CLEAN FINAL PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

DULOXETINE TEVA DR 30 (30 mg), gastro-resistant hard capsules

DULOXETINE TEVA DR 60 (60 mg), gastro-resistant hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

DULOXETINE TEVA DR 30: Each gastro-resistant hard capsule contains duloxetine hydrochloride equivalent to 30 mg duloxetine.

DULOXETINE TEVA DR 60: Each gastro-resistant hard capsule contains duloxetine hydrochloride equivalent to 60 mg duloxetine.

Excipient with known effect:

Each 30 mg capsule contains 101 mg sucrose.

Each 60 mg capsule contains 201 mg sucrose.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Hard gastro-resistant capsule.

DULOXETINE TEVA DR 30: Hard capsules, size 2 with grey opaque body and blue opaque cap. Marking DLX 30.

DULOXETINE TEVA DR 60: Hard capsules, size 1EL with grey opaque body and white opaque cap. Marking DLX 60.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

DULOXETINE TEVA DR is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).

4.2 Posology and method of administration:

Posology:

Depression:

DULOXETINE TEVA DR 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 TEVA DR 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.

Special populations:

Renal impairment:

Initial dose should be 30 mg once daily in patients with mild to moderate impairment of renal function (see **section 4.3** and **5.2**).

Hepatic impairment:

Initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function (see **section 4.3** and **5.2**).

Age:

No dosage adjustment is recommended for elderly patients on the basis of age. 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.
- Severe impairment of hepatic function.
- Advanced renal impairment (creatinine clearance < 30 ml/min).
- Concomitant use of monoamine oxidase inhibitors (MAOIs) (see **section 4.4**).
- The initiation of treatment with **DULOXETINE TEVA DR** is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see **sections 4.4** and **4.8**).

4.4 Special warnings and precautions for us:

MAOIs (Monoamine Oxidase Inhibitors):

DULOXETINE TEVA DR should not be used within at least 14 days of discontinuing treatment with a MAOI. Based on the half-life of **DULOXETINE TEVA DR**, at least 5 days should be allowed after stopping **DULOXETINE TEVA DR**, before starting a MAOI.

Mania and seizures:

DULOXETINE TEVA DR 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 TEVA DR** to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate:

DULOXETINE TEVA DR 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. **DULOXETINE TEVA DR** 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 is used with medicines that may impair its metabolism (see **section 4.5**). For patients who experience a sustained increase in blood pressure while receiving **DULOXETINE**

TEVA DR either dose reduction or gradual discontinuation should be considered (see **section 4.8**). In patients with uncontrolled hypertension **DULOXETINE TEVA DR** should not be initiated (see **section 4.3**).

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.

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, inco-ordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If concomitant treatment with **DULOXETINE TEVA DR** 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 TEVA DR** and herbal preparations containing St John's Wort (*Hypericum perforatum*).

Suicide:

The possibility of an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events) is inherent in depression, major depressive disorder and other psychiatric conditions and may persist 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. Close supervision of high-risk patients (with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment especially if they are under 25 years old) should accompany initial **DULOXETINE TEVA DR** therapy and following dose changes. Cases of suicidal ideation and suicidal behaviours have been reported during **DULOXETINE TEVA DR** therapy or early after treatment discontinuation.

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.

Medical practitioners should encourage patients to report any distressing thoughts or feelings at any time.

Use in children and adolescents under 18 years of age:

DULOXETINE TEVA DR should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour, and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms (see **section 5.1**). In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking (see **section 4.8**).

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. **DULOXETINE TEVA DR** 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 (ASA)), and in patients with known bleeding tendencies.

Hyponatraemia:

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

Discontinuation of treatment:

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

The risk of withdrawal symptoms seen with SSRIs and SNRIs may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in **section 4.8**. Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see **section 4.2**).

Elderly:

Data on the use of **DULOXETINE TEVA DR** 120 mg in elderly patients with major depressive disorder and generalised anxiety 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 TEVA DR** 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 (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). 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**). Most of them occurred during the first months of

treatment. The pattern of liver damage was predominantly hepatocellular. **DULOXETINE TEVA DR** should be used with caution in patients treated with other medicines associated with hepatic injury.

Sexual dysfunction:

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see **section 4.8**). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Sucrose:

DULOXETINE TEVA DR hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction:

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

The concomitant use of **DULOXETINE TEVA DR** with selective, reversible MAOIs, like moclobemide, is not recommended (see **section 4.4**). The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with **DULOXETINE TEVA DR** (see **section 4.4**).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77 % and increased AUC_{o-t} 6-fold. Therefore, **DULOXETINE TEVA DR** should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine. Caution is advised if administering **DULOXETINE TEVA DR** with inhibitors of CYP1A2 (e.g. quinolone antibiotics) and a lower **DULOXETINE TEVA DR** dose should be used.

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

CNS medicines: The risk of using duloxetine 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 TEVA DR** 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*:** In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic medicines. Caution is advisable if **DULOXETINE TEVA DR** is used concomitantly with serotonergic medicines like SSRIs such as paroxetine, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's Wort (*Hypericum perforatum*) or triptans, tramadol, pethidine, and tryptophan (see **section 4.4**).

Effect of Duloxetine on other medicines:

Medicines metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily). **DULOXETINE TEVA DR** is therefore unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Medicines metabolised by CYP2D6: Duloxetine 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 TEVA DR** 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).

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* medicine interaction studies have not been performed.

***Anticoagulants and antiplatelet medicines*:** Caution should be exercised when **DULOXETINE TEVA DR** 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.

Effects of other medicines on duloxetine:

Antacids and H2 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.

Medicines highly bound to plasma protein: Duloxetine is highly bound to plasma proteins (> 90 %). Therefore, administration of **DULOXETINE TEVA DR** 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:

Women of childbearing potential / Contraception in males and females:

Women should be advised to notify their medical practitioner if they become pregnant, or intend to become pregnant, during therapy.

Pregnancy:

Safety in pregnant women has not been established, therefore **DULOXETINE TEVA DR** should not be taken during pregnancy.

Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see **section 5.3**). There was no evidence of teratogenicity in animal studies (see **section 4.3**).

Breastfeeding:

The safety of duloxetine has not been established and not recommended during lactation. **DULOXETINE TEVA DR** and/or its metabolites are excreted into the milk of lactating rats (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:

DULOXETINE TEVA DR may be associated with undesirable effects such as sedation and dizziness. Therefore patients should be cautioned that if they experience sedation or dizziness they should avoid driving or operating machinery while taking **DULOXETINE TEVA DR**.

4.8 Undesirable effects:

a. Summary of the safety profile:

The most commonly reported adverse reactions in patients treated with **DULOXETINE TEVA DR** 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.

b. Tabulated summary of adverse reactions:

TABLE 1 GIVES THE ADVERSE REACTIONS OBSERVED FROM SPONTANEOUS REPORTING AND IN PLACEBO-CONTROLLED CLINICAL TRIALS.

Infections and infestations:	
Less frequent	Laryngitis

Immune system disorders:

Less frequent	Anaphylactic reaction, hypersensitivity disorder, angioedema

Endocrine disorders:	
Less frequent	Hypothyroidsim

Metabolism and nutrition disorders:	
Frequent	Decreased appetite
Less frequent	Hyperglycaemia (reported especially in diabetic patients), dehydration, hyponatraemia, SIADH[6]

Psychiatric disorders:	
Frequent	Insomnia, agitation, decreased libido, anxiety, abnormal orgasm, abnormal dreams
Less frequent	Suicidal ideation[5,7], sleep disorder, bruxism, disorientation, apathy, suicidal behaviour[5,7], mania, hallucinations, aggression and anger[4]

Nervous system disorders:	
Frequent	Headache, somnolence, dizziness, lethargy, tremor, paraesthesia
Less frequent	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 symptoms[6]

Eye disorders:	
Frequent	Blurred vision
Less frequent	Mydriasis, visual impairment, glaucoma

Ear and labyrinth disorders:	
Frequent	Tinnitus[1]
Less frequent	Vertigo, ear pain

Cardiac disorders:	
Frequent	Palpitations
Less frequent	Tachycardia, supraventricular, dysrhythmia, mainly atrial fibrillation

Vascular disorders:	
Frequent	Blood pressure increase[3], flushing,
Less frequent	Syncope[2], hypertension[3, 7], orthostatic hypotension[2], peripheral coldness, hypertensive crisis[3,6]

Respiratory, thoracic and mediastinal disorders:	
Frequent	Yawning
Less frequent	Throat tightness, epistaxis, interstitial lung

	disease[10], eosinophilic pneumonia[6]

Gastrointestinal disorders:	
Frequent	Nausea, dry mouth, constipation, diarrhoea, abdominal pain, vomiting, dyspepsia, flatulence
Less frequent	Gastrointestinal haemorrhage[7], gastroenteritis, eructation, gastritis, dysphagia, stomatitis, haematochezia, breath odour, microscopic colitis[9]

Hepato-biliary disorders:	
Less frequent	Hepatitis[3], elevated liver enzymes (ALT, AST, alkaline phosphatase), acute liver injury, hepatic failure[6], jaundice[6]

Skin and subcutaneous tissue disorders:	
Frequent	Sweating increased, rash
Less frequent	Night sweats, urticaria, contact dermatitis, cold sweat, photosensitivity reactions, increased tendency to bruise, Stevens-Johnson Syndrome[6], cutaneous vasculitis

Musculoskeletal and connective tissue disorders:	
Frequent	Musculoskeletal pain, muscle spasm
Less frequent	Muscle tightness, muscle twitching, trismus

Renal and urinary disorders:	
Frequent	Dysuria, pollakiuria
Less frequent	Urinary retention, urinary hesitation, nocturia, polyuria, urine flow decreased, urine odour abnormal

Reproductive system and breast disorders:	
Frequent	Erectile dysfunction, ejaculation disorder, ejaculation delayed
Less frequent	Gynaecological haemorrhage, menstrual disorder, sexual dysfunction, testicular pain, menopausal symptoms, galactorrhoea, hyperprolactinaemia, postpartum haemorrhage[6]

General disorders and administration site conditions:	
Frequent	Falls[8], fatigue
Less frequent	Chest pain[7], feeling abnormal, feeling cold, thirst chills, malaise, feeling hot, gait disturbance

Investigations:	
Frequent	Decreased weight
Less frequent	Weight increase, increased blood creatine phosphokinase, increased blood potassium, increased blood cholesterol

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

[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 TEVA DR** (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**).

d. Paediatric population:

It has been reported in clinical trials that in general, the adverse reaction profile of duloxetine in children and adolescents was similar to that seen for adults.

Reports from clinical trials have shown that patients on average trended toward recovery to their expected baseline weight percentile based on population data from age- and gender-matched peers.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications:

https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA

4.9 Overdose:

Signs and symptoms:

There is limited clinical experience with **DULOXETINE TEVA DR** overdose in humans. In pre-marketing clinical trials, no cases of fatal overdose of duloxetine have been reported. Four non-fatal acute ingestions of **DULOXETINE TEVA DR** (300 to 1 400 mg), alone or in combination with other

medicines have been reported. The predicted signs would be related to the central nervous and gastrointestinal systems (e.g. tremors, clonic convulsions, ataxia, emesis and decreased appetite).

Management of overdose:

No specific antidote is known for **DULOXETINE TEVA DR**, 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:

A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Duloxetine is a serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake inhibitor (SNRI) and is chemically unrelated to tricyclic and tetracyclic antidepressant medicines. Duloxetine weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors.

Duloxetine dose-dependently increased extracellular levels of serotonin and norepinephrine in various brain areas of animals.

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

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

5.2 Pharmacokinetic properties:

Absorption:

Duloxetine is well absorbed after oral administration, with the C_{max} occurring 6 hours post-dose. Food delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately

11 %). Steady-state plasma concentrations are achieved after 3 days of dosing.

Distribution:

Duloxetine is highly bound (> 90 %) to plasma proteins; primarily to albumin and α_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 CYP2D6 and CYP1A2 catalyze the formation of two major metabolites (glucuronide conjugate of 4-hydroxy duloxetine, sulphate conjugate of 5-hydroxy, 6-methoxy duloxetine). Circulating metabolites are not pharmacologically active.

Elimination:

The mean elimination half-life of duloxetine is 12,1 hours. The mean plasma clearance of duloxetine is 101 L/hr.

Special populations:

Gender:

Pharmacokinetic differences have been identified between males and females. The mean plasma clearance was 9 % to 55 % lower in females, but the duloxetine half-life was similar between males and females.

Smoking status:

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

Age:

Pharmacokinetic differences have been identified between middle age and elderly females (AUC is 24 % higher and half-life is 4,3 hours longer in the elderly).

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 **section 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 **section 4.2** and **4.3**).

5.3 Preclinical safety data:

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Capsule content:

Sugar spheres (sucrose, maize starch)

Hypromellose phthalate

Hypromellose

Triethyl citrate

Hydroxypropyl cellulose

Talc

Capsule shell:

30 mg:

Black iron oxide (E172)

Brilliant Blue FCF (E133)

Hypromellose (E464)

Titanium dioxide (E171)

Printing ink

60 mg:

Black iron oxide (E172)

Hypromellose (E464)

Titanium dioxide (E171)

Printing ink

Printing ink contains:

Black iron oxide (E172)

Potassium hydroxide

Propylene Glycol

Shellac

Strong ammonia solution

6.2 Incompatibilities:

Not relevant.

6.3 Shelf life:

2 years.

6.4 Special precautions for storage:

Store at or below 25 °C.

Keep the capsules in the original container until required for use.

6.5 Nature and contents of container:

HDPE containers with twist-off PP cap with integrated silica gel desiccant:

- 100 capsules.

OPA/Al/PVC-Al blister:

- 30 mg: 7, 14, 28, 30, 56, 98 and 100 capsules.

- 60 mg: 14, 28, 30, 56, 98 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:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park,

Magwa Crescent West,

Waterfall City, Midrand,

Gauteng,

2090

8. REGISTRATION NUMBER:

Duloxetine Teva DR 30: 55/1.2/0307

Duloxetine Teva DR 60: 55/1.2/0308

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

25 January 2022

10. DATE OF REVISION OF THE TEXT: