Professional Information for DULOXETINE XR 30 & 60 BIOTECH

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DULOXETINE XR 30 BIOTECH hard gastro-resistant capsules

DULOXETINE XR 60 BIOTECH hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DULOXETINE XR 30 BIOTECH: Each capsule contains 30 mg duloxetine (as hydrochloride).

DULOXETINE XR 60 BIOTECH: Each capsule contains 60 mg duloxetine (as hydrochloride).

Excipients with known effect:

Contains sugar (sucrose).

DULOXETINE XR 30 BIOTECH: Each capsule contains 51,5 mg sucrose.

DULOXETINE XR 60 BIOTECH: Each capsule contains 103,0 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsules.

DULOXETINE XR 30 BIOTECH: Opaque blue/opaque white, size 3, hard gelatine capsule, with “157” printed on the body and “A” on the cap with green ink, filled with white to off-white pellets.

DULOXETINE XR 60 BIOTECH: Opaque blue/opaque green, size 1, hard gelatine capsule, with “158” printed on the body and “A” on the cap with white ink, filled with white to off-white pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DULOXETINE XR BIOTECH is indicated for:

- The treatment of depression (as defined by DSM-IV criteria).
- The treatment of diabetic peripheral neuropathic pain (DPNP).

4.2 Posology and method of administration

Posology:

Depression:

DULOXETINE XR BIOTECH 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 XR BIOTECH 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 XR BIOTECH should be avoided. When stopping treatment with DULOXETINE XR BIOTECH the dose should be gradually reduced over a period of at least two weeks in order 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:

The initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal

function (see sections 4.4 and 5.2). DULOXETINE XR BIOTECH must not be used in patients with severe renal impairment (see section 4.3).

Hepatic impairment:

The 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).

DULOXETINE XR BIOTECH must not be used in patients with severe hepatic impairment (see section 4.3).

Elderly patients:

No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating elderly patients, especially with a dose of 120 mg DULOXETINE XR BIOTECH per day for depressive disorder, for which data are limited (see sections 4.4 and 5.2).

Paediatric population:

Safety and efficacy have not been established in patients under the age of 18 years. Also see section 4.4.

Method of administration:

For oral use.

4.3 Contraindications

- Hypersensitivity to duloxetine or to any of the components of DULOXETINE XR BIOTECH (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Severe impairment of hepatic function.
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Concomitant use of DULOXETINE XR BIOTECH with monoamine oxidase inhibitors (MAOIs) (see

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:

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
medicines 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 XR BIOTECH therapy or early after treatment discontinuation (see section 4.8).

Close supervision of patients, and in particular those at high risk, should accompany medicine therapy, especially in early treatment and following dose changes.

Patients with major depressive disorder, 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 casual link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing DULOXETINE XR BIOTECH , 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 XR BIOTECH should be tapered (see below and section 4.2).

As with other medicines with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation.
Doctors should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age:
DULOXETINE XR BIOTECH 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 XR BIOTECH 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 XR BIOTECH to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate:

DULOXETINE XR BIOTECH 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 XR BIOTECH, 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. DULOXETINE XR BIOTECH 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 XR BIOTECH is used with medicines that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while treated with DULOXETINE XR BIOTECH, either dose reduction or gradual discontinuation should be considered (see section 4.8).

In patients with uncontrolled hypertension DULOXETINE XR BIOTECH should not be initiated.

Renal impairment:

Increased plasma concentrations of DULOXETINE XR BIOTECH occur in patients with severe renal

impairment on haemodialysis (creatinine clearance < 30 mL/min). A lower starting dose should be used in such patients (see section 4.2). 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 XR BIOTECH 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 XR BIOTECH 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 and dose increases.

St John's wort:

Adverse reactions may be more common during concomitant use of DULOXETINE XR BIOTECH 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 DULOXETINE XR BIOTECH. DULOXETINE XR BIOTECH may increase the risk of postpartum haemorrhage (see section 4.6). Caution is advised in patients taking anticoagulants and/or medicines known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid), and in patients with known bleeding tendencies.

Hyponatraemia:

Hyponatraemia has been reported when administering DULOXETINE XR BIOTECH, including cases with serum sodium lower than 110 mmol/L. Hyponatraemia may be due to a syndrome of inappropriate antidiuretic hormone secretion (SIADH) (see section 4.8). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition predisposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly patients, 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 duloxetine as contained in with DULOXETINE XR BIOTECH 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 XR BIOTECH 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 patients:

Data on the use of 120 mg of DULOXETINE XR BIOTECH in elderly patients with major depressive disorder are 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 DULOXETINE XR BIOTECH 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.

Medicines 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 the upper limit of normal), hepatitis and jaundice have been reported with DULOXETINE XR BIOTECH (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 XR BIOTECH should be used with caution in patients treated with other medicines associated with hepatic injury.

DULOXETINE XR BIOTECH should also be used with caution in patients with sustantial alcohol use.

Sexual dysfunction:

DULOXETINE XR BIOTECH may cause symptoms of sexual dysfunction (see section 4.8). These

may continue despite discontinuation of DULOXETINE XR BIOTECH.

Sucrose:

DULOXETINE XR BIOTECH capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take DULOXETINE XR BIOTECH.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

Due to the risk of serotonin syndrome, DULOXETINE XR BIOTECH 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 XR BIOTECH before starting an MAOI (see section 4.3).

The antibiotic linezolid is an MAOI and should not be given to patients treated with DULOXETINE XR BIOTECH (see sections 4.3 and 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in DULOXETINE XR BIOTECH metabolism, concomitant use of DULOXETINE XR BIOTECH 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 XR BIOTECH by about 77 % and increased AUC_{o-t} 6-fold. Therefore, DULOXETINE XR BIOTECH should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine.

Central nervous system (CNS) medicines: The risk of using DULOXETINE XR BIOTECH in combination with other CNS-active medicines has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when DULOXETINE XR BIOTECH is taken in combination with other centrally-acting medicines or substances, including alcohol and sedative medicines (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 XR BIOTECH 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 MOAIs, including moclobemide or linezolid, is contraindicated (see section 4.3).

Effect of DULOXETINE XR BIOTECH on other medicines:

Medicines metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine as contained in DULOXETINE XR BIOTECH (60 mg twice daily). These results suggest that DULOXETINE XR BIOTECH is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Medicines metabolised by CYP2D6: DULOXETINE XR BIOTECH is a moderate inhibitor of CYP2D6. When duloxetine 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 DULOXETINE XR BIOTECH is co-administered with medicines 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).

Inhibitors of CYP2D6: Because CYP2D6 is involved in DULOXETINE XR BIOTECH metabolism, concomitant use of DULOXETINE XR BIOTECH with inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg once daily) decreased the apparent plasma

clearance of duloxetine by about 37 %. Caution is advised if duloxetine is administered with inhibitors of CYP2D6 (e.g. SSRIs).

Oral contraceptives and other steroidal medicines: Results of *in vitro* studies demonstrate that duloxetine (as in DULOXETINE XR BIOTECH) does not induce the catalytic activity of CYP3A. Specific *in vivo* medicine interaction studies have not been performed.

Anticoagulants and antiplatelet medicines: Caution should be exercised when DULOXETINE XR BIOTECH 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 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.

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

Effects of other medicines on duloxetine:

Antacids and H_2 antagonists: Co-administration of duloxetine 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of DULOXETINE XR BIOTECH in pregnant women has not been established (see section 4.3). Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to DULOXETINE XR BIOTECH within the month prior to birth.

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 new-born (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).

Discontinuation symptoms may occur in the neonate after maternal duloxetine use near term as contained in DULOXETINE XR BIOTECH. 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:

Safety of DULOXETINE XR BIOTECH during breastfeeding has not been established (see section 4.3). DULOXETINE XR BIOTECH and/or its metabolites are excreted into the milk.

Fertility:

In animal studies, DULOXETINE XR BIOTECH 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

DULOXETINE XR BIOTECH 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

Summary of the safety profile:

The most frequent reported adverse reactions in patients treated with DULOXETINE XR BIOTECH 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 XR BIOTECH .

Tabulated summary of adverse reactions:

Frequent	Less frequent
Infections and infestations	
	Laryngitis
Immune system disorders	
	Anaphylactic reaction Hypersensitivity disorder
Endocrine disorders	
	Hypothyroidism
Metabolism and nutrition disorders	
Decreased appetite	Hyperglycaemia (reported especially in diabetic patients) Dehydration Hyponatraemia SIADH[6]
Psychiatric disorders	
Insomnia Agitation Libido decreased Anxiety	Suicidal ideation[5,7] Sleep disorder Bruxism Disorientation

Orgasm abnormal Abnormal dreams	Apathy Suicidal behaviour[5,7] Mania Hallucinations Aggression and anger[4]
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] Convulsions[1] Psychomotor restlessness[6] Extra-pyramidal symptoms[6]
Eye disorders	
Blurred vision	Mydriasis Visual impairment Glaucoma
Ear and labyrinth disorders	
Tinnitus[1]	Vertigo Ear pain
Cardiac disorders	
Palpitations	Tachycardia Supraventricular dysrhythmia,

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

	Jaundice[6] Bilirubin increased
Skin and subcutaneous tissue disorders	
Sweating increased Rash	Night sweats Urticaria Contact dermatitis Cold sweat Photosensitivity reactions Increased tendency to bruise Stevens-Johnson syndrome[6] Angioneurotic oedema[6] Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Musculoskeletal 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 Hyperprolactinaemia Postpartum haemorrhage[6]
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 XR BIOTECH 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.

Description of selected adverse reactions:

Discontinuation of DULOXETINE XR BIOTECH (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 XR BIOTECH 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 DULOXETINE XR BIOTECH is important. It allows continued monitoring of the benefit/risk balance of DULOXETINE XR BIOTECH. Health care providers are asked to report any suspected adverse reactions 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 medicines, with duloxetine doses of 5 400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1 000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicines) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for DULOXETINE XR BIOTECH, 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

Category and class: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Other antidepressants.

ATC code: N06AX21.

Mechanism of action:

Duloxetine is a combined serotonin (5-hydroxytryptamine, 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 intersubject variability (generally 50 – 60 %), partly due to gender, age, smoking status, and CYP2D6 metaboliser status.

Absorption:

Duloxetine is well absorbed after oral administration, with a C_{max} occurring 6 hours post-dose. The

absolute oral bioavailability of duloxetine ranged from 32 % to 80 % (mean of 50 %). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance. Steady-state plasma concentrations are achieved after 3 days of dosing.

Distribution:

Duloxetine is approximately 96 % bound to human plasma proteins. Duloxetine binds to both albumin and alpha$_1$-acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation:

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites, glucuronide conjugate of 4-hydroxy duloxetine and sulphate 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/h to 46 L/h (mean of 36 L/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 L/h to 261 l L/h (mean 101 L/h).

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).

Smoking status:

Duloxetine bioavailability appears to be 34 % lower in smokers than in non-smokers.

Renal impairment:

End-stage renal disease patients receiving chronic intermittent haemodialysis had 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Therefore, a lower dose should be used in patients with clinically significant renal impairment (see sections 4.2 and 4.3).

Hepatic impairment:

The half-life of duloxetine was 34 hours longer in patients with cirrhosis of the liver and clearance was approximately 15 % of that for age and gender-matched healthy subjects. Therefore, a lower dose should be used for patients with mild to moderate liver impairment (see sections 4.2 and 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Sugar spheres (consisting of sucrose and maize starch)

Hypromellose

Talc

Sucrose

Hypromellose phthalate

Triethyl citrate.

Capsule shell:

Gelatine

FD&C Blue 2 (E132)

Titanium dioxide (E171)

Yellow iron oxide (E172) (only in DULOXETINE XR 60 BIOTECH).

Printing ink (edible):

Shellac

Dehydrated alcohol

Isopropyl alcohol

Butyl alcohol

Propylene glycol

Strong ammonia solution

Purified water

Titanium dioxide (E171)

Yellow iron oxide (E172) (only in DULOXETINE XR 30 BIOTECH)

FD&C Blue 2 (E132) (only in DULOXETINE XR 30 BIOTECH)

Potassium hydroxide (only in DULOXETINE XR 60 BIOTECH).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

Silver aluminium/aluminium blister strips, or

Silver aluminium/clear transparent PVC/Aclar blister strips.

Pack sizes: 28, 30 or 80 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

Biotech Laboratories (Pty) Ltd

Ground Floor Block K West Central Park

400 16th Road, Randjespark

Halfway House

Midrand 1685

8. REGISTRATION NUMBERS

DULOXETINE XR 30 BIOTECH: 50/1.2/0849

DULOXETINE XR 60 BIOTECH: 50/1.2/0850

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 February 2021

10. DATE OF REVISION OF THE TEXT

16 February 2021