Approval received: 18 March 2021

Version 01

PROFESSIONAL INFORMATION

DULOXETINE MR UNICORN

SCHEDULING STATUS

Schedule 5.

1. NAME OF THE MEDICINE

DULOXETINE MR 30 UNICORN (30 mg duloxetine) hard gastro resistant capsules.

DULOXETINE MR 60 UNICORN (60 mg duloxetine) hard gastro resistant capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each hard gastro resistant capsule of **DULOXETINE MR 30 UNICORN** contains 33,66 mg duloxetine hydrochloride, which is equivalent to 30 mg duloxetine base.

Each hard gastro resistant capsule of **DULOXETINE MR 60 UNICORN** contains 67,32 mg duloxetine hydrochloride, which is equivalent to 60 mg duloxetine base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro resistant capsule

DULOXETINE MR 30 UNICORN: Opaque dark blue cap-opaque white body printed with “30”, size 2 hard gelatin capsules, containing 4 white to off white, round, biconvex tablets per capsule.

DULOXETINE MR 60 UNICORN: Opaque dark blue cap-opaque yellowish green body printed with “60”, size 0E hard gelatin capsules, containing 8 white to off white, round, biconvex tablets per capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DULOXETINE MR UNICORN is indicated in adults for:

- The treatment of major depressive disorder (as defined by DSM-IV criteria).
- The treatment of diabetic peripheral neuropathic pain.

4.2 Posology and method of administration

Posology

Depression:

The recommended starting and maintenance dose is 60 mg once daily with or without food. Doses of 120 mg daily have been evaluated, but the efficacy of this dose is not statiscally significant when compared to a dose of 60 mg. The adverse event rate was higher with the 120 mg dose.

Diabetic Peripheral Neuropathic Pain:

The recommended starting dose is 60 mg once daily with or without food. Doses of 120 mg daily have been evaluated, but the efficacy of this dose is not statiscally significant when compared to a dose of 60 mg. The adverse event rate was higher with the 120 mg dose.

Special Populations:

Age:

DULOXETINE MR UNICORN should not be used in patients under the age of 18 since safety and efficacy have not yet been established.

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

Renal Impairment:

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

Hepatic Impairment:

The initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function.

Method of administration

DULOXETINE MR UNICORN should be taken orally.

4.3 Contraindications:

- Hypersensitivity to duloxetine or any of the inactive excipients of **DULOXETINE MR UNICORN**.
- The use of **DULOXETINE MR UNICORN** with monoamine oxidase inhibitors (MAOIs) is contraindicated. The use of **DULOXETINE MR UNICORN** should not be used within 2 weeks of discontinuing therapy with a MAOI. Considering the half-life of duloxetine, do not start therapy with a MAOI within 5 days of discontinuing therapy with **DULOXETINE MR UNICORN**.
- Pregnancy and lactation.
- Severe hepatic impairment due to liver disease.

- Severe renal impairment (creatinine clearance < 30 ml/min).
- In patients with uncontrolled hypertension.

4.4 Special warnings and precautions for use

Mydriasis

Duloxetine is associated with mydriasis. **DULOXETINE MR UNICORN** must be prescribed with caution in patients with increased intraocular pressure or in patients at risk of acute narrow-angle glaucoma.

Mania and Seizures

Caution is advised when using **DULOXETINE MR UNICORN** in patients with a history of mania or who have been diagnosed with bipolar disorder; and/or seizures.

Blood pressure and heart rate

DULOXETINE MR UNICORN may increase blood pressure, and clinically significant hypertension in certain patients, due to the noradrenergic effect of duloxetine. Hypertensive crisis may occur, especially in patients with pre-existing hypertension. Blood pressure monitoring is recommended in patients with known hypertension and/or cardiac disease, especially during the first month of treatment with **DULOXETINE MR UNICORN**. Caution is advised in patients whose conditions may be compromised by an increased heart rate or blood pressure. **DULOXETINE MR UNICORN** should be prescribed with caution in patients who are using medicines that affect the metabolism of duloxetine. A reduction in the dose or gradual discontinuation of **DULOXETINE MR UNICORN** should be considered in patients who experience a constant increase in blood pressure.

Serotonin syndrome

Serotonin syndrome, which is a potentially life-threatening condition, may occur when using **DULOXETINE MR UNICORN**, especially when used concomitantly with medicines which affect serotoninergic neurotransmitter systems. The symptoms may include mental status changes (for example, agitation, hallucinations, coma); autonomic instability (for example; tachycardia, unstable blood pressure, hyperthermia); neuromuscular irregularities (for example; hyperreflexia, lack of coordination) and/or gastrointestinal symptoms (for example, nausea, vomiting, diarrhoea). Careful observation is required when **DULOXETINE MR UNICORN** is prescribed in patients using other serotoninergic medicines affecting the serotoninergic and/or dopaminergic neurotransmitter systems ~~agents~~ medicines (for example, SSRIs, SNRIs, tricyclic antidepressants or triptans), with medicines that affect the metabolism of serotonin (for example, MAOIs), or other anti-psychotic medicines and dopamine antagonists. This is especially warranted at the initiation of therapy or at dose increases (see section 4.5).

DULOXETINE MR UNICORN should not be administered in combination with potent inhibitors of CYP1A2 such as fluvoxamine, ciprofloxacin or enoxacin because the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

St John's Wort

Side effects may occur more frequently when using **DULOXETINE MR UNICORN** with herbal preparations containing herbal preparations containing St John's Wort (*Hypericum perforatum*).

Suicide

Major depressive disorder may be associated with an increased risk of suicide-related events (suicidal thoughts, self-harm and suicide). These feelings may persist until significant remission occurs. Therefore, patients should be closely monitored until improvement occurs, especially in early treatment, following dose changes and following discontinuation of therapy. Patients and

caregivers must be informed on the need to monitor clinical worsening, suicidal behaviour or thoughts, and unusual changes in behaviour; and to seek medical attention if symptoms such as distressing thoughts or feelings present at any time.

Patients with a history of suicidal events or display a high risk of suicide before initiation of treatment, require careful monitoring during treatment, especially in patients under the age of 25 years old. **DULOXETINE MR UNICORN** should not be prescribed in patients under the age of 18 years, as these suicidal effects are more frequently observed in children and adolescents.

Renal Impairment

The plasma concentration of duloxetine is increased in patients with severe renal impairment (creatinine clearance < 30 ml/min) on haemodialysis.

Haemorrhage

The use of **DULOXETINE MR UNICORN** may be associated with bleeding abnormalities. Caution is advised in patients taking anti-coagulants, and/or medicines known to affect the platelet function (for example, aspirin or NSAIDs); and in patients with bleeding disorders.

Hyponatraemia

Hyponatraemia, with serum sodium levels below 110 mmol/l, may occur with the use of **DULOXETINE MR UNICORN**. This may occur as a result of a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Hyponatraemia is more common in the elderly, especially in those with altered fluid balance.

Discontinuation of treatment

Withdrawal symptoms occur when treatment of **DULOXETINE MR UNICORN** is discontinued, especially when therapy is stopped abruptly. The risk of withdrawal symptoms may be increased

by several factors, including duration and dose of treatment and the rate of dose reduction. The intensity of these reactions may vary from mild to moderate, and severe. These effects usually occur within a few days of discontinuing therapy, and are self-limiting. This usually resolves within 2 weeks, however, these effects may be prolonged (2 – 3 months). It is recommended to gradually taper the dose over a period of 2 weeks.

Akathisia/Psychomotor restlessness

The use of **DULOXETINE MR UNICORN** may be associated with the development of akathisia, characterised by unpleasant or distressing restlessness, with the inability to sit or stand still.

Hepatitis or increased liver enzymes

The use of **DULOXETINE MR UNICORN** may be associated with liver injury, including severe elevations of liver enzymes, hepatitis and jaundice. This occurred within the first months of treatment. **DULOXETINE MR UNICORN** must be prescribed with caution in patients taking medicines associated with hepatic injury. The plasma concentration of duloxetine is increased in patients with hepatic impairment, therefore a lower dose should be used in these patients.

***Information of excipients of* DULOXETINE MR UNICORN**

Lactose

DULOXETINE MR UNICORN contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicines metabolised by CYP1A2 (for example, theophylline):

It is unlikely that **DULOXETINE MR UNICORN** will have any clinically significant effect when used in combination with these medicines.

Inhibitors of CYP1A2 (for example, fluvoxamine and quinolone antibiotics):

The enzyme CYP1A2 is involved in the metabolism of duloxetine. Therefore, when **DULOXETINE MR UNICORN** is used with inhibitors of this enzyme, the blood concentration of duloxetine will be increased, because of the decreased plasma clearance. It is recommended to use **DULOXETINE MR UNICORN** with caution in combination with these medicines, and to prescribe a lower dose of **DULOXETINE MR UNICORN**.

Medicines metabolised by CYP2D6 (for example, desipramine, risperidone and tricyclic antidepressants):

Duloxetine is a mild inhibitor of the enzyme CYP2D6. When **DULOXETINE MR UNICORN** is administered with medicines metabolised by this enzyme, the plasma concentration of these medicines are increased. Caution is advised when prescribing this combination, especially with medicines having a narrow therapeutic index (for example, flecainide, propafenine and metoprolol).

Inhibitors of CYP2D6 (for example, paroxetine):

The enzyme, CYP2D6 is involved in the metabolism of duloxetine. Therefore, when **DULOXETINE MR UNICORN** is used with inhibitors of this enzyme, the blood concentration of duloxetine will be increased, because of the decreased plasma clearance. It is recommended to use **DULOXETINE MR UNICORN** with caution in combination with these medicines.

CNS medicines (for example, alcohol and sedative medicinal products):

Caution is recommended when using **DULOXETINE MR UNICORN** in combination with other medicines that affect the central nervous system, including benzodiazepines, antipsychotics, phenobarbital and sedative antihistamines.

Medicines highly bound to plasma protein:

DULOXETINE MR UNICORN is highly bound to plasma proteins. Therefore, when used in combination with another medicine that is highly protein bound, there may be an increase in the concentration of the free forms of either medicine.

Anticoagulants and anti-platelet medicines:

Duloxetine is known to increase the risk of bleeding (see section 4.4). Therefore, caution is advised when using **DULOXETINE MR UNICORN** in combination with oral anti-coagulants or anti-platelet medicines. There may be a risk of increased INR values in patients using warfarin, therefore close monitoring of patients using this combination is required.

Serotonergic medicines:

This combination of **DULOXETINE MR UNICORN** with other serotoninergic medicines may lead to an increased risk of serotonin syndrome (see section 4.4). Caution is advised when using **DULOXETINE MR UNICORN** with SSRIs, SNRIs, tricyclic antidepressants, such as clomipramine or amitryiptyline; MAOIs, St John's Wort or triptans, tramadol, pethidine and tryptophan. Non-selective, irreversible (for example, linezolid) and selective, reversible (for example, moclobemide) monoamine oxidase inhibitors MAOIs should not be used together or within 2 weeks of discontinuing therapy with a MAOI. Due to the half-life of duloxetine, therapy with a MAOI should not be initiated within 5 days of discontinuing therapy with **DULOXETINE MR UNICORN**.

Inducers of CYP1A2 (for example, cigarette smoking):

The plasma concentration of **DULOXETINE MR UNICORN** is almost 50 % lower in patients that smoke tobacco cigarettes (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. Animal studies have shown reproductive toxicity, however the potential risk in humans is unknown (see section 4.3)

It has been suggested that the use of **DULOXETINE MR UNICORN** in pregnancy, especially late pregnancy may result in an increased risk of persistent pulmonary hypertension in the new born.

Discontinuation symptoms, including hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures, may occur in the neonate following maternal duloxetine use near term.

The use of **DULOXETINE MR UNICORN** in pregnancy is contraindicated. It is advised for women to notify their doctor if they become pregnant, or intend to become pregnant during therapy.

Lactation

The safety of duloxetine in infants is unknown, therefore the use of **DULOXETINE MR UNICORN** during breast-feeding is not recommended.

Fertility

In animal studies**, DULOXETINE MR UNICORN** had no effect on the fertility of men, but demonstrated effects on women. However, this only occurred at doses that caused maternal toxicity.

4.7 Effects on ability to drive and operate machinery

DULOXETINE MR UNICORN commonly causes dizziness, sedation and somnolence. Therefore, patients should be advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether **DULOXETINE MR UNICORN** affects their ability to perform such activities.

4.8 Undesirable effects

The most frequent adverse reactions include dry mouth, dizziness, headache, nausea and somnolence. Adverse reactions are usually mild to moderate in intensity, occurring at the start of therapy, and subsiding during continuation of therapy.

Infections and infestations

Less frequent: Laryngitis.

Immune system disorders

Less frequent: Anaphylactic reaction, angioedema, hyper-sensitivity disorder.

Endocrine disorders

Less frequent: Hypothyroidism.

Metabolism and nutrition disorders

Frequent: Decreased appetite.

Less frequent: Dehydration, hyperglycaemia*, hyponatraemia, syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

*This has been reported in diabetic patients.

Psychiatric disorders

Frequent: Abnormal dreams, agitation, anxiety, anorgasmia, insomnia, decreased libido.

Less frequent: Aggression and anger, apathy, bruxism, disorientation, hallucinations, mania, sleep disorder, suicidal behaviour and ideation.

Nervous system disorders

Frequent: Dizziness, headache, lethargy, paraesthesia, somnolence, tremor.

Less frequent: Akathisia, convulsions, disturbance in attention, dysgeusia, dyskinesia, extra-pyramidal symptoms, myoclonus, nervousness, poor quality in sleep, psychomotor restlessness, restless legs syndrome, serotonin syndrome.

Eye disorders

Frequent: Blurred vision.

Less frequent: Glaucoma, mydriasis, visual impairment.

Ear and labyrinth disorders

Frequent: Tinnitus.

Less frequent: Ear pain, vertigo.

Cardiac Disorders:

Frequent: Palpitations.

Less frequent: Supraventricular dysrhythmia, mainly atrial fibrillation; tachycardia.

Vascular disorders:

Frequent: Increase in Blood pressure, flushing.

Less frequent: Hypertension, hypertensive crisis, orthostatic hypotension (especially at the initiation of therapy), peripheral coldness, syncope (especially at the initiation of therapy).

Respiratory, thoracic and mediastinal disorders

Frequent: Yawning.

Less frequent: Epistaxis, throat tightness.

Gastrointestinal disorders

Frequent: Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, flatulence, nausea, vomiting.

Less frequent: Breath odour, dysphagia, eructation, gastritis, gastroenteritis, gastrointestinal haemorrhage, haematochezia, microscopic colitis, stomatitis.

Hepato-biliary disorders

Less frequent: Acute liver injury, elevated liver enzymes (ALT, AST, and alkaline phosphatase), hepatic failure, hepatitis, jaundice.

Skin and subcutaneous tissue disorders

Frequent: Rash, increased sweating.

Less frequent: Cold sweat, contact dermatitis, hyperhidrosis, cutaneous vasculitis, increased tendency to bruise, night sweats, photo-sensitivity reactions, Stevens-Johnson syndrome, urticaria.

Musculoskeletal and connective tissue disorders

Frequent: Muscle spasm, musculoskeletal pain.

Less frequent: Muscle tightness, muscle twitching, trismus.

Renal and urinary disorders

Frequent: Dysuria, pollakiuria.

Less frequent: Abnormal urine odour, nocturia, polyuria, urinary hesitation, urinary retention, decreased urine flow.

Reproductive system and breast disorders

Frequent: Delayed ejaculation, ejaculation disorder, erectile dysfunction.

Less frequent: Galactorrhoea*,* gynaecological haemorrhage, hyperprolactinaemia~~l~~, menopausal symptoms, menstrual disorder, sexual dysfunction, testicular pain.

General disorders and administration site conditions

Frequent: Falls, fatigue.

Less frequent: Chest pain, chills, feeling abnormal, feeling cold and/or hot, gait disturbance, malaise, thirst.

Investigations

Frequent: Weight decrease.

Less frequent: Blood cholesterol increased, blood creatine phosphokinase increased, blood potassium increased, weight increase.

Discontinuation of **DULOXETINE MR UNICORN**, especially when stopped abruptly, commonly leads to withdrawal symptoms. Agitation or anxiety, diarrhoea, dizziness, fatigue, headache, hyperhidrosis, irritability, myalgia, nausea and/or vomiting, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances

(including insomnia and intense dreams), somnolence, tremor, and vertigo are the most frequently reported adverse events (see section 4.4).

4.9 Overdose

Signs and symptoms

There is limited clinical data regarding the duloxetine overdose. No fatal overdoses have occurred during pre-marketing clinical trials, however four non-fatal acute ingestions of duloxetine (300 to 400 mg), alone or in combination with other medicines have been recorded. Signs and symptoms of overdose may be related to the central nervous system and gastrointestinal systems such as ataxia, clonic convulsions, decreased appetite, emesis and tremors.

Management of overdose

There is no specific antidote known for duloxetine. A free airway should be established. Appropriate symptomatic and supportive measures is recommended, along with monitoring of cardiac and vital signs. To limit absorption, activated charcoal may be useful. **DULOXETINE MR UNICORN** has a large volume of distribution and therefore it is unlikely that forced diuresis, haemoperfusion, and exchange perfusion will be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Pharmacological Class: A 1.2 Psychoanaleptics (antidepressants).

Duloxetine is classified as a serotonin noradrenaline reuptake inhibitor (SNRI).

Mechanism of action:

Duloxetine inhibits the neuronal uptake of serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NA), while it weakly inhibits dopamine reuptake, with no significant affinity for adrenergic, cholinergic, dopaminergic and histaminergic receptors. Duloxetine is chemically unrelated to tricyclic and tetracyclic antidepressant medicines.

It dose-dependently increases extracellular concentrations of serotonin and noradrenaline in various brain areas of animals, enhancing both serotonin and noradrenaline neurotransmission in the central nervous system (CNS).

Duloxetine has demonstrated to normalise pain thresholds, via the potentiation of the descending inhibitory pathways within the CNS, which results in the pain inhibitory action of duloxetine.

5.2 Pharmacokinetic Properties

Absorption:

Following oral administration, duloxetine is well absorbed, with a peak concentration occurring 6 hours after dosing. The time to reach the maximum concentration is delayed by food, from 6 hours to 10 hours, combined with a decrease in the bioavailability to approximately 11 %. Steady state is achieved within 3 days after dosing.

Distribution

Duloxetine is extensively bound to human plasma protein (approximately 90 %), binding to both albumin and α_1-acid glycoprotein. Renal or hepatic impairment does not affect protein binding.

Metabolism

Duloxetine is extensively metabolised by the oxidative enzymes, CYP1A2 and CYP2D6. The metabolites are excreted primarily in the urine. Both enzymes catalyse the formation of two major metabolites (glucuronide conjugate of 4-hydroxy duloxetine and the sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine), which are pharmacologically inactive.

Excretion

The estimated elimination half-life of duloxetine is approximately 12,1 hours. Following oral administration, the mean plasma clearance of duloxetine is 101 l/hr.

Pharmacokinetics in Special Patient Groups:

Gender

There have been pharmacokinetic differences have been identified in females and males. The mean clearance of duloxetine was 9 – 55 % lower in females. The half-life of duloxetine was similar between females and males.

Elderly (over 65 years of age)

Differences in the pharmacokinetics of duloxetine have been identified between middle aged and elderly females (> 65 years). It has been demonstrated that the AUC is 24 % and the half-life is about 4,3 hours longer in the elderly.

Renal impairment

The AUC and C_{max} values of duloxetine is 2-fold higher in patients with end stage renal disease (ESRD) receiving chronic intermittent dialysis compared to healthy individuals. Therefore, a lower dose should be used in patients with clinically significant renal impairment.

Hepatic impairment

The pharmacokinetics of duloxetine is affected by moderate liver disease. The half-life of duloxetine was 34 hours longer in patients with cirrhosis of the liver and clearance was approximately 15 % when compared to age and gender-matched healthy individuals. Therefore, a lower dose should be used for patients with mild to moderate hepatic impairment.

Smoking status

The bioavailability of duloxetine in smokers has shown to be 34 % lower, when compared to that in non-smokers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients of **DULOXETINE MR UNICORN** include: Gelatin, Hypromellose HPMC 2910, Lactose Monohydrate, Macrogel, Magnesium stearate, Microcrystalline cellulose (type 102), Povidone, Starch Maize (pregelatinised), Sodium Stearate Fumarate, Talc and Titanium dioxide.

DULOXETINE MR UNICORN contains lactose monohydrate.

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 OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

DULOXETINE MR UNICORN hard gastro-resistant capsules are available in (PVC/PE/PCTFE//Al or PA/Al/PVC//Al) blisters in a cardboard box.

Pack sizes:

DULOXETINE MR 30 UNICORN: 7, 28 and 98 capsules

DULOXETINE MR 60 UNICORN: 28, 56, 84, 98, 100 and 500 capsules

DULOXETINE MR UNICORN hard gastro-resistant capsules are available in HDPE bottles with child-resistant PP screw cap in a cardboard box.

Pack size:

DULOXETINE MR 30 UNICORN & 60: 30 capsules

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town, 8001

South Africa

8 REGISTRATION NUMBER(S)

DULOXETINE MR 30 UNICORN: 540589

DULOXETINE MR 60 UNICORN: 540590

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: To be allocated by SAHPRA

10 DATE OF REVISION OF THE TEXT

18 March 2021