Approved Professional Information for Medicines for Human Use:

Duloxetine DR 30 mg, 60 mg Austell

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Duloxetine DR 30 mg Austell

Duloxetine DR 60 mg Austell

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Duloxetine DR 30 mg Austell:

Each hard gastro-resistant capsule contains Duloxetine hydrochloride equivalent to 30 mg duloxetine.

Duloxetine DR 60 mg Austell:

Each hard gastro-resistant capsule contains Duloxetine hydrochloride equivalent to 60 mg duloxetine.

Contains sugar.

Duloxetine DR 30 mg Austell:

Each hard gastro-resistant capsule may contain up to 100,57 mg sucrose.

Duloxetine DR 60 mg Austell:

Each hard gastro-resistant capsule may contain up to 201,26 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Duloxetine DR 30 mg Austell:

Opaque grey body imprinted with “DLX 30” and an opaque blue cap imprinted with “DLX 30”, length 18,0 mm.

Duloxetine DR 60 mg Austell:

Opaque grey body imprinted with “DLX 60” and an opaque white cap imprinted with “DLX 60”, length 20,4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Duloxetine DR Austell is indicated for the treatment of

- depression (as defined by DSM-IV criteria)
- diabetic peripheral neuropathic pain (DPNP)

4.2 Posology and method of administration

Posology

Depression: Duloxetine DR Austell 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 significantly 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: Duloxetine DR Austell 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 Duloxetine DR Austell should be avoided. When stopping treatment with Duloxetine DR Austell the dose should be gradually reduced over a period of at least two weeks in

order to reduce the risk of withdrawal reactions (see section 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 section 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 and 5.2).

Elderly population

No dosage adjustment is recommended for elderly patients on the basis of age. However, caution should be exercised when treating the elderly, especially with a dose of 120 mg Duloxetine DR Austell per day for depression, for which data are limited.

Paediatric population

Safety and efficacy have not been established in patients under the age of 18 years.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to duloxetine or to any of the excipients listed in section 6.1.

- Pregnancy and lactation. (See section 4.6).
- Severe impairment of hepatic function.
- Advanced renal impairment (creatinine clearance < 30 mL / min).
- Concomitant use of Monoamine oxidase inhibitors (MAOI's). (See sections 4.4 and 4.5).
- 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 with Duloxetine DR Austell, 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 with Duloxetine DR Austell, 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 duloxetine therapy or early after treatment discontinuation (see section 4.8).

Close supervision of patients, and in particular those at high risk, should accompany medicinal product therapy, especially in early treatment of Duloxetine DR Austell 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 Duloxetine DR Austell, 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, Duloxetine DR Austell should be tapered (see below and section 4.2).

Paediatric population and under 18 years

Duloxetine DR Austell should not be used in the treatment of children and adolescents under the age of 18 years as safety and efficacy have 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 4.8). In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking.

Mania and Seizures

Duloxetine DR Austell 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 Duloxetine DR Austell to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Blood Pressure and Heart Rate

Duloxetine as contained in Duloxetine DR Austell, 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 duloxetine, 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 with Duloxetine DR Austell. Duloxetine DR Austell 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 Duloxetine DR Austell 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 Duloxetine DR Austell, either dose reduction or gradual discontinuation should be considered (see section 4.8).

In patients with uncontrolled hypertension, Duloxetine DR Austell should not be initiated.

Renal Impairment

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance < 30 mL / min). For patients with severe renal impairment, see section 4.3. See section 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. A lower starting dose should be used in such patients (see section 4.2).

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine 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 duloxetine and other serotonergic medicines that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation with Duloxetine DR Austell and dose increases.

St John's Wort

Adverse reactions may be more common during concomitant use of Duloxetine DR Austell and herbal preparations containing St John's Wort (*Hypericum perforatum*).

Diabetic Peripheral Neuropathic Pain

As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine 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 when taking Duloxetine DR Austell.

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 duloxetine. 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 Duloxetine DR Austell, 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 with Duloxetine DR Austell 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 Duloxetine 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 reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 - 3 months or more). It is therefore advised that Duloxetine DR Austell 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).

Akathisia/Psychomotor Restlessness

The use of duloxetine 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. Patients taking Duloxetine DR Austell should be warned about this.

Medicinal Products Containing Duloxetine

Duloxetine is used under different trademarks 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 duloxetine (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. Duloxetine DR Austell should be used with caution in patients treated with other medicinal products associated with hepatic injury. Duloxetine DR Austell should also be used with caution in patients with substantial use.

Sexual dysfunction

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

Elderly population

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

Excipients: Sucrose

Duloxetine DR Austell capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-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 Duloxetine DR Austell before starting an MAOI (see section 4.3).

The antibiotic linezolid is a MAOI and should not be given to patients treated with Duloxetine DR Austell (see sections 4.3 and 4.4).

Inhibitors of CYP1A2

Because CYP1A2 is involved in duloxetine metabolism, concomitant use of Duloxetine DR Austell 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 AUCo-t 6-fold. Therefore, Duloxetine DR Austell should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

CNS Medicinal Products

The risk of using duloxetine 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 Duloxetine DR Austell 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

Serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic medicines. Caution is advisable if Duloxetine DR Austell is used concomitantly with serotonergic medicines 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 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 Duloxetine DR Austell (60 mg twice daily).

Medicinal products metabolised by CYP2D6

Duloxetine is a moderate inhibitor of CYP2D6. When Duloxetine DR Austell is 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 Duloxetine DR Austell 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 Duloxetine DR Austell 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 duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of Duloxetine DR Austell 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.

Effects of Other Medicinal Products on Duloxetine

Antacids and H2 antagonists

Co-administration of Duloxetine DR Austell with aluminium- and magnesium-containing antacids, or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine 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 duloxetine compared with non-smokers.

Inhibitors of CYP2D6

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

Medicines highly bound to plasma protein

Duloxetine is highly bound to plasma proteins (> 90 %). Therefore, administration of Duloxetine DR Austell to a patient taking another medicine that is highly protein bound may cause an increase in free concentrations of either medicine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Duloxetine DR Austell in pregnancy has not been established (see section 4.3).

Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine 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 duloxetine, 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 duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

Breastfeeding

Duloxetine is excreted into human milk. The use of Duloxetine DR Austell while breast-feeding is contraindicated (see section 4.3).

Fertility

In animal studies, duloxetine 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 on the effects on the ability to drive and use machines have been performed. Duloxetine DR Austell 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 Duloxetine DR Austell 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 Duloxetine DR Austell.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed from spontaneous reporting and in placebo-controlled clinical trials.

Table 1

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Laryngitis	
Immune system disorders		Anaphylactic reaction, Hyper-sensitivity disorder	

Endocrine disorders		Hypo-thyroidism	
Metabolism and nutrition disorders	Decreased appetite	Hyperglycaemia (reported especially in diabetic patients), Dehydration, Hyponatraemia, SIADH[6]	
Psychiatric disorders	Insomnia, Agitation, Libido decreased, Anxiety, Orgasm abnormal, Abnormal dreams	Suicidal ideation [5,7], Sleep disorder, Bruxism, Disorientation, Suicidal behaviour[5,7], Mania, Hallucinations, Aggression and anger	
Nervous system disorders	Headache, Somnolence, Dizziness, Lethargy, Tremor, Paraesthesia	Myoclonus, Akathisia[7], Nervousness, Disturbance in attention, Dysgeusia. Dyskinesia, Restless legs syndrome, Poor quality sleep, Serotonin syndrome[6], Convulsion[1], Psychomotor restlessness[6], Extra-pyramidal symptoms6	
Eye disorders	Blurred vision	Mydriasis, Visual impairment, Glaucoma	
Ear and labyrinth disorders	Tinnitus[1]	Vertigo, Ear pain	

Cardiac disorders	Palpitations	Tachycardia, Supra-ventricular dysrhythmia, mainly atrial fibrillation	
Vascular disorders	Blood pressure increase[3], Flushing	Syncope[2], Hypertension[3,7], Orthostatic hypotension2, Peripheral coldness, Hypertensive crisis[3,6]	
Respiratory, thoracic and mediastinal disorders	Yawning	Throat tightness, Epistaxis, Interstitial lung disease[10] Eosinophilic pneumonia[6]	
Gastrointestinal disorders	Constipation, Diarrhoea, Abdominal pain, Vomiting, Dyspepsia, Flatulence	Gastrointestinal, haemorrhage[7], Gastroenteritis, Eructation, Gastritis, Dysphagia, Stomatitis, Haematochezia, Breath odour, Microscopic colitis[9]	
Hepatobiliary disorders		Hepatitis[3], Elevated liver enzymes (ALT, AST, alkaline phosphatase), Acute liver injury, Hepatic failure[6], Jaundice[6]	

Skin and subcutaneous tissue disorders	Sweating increased, Rash	Night sweats, Urticaria, Dermatitis contact, Cold sweat, Photosensitivity Reactions, Increased tendency to Bruise, Stevens-Johnson Syndrome[6], Angio-neurotic oedema[6], 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[8], Fatigue	Chest pain[7], feeling abnormal, Feeling cold, Thirst, Chills, Malaise, Feeling hot, Gait disturbance	
Investigations	Weight decrease	Weight increase, Blood creatine phosphokinase increased, Blood potassium Increased, Blood cholesterol increased	

[1] Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.

[2] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

[3] See section 4.4.

[4] Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

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

[6] Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

[7] Not statistically significantly different from placebo.

[8] Falls were more common in the elderly (≥65 years old).

[9] Estimated frequency based on all clinical trial data.

[10] Estimated frequency based on placebo-controlled clinical trials.

c. Description of selected adverse reactions

Discontinuation of duloxetine (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 duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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

Somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

Treatment

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 Pharmacodynamic properties

Pharmacological Classification/Category and Class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants

ATC Code: N06AX21.

Mechanism of action

Duloxetine is a combined serotonin (5-hydroxytrotamine. 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.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. 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 inter-subject variability (generally 50 – 60 %), partly due to gender, age, smoking status, and CYP2D6 metaboliser status.

Absorption

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

Distribution

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

Biotransformation

Duloxetine is extensively metabolized 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 Cmax 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.

Breast-feeding 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 7µg/day while on 40 mg twice-daily dosing. Lactation did not influence duloxetine pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Content

Hydroxypropyl cellulose (Klucel LF)

Hypromellose (E464, E15 LV)

Hypromellose phthalate (HP-55)

Sugar spheres (sucrose, maize starch)

Talc

Triethyl citrate

Capsule Shell

Duloxetine DR Austell 30 mg: Black iron oxide (E172), brilliant blue FCF (FD&C Blue 1) (E133), hypromellose (E464), titanium dioxide (E171).

Duloxetine DR Austell 60 mg: Black iron oxide (E172), hypromellose (E464), titanium dioxide (E171).

Printing ink:

Shellac (E904), dehydrated alcohol (E1510), isopropyl alcohol, butyl alcohol, propylene glycol (E1520), strong ammonia solution (E527), black iron oxide (E172), potassium hydroxide (E525).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from moisture.

6.5 Nature and contents of container

HDPE containers with dessicant:

Pack sizes for 30 mg: 28, 30, 56, 60, 84, 90, 98 and 100 capsules.

Pack sizes for 60 mg: 28, 30, 56, 60, 84 and 90 capsules.

OPA/Alu/PVC-Aluminium foil blister:

Pack sizes for 30 mg: 7, 10, 14, 28, 30 and 100 capsules.

Pack sizes for 60 mg: 7, 10, 14, 28, 30, 56 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

Duloxetine DR 30 mg Austell: 49/1.2/0316

Duloxetine DR 60 mg Austell: 49/1.2/0317

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 December 2020

10. DATE OF REVISION OF THE TEXT

N/A