In die verlengingsfase van hierdie studies, wat tot 52 weke geduur het, was daar 'n toename in HbA1c in beide die duloksetien- en roetineversorgingsgroepe, maar die gemiddelde toename was 0,3 % groter in die groep wat met duloksetien behandel is. Daar was ook 'n klein toename in vastende bloedglukose- en totale cholesterolvlakke in pasiënte wat met duloksetien behandel is, terwyl die laboratoriumtoetse 'n effense afname in die groep met roetineversorging getoon het.

Die hartklop-gekorrigeerde QT-interval van pasiënte wat met duloksetien behandel is, het nie verskil van dit wat in placebo-behandelde pasiënte gesien is nie. Geen klinies beduidende verskille is waargeneem vir QT-, PR-, QRS- of QTcB-metings tussen pasiënte wat met duloksetien of placebo behandel was nie.

Aanmeld van vermeende nadelige reaksies
Dit is belangrik om vermeende nadelige reaksies wat na magtiging van die medisyne voorkom, aan te meld. Dit maak voortgesette monitering van die balans tussen voordeel en risiko vir die medisyne moontlik. Gesondheidsorgverskaffers word versoek om vermeende nadelige reaksies by SAHPRA aan te meld die vorm "6.04 Adverse Drug Reaction Reporting Form" wat aanlyn by SAHPRA se publikasies gekry kan word:
https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA

4.9 Oordosis
Gevalle van oordosisse, alleen of in kombinasie met ander medisyne, met dosisse van 5400 mg duloksetien is gerapporteer. 'n Paar sterftes het voorgekom, hoofsaaklik met gemengde oordosisse, maar ook met slegs duloksetien teen 'n dosis van ongeveer 1000 mg. Tekens en simptome van 'n oordosis duloksetien alleen of in kombinasie met ander medisyne is onder meer slaperigheid, koma, serotoniensindroom, aanvalle, braking en tagikardie.
Geen spesifieke teenmiddel vir duloksetien is bekend nie, maar as die serotoniensindroom ontstaan, kan spesifieke behandeling (soos met siproheptadien en/of temperatuurbeheer) oorweeg word. 'n Oop lugweg moet gehandhaaf word. Monitering van die hart en vitale tekens word saam met geskikte simptomatiese en ondersteunende maatreëls aanbeveel. Geaktiveerde houtskool kan nuttig wees om absorpsie te beperk. Duloksetien het 'n groot volume van verspreiding dit is onwaarskynlik dat gedwonge diurese, hemoperfusie en transfusie van enige waarde sal wees.

5 FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe
Kategorie en klas: A.1.2 Psigoanaleptika (antidepressante)
Farmakoterapeutiese groep: Ander antidepressante. ATC-kode: N06AX21.

Werkingsmeganisme
Duloksetien is 'n gekombineerde serotonien- (5-hidroksitriptamien, 5-HT) en noradrenalien (NA) (norepinefrien) heropnameremmer. Dit rem die heropname van dopamien swak, met geen beduidende affiniteit vir histaminerge, dopaminerge, cholinerge en adrenerge reseptore nie. Duloksetien verhoog ekstrasellulêre vlakke van serotonien en noradrenalien (norepinefrien) in verskillende breingebiede van diere dosisafhanklik.

Neurochemiese en gedragstudies met laboratoriumdiere het 'n verbetering van beide serotonien- en noradrenalien (norepinefrien) neurotransmissie in die sentrale senustelsel (SSS) getoon.

Die vermeende werkingsmeganisme van duloksetien in die behandeling van depressie is vermoedelik vanweë die remming van neuronale opname van serotonien en norepinefrien en 'n gevolglike toename in serotonerge en noradrenerge neurotransmissie in die SSS.
Dit word geglo dat die pynverlagende werking van duloksetien die gevolg is van versterking van dalende remmende pynroetes binne die sentrale senustelsel.

5.2 Farmakokinetiese eienskappe
Duloksetien word as 'n enkele enantiomeer toegedien. Duloksetien word grootskaals deur oksidatiewe ensieme (CYP1A2 en die polimorfe CYP2D6) gemetaboliseer, gevolg deur konjugasie. Die farmakokinetika van duloksetien toon groot wisseling tussen persone (gewoonlik 50-60 %), deels as gevolg van geslag, ouderdom, rookstatus en CYP2D6-metaboliseringstatus.

Absorpsie: Duloksetien word na orale toediening vinnig geabsorbeer met C_{maks} binne 2 uur na dosering. Die absolute orale biobeskikbaarheid van duloksetien wissel van 32 % tot 80 % (gemiddeld van 50 %). Voedsel vertraag die tyd om die piek konsentrasie te bereik van 6 tot 10 uur, en dit verminder die mate van absorpsie (ongeveer 11%). Hierdie veranderinge het geen kliniese betekenis nie. Gelykvlakke in die plasma word na dosering van 3 dae bereik.

Verspreiding: Ongeveer 96 % van die duloksetien is aan plasmaproteïene gebind. Duloksetien bind aan sowel albumien as aan alfa1-suurglikoproteïen. Proteïenbinding word nie deur swak nier- of lewerfunksie beïnvloed nie.

Biotransformasie: Duloksetien word tot 'n groot mate gemetaboliseer en die metaboliete word hoofsaaklik in die urien uitgeskei. Beide sitochroom P450-2D6 en 1A2 kataliseer die vorming van die twee belangrikste metaboliete, glukuroniedkonjugaat van 4-hidroksiduloksetien en sulfaatkonjugaat van 5-hidroksi-6-metoksiduloksetien. Op grond van *in vitro*-studies word die sirkulerende metaboliete van duloksetien as farmakologies onaktief beskou. Die farmakokinetika van duloksetien in pasiënte wat swak metaboliseerders met betrekking tot CYP2D6 is, is nie spesifiek ondersoek nie. Beperkte data dui daarop dat die plasmavlakke van duloksetien in hierdie pasiënte hoër is.

Uitskeiding: Die uitskeidingshalfleeftyd van duloksetien wissel tussen 8 en 17 uur (gemiddeld 12 uur). Na 'n intraveneuse dosis wissel die plasma-opruiming van duloksetien van 22 L/uur tot 46 L/uur (gemiddeld 36 L/uur). Na 'n orale dosis wissel die skynbare plasma-opruiming van duloksetien van 33 tot 261 L/uur (gemiddeld 101 L/uur).

Spesiale populasies
Geslag: Farmakokinetiese verskille is tussen mans en vroue geïdentifiseer (skynbare plasma-opruiming is ongeveer 50 % laer in vroue). Op grond van die oorvleueling in die opruiming, regverdig farmakokinetiese verskille tussen geslagte nie die aanbeveling om 'n laer dosis vir vroulike pasiënte te gebruik nie.

Ouderdom: Farmakokinetiese verskille is geïdentifiseer tussen jonger en bejaarde vroue (≥ 65 jaar) (AOK ongeveer 25 % hoër en die halfleeftyd is ongeveer 25% langer in bejaardes), hoewel die omvang van hierdie veranderinge nie voldoende is om aanpassings in die dosis te regverdig nie. As algemene aanbeveling moet bejaardes versigtig behandel word (kyk afdelings 4.2 en 4.4).

Swak nierfunksie: Die C_{maks} en AOK-waardes van duloksetien van pasiënte met eindstadium niersiekte (ESNS) wat dialise ontvang het, is twee keer hoër as in gesonde proefpersone. Farmakokinetiese data van duloksetien in pasiënte met ligte tot matige swak nierfunksie is beperk.

Swak lewerfunksie: Matige lewersiekte (Child-Pugh Klas B) beïnvloed die farmakokinetika van duloksetien. In vergelyking met gesonde proefpersone is die skynbare plasma-opruiming van duloksetien 79 % laer, die skynbare terminale halfleeftyd is 2,3 keer langer en die AOK is 3,7 keer hoër in pasiënte met matige lewersiekte. Die farmakokinetika van duloksetien is nog nie in pasiënte met matige tot erge swak lewerfunksie bestudeer nie.

Voedende moeders: Die verdeling van duloksetien is bestudeer in 6 lakterende vroue wat minstens 12 weke postpartum was. Duloksetien word in borsmelk opgespoor, en die konsentrasies by gelykvlakke in borsmelk is ongeveer 'n kwart van dié in plasma. Die hoeveelheid duloksetien in borsmelk is ongeveer 7 µg/dag met toediening van 40 mg tweemaal per dag. Laktasie het geen invloed op die farmakokinetika van duloksetien nie.

6 FARMASEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe
Die ander bestanddele van **DEPRETA** is suikersfere, hipromellose, hidroksipropielsellulose, kruispovidoon, talk, triëtielsitraat en titaandioksied.
DEPRETA: Die kapsuledop bevat gelatien, natriumlourielsulfaat, FD & C Blue 2 (CI Nr.: 73015), titaandioksied (CI Nr.: 77891).
DEPRETA: Die swart ink bevat skellak, gedehidreerde alkohol, isopropielalkohol, butielalkohol, propileenglikol, sterk ammoniakoplossing, swart ysteroksied (CI Nr.: 77499) en kaliumhidroksied.

6.2 Onverenigbaarhede
Nie toepaslik nie

6.3 Rakleeftyd
36 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring
Bêre by of onder 25 ºC.
Hou die stulpstroke in die karton totdat dit benodig word.
Hou die HDPE-houers dig geslote.
HOU BUITE BEREIK VAN KINDERS.

6.5 Aard en inhoud van die houer
DEPRETA 30:
1) Stulppak:
Kapsules is verpak in 60 mikron-PVC-film/25 mikron-poliamied/60 mikron-aluminiumfolie/60 mikron-PVC-film as die vormende materiaal en 25 µm aluminiumfoelie met 7 g/vkm hitteseëllak as dekmateriaal.
__Pakgroote: 30s__ - elke karton bevat 3 stulpstroke met 10 kapsules elk.

2) HDPE-pak:
Wit ondeursigtige ronde HDPE-houer van 40 mL met nek van 33 mm met wit ondeursigtige, geribde prop van polipropileen van 33 mm, met induksie-seëlvoering wat een 1 g silika-sakkie bevat.
__Pakgroote: 30s__ - een HDPE-houer bevat 30 kapsules.

DEPRETA 60:
Stulppak:
Kapsules is verpak in 60 mikron-PVC-film/25 mikron-poliamied/60 mikron-aluminiumfolie/60 mikron-PVC-film as die vormende materiaal en 25 µm aluminiumfoelie met 7 g/vkm hitteseëllak as dekmateriaal.
__Pakgroote: 30s__ - elke karton bevat 3 stulpstroke met 10 kapsules elk.

2) HDPE-pak:
Wit ondeursigtige ronde HDPE-houer van 40 mL met nek van 33 mm met wit ondeursigtige, geribde prop van polipropileen van 33 mm, met induksie-seëlvoering wat een 1 g silika-sakkie bevat.

__Pakgroote: 30s__ - een HDPE-houer bevat 30 kapsules.

6.6 Spesiale voorsorgmaatreëls vir die wegdoen van gebruikte medisyne of afvalstowwe wat uit sodanige medisyne verkry word, en ander hantering van die produk
Alle ongebruikte medisinale produk of oorblywende materiaal moet volgens plaaslike vereistes weggedoen word.

7 HOUER VAN DIE REGISTRASIESERTIFIKAAT
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Phillip Engelbrechtlaan 53
Meyersdal Uitbr. 12, 1448
Johannesburg
Suid-Afrika

8 REGISTRASIENOMMER(S)
DEPRETA 30: 47/1.2/0097
DEPRETA 60: 47/1.2/0098

9 DATUM VAN EERSTE MAGTIGING
13 April 2021

P1527346

DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBLAD

S5

DEPRETA 30 (kapsules)
DEPRETA 60 (kapsules)
Duloksetienhidrochloried.
Bevat suiker: 78 mg en 156 mg sukrose onderskeidelik.

Lees hierdie hele blad noukeurig deur voordat u begin om DEPRETA te drink.
- Hou hierdie blad. Dit mag nodig wees dat u dit weer moet lees.
- As u nog vrae het, moet u asseblief vir u dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer vra.
- **DEPRETA** is vir u persoonlik voorgeskryf en u moet nie u medisyne vir ander mense gee nie. Dit kan hulle skaad, selfs al is hulle simptome dieselfde as u s'n.

Wat in hierdie blad is:
1. Wat **DEPRETA** is en waarvoor dit gebruik word
2. Wat u moet weet voordat u **DEPRETA** gebruik
3. Hoe om **DEPRETA** te gebruik
4. Moontlike newe-effekte
5. Hoe om **DEPRETA** te bêre
6. Inhoud van die pak en ander inligting

1. Wat DEPRETA is en waarvoor dit gebruik word
DEPRETA bevat die aktiewe stof duloksetien. Duloksetien verhoog die vlakke van serotonien en noradrenalien in die senustelsel.
DEPRETA word gebruik om die volgende te behandel:
- depressie
- diabetiese neuropatiese pyn (dikwels beskryf as brand, steek, prik, skiet of seer of soos van 'n elektriese skok. Daar kan 'n verlies aan gevoel in die aangetaste area wees, of sensasies soos aanraking, hitte, koue of druk kan pyn veroorsaak).

2. Wat u moet weet voordat u DEPRETA gebruik
Moenie DEPRETA drink nie as u:
- allergies vir duloksetien of vir enige van die ander bestanddele van hierdie medisyne is
- swanger is of borsvoed
- 'n lewersiekte het
- 'n erge niersiekte het
- medisyne bekend as 'n monoamienoksidaseremmer (MAOR) drink of dit in die afgelope 14 dae gedrink het
- **DEPRETA** moet nie vir kinders jonger as 18 jaar gebruik word nie, aangesien veiligheid nie bepaal is nie.

Waarskuwings en voorsorgmaatreëls
Wees veral versigtig met DEPRETA as u:
- ander medisyne vir die behandeling van depressie gebruik
- Sint Janskruid (Hypericum perforatum), 'n kruiemiddel, gebruik
- 'n niersiekte het
- toevalle (stuiptrekkings) gehad het
- aan bipolêre versteuring ly
- oogprobleme het, soos sekere tipes gloukoom (hoër druk in die oë)
- 'n geskiedenis van bloedingsversteurings het (geneig is om kneusplekke te kry)
- 'n risiko vir lae natriumvlakke het (as u byvoorbeeld diuretika drink en veral as u bejaard is)
- hoë bloeddruk het
- tans met ander medisyne behandel word wat lewerskade kan veroorsaak of as u alkohol in groot hoeveelhede gebruik
- **DEPRETA** kan 'n gevoel van rusteloosheid veroorsaak of die onvermoë om stil te sit of stil te staan.
- As u depressief is, kan u soms daaraan dink om uself te beseer of dood te maak. Dit kan erger word as u met behandeling met antidepressante begin, aangesien hierdie medisyne tyd neem om te werk, gewoonlik ongeveer twee weke, maar soms langer.

Ander medisyne en DEPRETA:
Sê altyd vir u gesondheidspraktisyn as u enige ander medisyne gebruik (waaronder aanvullende of tradisionele medisyne).
DEPRETA kan 'n effek op ander medisyne hê, of ander medisyne kan 'n effek op **DEPRETA** hê.
- Monoamienoksidaseremmers (MAOR's): u mag **DEPRETA** nie drink as u 'n ander antidepressant, 'n monoamienoksidaseremmer (MAO-remmer), gebruik of onlangs (binne die afgelope 14 dae) gebruik het nie. Voorbeelde van MAO-remmers is moklobemied ('n antidepressant) en linesolied ('n antibiotikum). Gebruik van 'n MAOR saam met verskeie voorskrifmiddels, waaronder **DEPRETA**, kan ernstige of selfs lewensgevaarlike newe-effekte veroorsaak. U moet ten minste 14 dae wag nadat u opgehou het om linesolied of 'n MAOR te drink voordat u **DEPRETA** kan drink. U moet ook ten minste 5 dae wag nadat u opgehou het om **DEPRETA** te drink voordat u 'n MAOR drink.
- Medisyne wat slaperigheid veroorsaak: dit is onder meer medisyne wat u dokter voorskryf, waaronder bensodiasepiene, sterk pynstillers, antipsigotika, fenobarbitoon, antihistamiene.
- Medisyne wat die serotonienvlak verhoog: triptane, tramadol, triptofaan, SSHR's (selektiewe serotonienheropnameremmers soos paroksetien en fluoksetien), SNHR's (serotonien-noradrenalienheropnameremmers), trisikliese antidepressante (soos klomipramien, amitriptilien), petidien, Sint Janskruid en MAOR's. Hierdie medisyne verhoog die risiko vir newe-effekte; as u enige ongewone simptome kry as u **DEPRETA** drink, moet u u dokter raadpleeg.
- Orale antistolmiddels of medisyne teen bloedplaatjies: medisyne wat die bloed dun maak of voorkom dat die bloed stol. Hierdie medisyne kan die risiko vir bloeding verhoog.

Die hoofbestanddeel van **DEPRETA**, duloksetien, word ook in ander medisyne vir ander toestande gebruik. U moet nie een van hierdie medisynes op dieselfde tyd as **DEPRETA** gebruik nie. Sê vir u dokter as u reeds ander medisyne gebruik wat duloksetien bevat.

DEPRETA saam met voedsel en drank
DEPRETA kan met of sonder voedsel gedrink word.

Swangerskap, borsvoeding en vrugbaarheid
U moet nie **DEPRETA** drink as u swanger is nie (kyk "Moenie **DEPRETA** drink nie").
As u swanger is of u baba borsvoed, moet u u dokter, apteker of ander gesondheidskundige asseblief om advies raadpleeg voordat u **DEPRETA** drink.
Sê vir u dokter as u borsvoed. Die gebruik van **DEPRETA** tydens borsvoeding is teenaangedui (kyk "Moenie **DEPRETA** drink nie").

Motorbestuur en gebruik van masjinerie
DEPRETA kan u lomerig of duiselig maak. Moenie 'n voertuig bestuur of enige gereedskap of masjiene gebruik nie totdat u weet hoe DEPRETA u beïnvloed.

DEPRETA bevat sukrose
DEPRETA bevat sukrose wat 'n tipe suiker is.
As u dokter vir u gesê het dat u 'n onverdraagbaarheid teenoor sekere suikers het, moet u u dokter skakel voordat u hierdie medisyne gebruik.

3. Hoe om DEPRETA te drink
Moenie medisyne wat vir u voorgeskryf is vir enige ander persoon gee nie.

DEPRETA is vir mondelinge gebruik. U moet u kapsule heel met 'n glas water afsluk.

__Vir depressie en diabetiese neuropatiese pyn:__

Die gewone dosis **DEPRETA** is een kapsule (60 mg duloksetien) een keer per dag, maar u dokter sal die dosis voorskryf wat vir u reg is.

Drink **DEPRETA** altyd presies soos wat u dokter vir u gesê het. Raadpleeg u dokter of apteker as u nie seker is nie. U dokter sal vir u sê hoe lank u behandeling met **DEPRETA** sal duur. Moenie met u behandeling ophou sonder om u dokter te raadpleeg nie. Praat met u dokter of apteker as u die indruk het dat **DEPRETA** te sterk of te swak is.

As u meer DEPRETA gedrink het as wat u moes
Raadpleeg jou dokter of apteker in geval van oordosering. As nie een beskikbaar is nie, kontak die naaste hospitaal of gifsentrum.

As u meer as die benodigde dosis drink, kan u simptome ervaar wat slaperigheid, koma, die serotoniensindroom ('n seldsame reaksie wat gevoelens van groot geluk, slaperigheid, lomperheid, rusteloosheid, dronk gevoel, koors, sweet of stywe spiere kan veroorsaak) toevalle, braking en vinnige hartklop kan insluit.
As u vergeet om DEPRETA te drink
As u vergeet om dosis te drink, drink dit sodra as wat u dit onthou, behalwe as dit bykans tyd vir u volgende dosis is. Moenie 'n dubbele dosis drink om vir vergete individuele dosisse op te maak nie.

4. Moontlike newe-effekte
DEPRETA kan newe-effekte veroorsaak.
Nie al die newe-effekte wat vir **DEPRETA** aangemeld is, is in hierdie blad opgeneem nie. As u algemene gesondheidstoestand versleg of as u enige newe-effekte ervaar terwyl u **DEPRETA** drink, moet u u gesondheidsorgverskaffer om advies raadpleeg.

Indien enige van die volgende voorkom, moet u ophou om **DEPRETA** te drink en onmiddellik vir u dokter sê of na die ongevalle-afdeling van u naaste hospitaal gaan:
- Moeilike asemhaling of duiseligheid met geswelde tong of lippe

Hierdie is almal baie ernstige newe-effekte. As u dit ervaar, kan dit wees dat u 'n ernstige allergiese reaksie op **DEPRETA** het. Dit mag wees dat u dringende mediese aandag of hospitalisasie nodig het.

Sê dadelik vir u dokter of gaan na die ongevalle-afdeling van u naaste hospitaal as u enige van die volgende opmerk:
- selfdoodgedagtes
- selfdoodgedrag, selfbesering, manie (ooraktiwiteit, jagende gedagtes en kleiner behoefte aan slaap), hallusinasies, aggressie en woede

Dit is ernstige newe-effekte. Dit mag wees dat u dringende mediese aandag nodig het.
Sê vir u dokter as u enige van die volgende opmerk:
Die volgende newe-effekte kom dikwels voor:
- hoofpyn, voel vaak
- voel naar (naarheid), droë mond
- gebrek aan eetlus
- angs, laer seksdrang, probleme met of onvermoë om 'n orgasme te ervaar, ongewone drome
- duiseligheid, trae gevoel, bewing, gevoelloosheid, waaronder gevoelloosheid, prikkeling of tinteling in die vel
- dowwe visie
- tinnitus (hoor klank in die oor as daar geen eksterne geluid is nie)
- voel die hart in die borskas pomp
- hoë bloeddruk, blosing
- meer gaap
- hardlywigheid, diarree, maagpyn, braking, sooibrand of slegte spysvertering, winde breek
- meer sweet, (jeukende) uitslag
- spierpyn, spierspasmas
- pynlike urinering, aanhoudende urinering
- probleme om 'n ereksie te kry, veranderinge in ejakulasie
- struikeling (meesal in bejaarde persone), moegheid
- gewigsverlies

Die volgende newe-effekte kom minder dikwels voor:
- keelontsteking wat 'n hees stem veroorsaak
- kners en maal van tande, voel gedisoriënteerd, gebrek aan motivering
- skielike onwillekeurige rukke of trekkings van die spiere, gevoel van rusteloosheid of 'n onvermoë om stil te sit of stil te staan, voel senuweeagtig, probleme om te konsentreer, veranderinge in smaaksensasie,
- probleme om beweging te beheer, bv. gebrek aan koördinasie of onwillekeurige bewegings van die spiere, rustelosebenesindroom
- groot pupille (die donker middelpunt van die oog), probleme met sig
- voel duiselig of dat alles "draai" (vertigo), oorpyn
- vinnige en/of onreëlmatige hartklop
- floute, duiseligheid, lighoofdigheid of floute tydens opstaan, koue vingers en/of tone
- toe keel, neusbloedings
- braking van bloed, of swart teeragtige stoelgang (feses),
- gastro-enteritis, winde opbreek, sukkel om te sluk
- inflammasie van die lewer wat buikpyn en geel verkleuring van die vel of wit van die oë kan veroorsaak
- nagsweet, galbulte, koue sweet, sensitiwiteit vir sonlig, groter neiging tot kneusplekke
- spierstyfheid, spiertrekkings
- probleme of onvermoë om te urineer, probleme om te begin urineer, gedurende die nag moet urineer, meer urien as normaal, met 'n verminderde urienvloei
- abnormale vaginale bloeding, abnormale menstruasies, insluitend swaar, pynlike, onreëlmatige of langdurige menstruasies, buitengewone ligte of oorgeslane menstruasies, pyn in die testikels of skrotum
- pyn op die bors, koue, dors, siddering, warm voel
- abnormale gang
- toename in gewig

As u enige newe-effekte opmerk wat nie in hierdie blad genoem word nie, moet u u dokter of apteker asseblief in kennis stel.

Aanmeld van newe-effekte
Praat met u dokter, apteker of verpleegkundige as u enige newe-effekte kry. Dit sluit alle moontlike newe-effekte in wat nie in hierdie blad gelys word nie. U kan newe-effekte ook by SAHPRA aanmeld via die vorm vir die aanmeld van nadelige geneesmiddelreaksies, naamlik "6.04 Adverse Drug Reaction Reporting Form" wat aanlyn by SAHPRA se publikasies gekry kan word: https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA. Deur newe-effekte aan te meld, kan u help om meer inligting oor die veiligheid van **DEPRETA** te gee.

5. Hoe om DEPRETA te bêre
Bêre by of onder 25 °C.
Hou die stulpstroke in die karton totdat dit benodig word.
Hou die HDPE-houers dig geslote.

HOU ALLE MEDISYNE BUITE BEREIK VAN KINDERS.
Gee alle ongebruikte medisyne terug aan u apteker.
Ongebruikte medisyne moet nie in dreinering- of rioolstelsels (bv. toilette) gegooi word nie.

6. Inhoud van die pak en ander inligting
Wat DEPRETA bevat
Die ander bestanddele van **DEPRETA** is hipromellose, hidroksipropielsellulose, kruispovidoon, talk, triëtielsitraat en titaandioksied.
DEPRETA: Die kapsuledop bevat gelatien, natriumlourielsulfaat, FD & C Blue 2 (CI Nr.: 73015), titaandioksied (CI Nr.: 77891).
DEPRETA: Die swart ink bevat skellak, gedehidreerde alkohol, isopropielalkohol, butielalkohol, propileenglikol, sterk ammoniakoplossing, swart ysteroksied (CI Nr.: 77499) en kaliumhidroksied.

Hoe DEPRETA lyk en die inhoud van die pakkie
DEPRETA 30:
Ondeursigtige blou/ondeursigtige wit grootte 3 hardegelatienkapsule wat wit tot afwit korrels bevat met "DLX" in swart ink op die ondeursigtige blou doppie en "30" op die ondeursigtige wit romp gedruk.

DEPRETA 60:
Ondeursigtige blou/ondeursigtige groen grootte 1 hardegelatienkapsule wat wit tot afwit korrels bevat met "DLX" in swart ink op die ondeursigtige blou doppie en "60" op die ondeursigtige groen romp gedruk.

Stulppak:
Kapsules is verpak in 60 mikron-PVC-film/25 mikron-poliamied/60 mikron-aluminiumfolie/60 mikron-PVC-film as die vormende materiaal en 25 µm aluminiumfoelie met 7 g/vkm hitteseëllak as dekmateriaal.
__Pakgrootte: 30's__ - elke karton bevat 3 stulpstroke met 10 kapsules elk.
HDPE-pak:
Wit ondeursigtige ronde HDPE-houer van 40 mL met nek van 33 mm met wit ondeursigtige, geribde prop van polipropileen van 33 mm, met induksie-seëlvoering wat een 1 g silika-sakkie bevat.

__Pakgrootte: 30's__ - een HDPE-houer bevat 30 kapsules.

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DEPRETA 30: 47/1.2/0097
DEPRETA 60: 47/1.2/0098

Hierdie inligtingsblad is laas hersien in:
13 April 2021