APPROVED PROFESSIONAL INFORMATION NON-REFERENCED

SCHEDULING STATUS

S5

1. DULTA 30 mg DELAYED RELEASE CAPSULES

DULTA 60 mg DELAYED RELEASE CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DULTA 30 mg: Each delayed release capsule contains duloxetine hydrochloride equivalent to 30 mg duloxetine.

DULTA 60 mg: Each delayed release capsule contains duloxetine hydrochloride equivalent to 60 mg duloxetine.

DULTA contains sugar in the form of lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

DULTA 30 mg: Size ’3’ capsules with dark blue cap and white body imprinted with “LU” in white ink on cap and “Q02” in black ink on body, containing six white to off white mini tablets

DULTA 60 mg: Size ’1’ capsules with dark blue cap and green body imprinted with “LU” in white ink on cap and “Q03” in black ink on body, containing twelve white to off white mini

tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DULTA 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

Depression:

DULTA 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 has not been statistically significantly different from that of 60 mg once daily, but with a higher adverse event rate.

Diabetic peripheral neuropathic pain:

The usual dose is 60 mg once daily without regard to meals. Although doses up to 120 mg per day have been used, the efficacy has not been statistically significantly different from that of 60 mg once daily, but with a higher adverse event rate.

Special populations

Renal impairment: In patients with mild to moderate renal impairment, the initial dose

should be 30 mg (see sections 4.3,4.4 and 5.2).

Hepatic impairment: In patients with mild to moderate hepatic impairment the initial dose should be lower or less frequent (see sections 4.3,4.4 and 5.2).

Elderly: No dosage adjustment on the basis of age is recommended for the elderly

Paediatric population

Children: Safety and efficacy have not been established in patients younger than 18 years of age (see section 4.3 and 4.4).

Method of administration

Oral use.

4.3 Contraindications

- Known hypersensitivity to duloxetine or any of the ingredients in DULTA
- Children under the age of 18 years (see section 4.4)
- Pregnancy and lactation (see section 4.6)
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance < 30 ml/min)
- Concomitant use of monoamine oxidase inhibitors (MAOIs) including linezolid (see section 4.4 and section 4.5)
- Uncontrolled narrow angle glaucoma

• Uncontrolled hypertension

• In combination with fluvoxamine, ciprofloxacin or enoxacin (i.e., potent CYP1A2 inhibitors), since the combination results in elevated plasma concentrations of DULTA (see section 4.5).

4.4 Special warnings and precautions for use

Monoamine Oxidase Inhibitors (MAOIs):

DULTA should not be used with a MAOI and at least 14 days should lapse after discontinuation of a MAOI and initiating treatment with DULTA (see section 4.3 and 4.5).

Major Depressive disorder and generalised anxiety disorder:

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. The risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with DULTA should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases. Cases of suicidal thoughts and suicidal behaviours have been reported during DULTA therapy or early after treatment discontinuation (see section 4.8). 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.

Activation of mania/hypomania:

DULTA should be used cautiously in patients with a history of mania or a diagnosis of bipolar disorder.

Seizures:

DULTA should be used cautiously in patients with a history of seizure disorder.

Mydriasis:

Use with caution when prescribing DULTA to patients with increased intraocular pressure or those patients at risk of acute narrow-angle glaucoma.

Renal impairment:

Increased plasma concentrations of DULTA occur in patients with severe renal impairment on haemodialysis (creatinine clearance < 30 ml/min). For patients with severe renal impairment see section 4.3. For patients with mild to moderate renal dysfunction see section 4.2.

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 DULTA, mostly during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Use DULTA with caution in patients treated with other medicines associated with hepatic injury and known alcohol abusers.

Increased blood pressure and heart rate:

DULTA has been associated with an increase in blood pressure and blood pressure monitoring is recommended, especially during the first month of treatment. 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. DULTA should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. For patients who experience a sustained increase in blood pressure while receiving DULTA, either dose reduction or gradual discontinuation should be considered. DULTA therapy should not be initiated in patients with uncontrolled hypertension (see section 4.3).

Akathisia/Psychomotor restlessness:

Treatment with DULTA has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by inability to sit or stand still. This is most likely to occur in the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Serotonin syndrome:

Serotonin syndrome is a potentially life-threatening condition which may occur with DULTA treatment, particularly with concomitant use of serotonergic medicines (including SSRIs, SNRIs, tricyclic antidepressants or triptans), with medicines that impair metabolism of serotonin such as MAOIs, with antipsychotics or other dopamine

antagonists that may affect the serotonergic neurotransmitter systems (see section 4.3 and 4.5).

Serotonin syndrome symptoms may include mental disturbances (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 DULTA and other serotonergic medicines that may affect serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation is advised, particularly during treatment initiation and dose increases.

Hyponatraemia:

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

St. John's Wort:

Adverse reactions may be more common during concomitant use of DULTA 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.

Caution is advised in patients taking anticoagulants and/or medicines known to affect platelet function and in patients with bleeding tendencies.

Postpartum haemorrhage

SNRIs, such as DULTA, may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

Suicide

Major Depressive Disorder and Generalised Anxiety Disorder: Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which DULTA is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at greater risk of

suicidal thoughts or suicidal behaviour and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8).

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

Diabetic Peripheral Neuropathic Pain:

As with other medicinal products with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Concerning risk factors for suicidality in depression, see above. Physicians should encourage patients to report any distressing thoughts or feelings at any time.

Elderly:

Caution is advised when treating elderly patients with the maximum dosage for depression, as data is limited.

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.

Discontinuation of treatment:

Abrupt discontinuation of DULTA can lead to withdrawal symptoms such as headache, nausea, vomiting, dizziness, insomnia, anxiety and paraesthesia. It is therefore recommended that DULTA be withdrawn gradually and the patient monitored to minimise the risk of withdrawal (see section 4.8). The dose should be gradually reduced over a period of at least one to two weeks. If intolerable symptoms occur following a decrease in dose or upon discontinuation of treatment, then resuming the previous prescribed dose may be considered and a more gradual reduction of the dose attempted.

Paediatric population

Use in children and adolescents under 18 years of age:

Safety and efficacy in children under 18 years of age have not been established (see section 4.3).

Information on excipients of DULTA:

DULTA contains lactose. Patients with the rare hereditary conditions galactose intolerance e.g. galactosaemia, Lapp-lactase deficiency or glucose-galactose malabsorption, should not take DULTA.

DULTA contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Monoamine Oxidase Inhibitors (MAOIs):

Due to the risk of serotonin syndrome, DULTA should not be used with a MAOI and at least 14 days should lapse between stopping a MAOI and initiating treatment with DULTA. At least 5 days should lapse after stopping DULTA, before initiating treatment with a MAOI or any medicine liable to provoke a serious reaction. The concomitant use of DULTA with selective, reversible MAOIs, like moclobemide, is not recommended. The antibiotic, linezolid is a reversible non-selective MAO inhibitor and should not be given to patients treated with DULTA (see section 4.3 and 4.4).

Medicines metabolised by CYP1A2:

The pharmacokinetics of theophylline are not significantly affected by co-administration with DULTA (60 mg twice daily), suggesting that DULTA is unlikely to clinically significantly affect CYP1A2 substrates.

Inhibitors of CYP1A2:

Because CYP1A2 is involved in duloxetine metabolism, concomitant use of DULTA with potent inhibitors of CYP1A2 (fluvoxamine, ciprofloxacin and enoxacin) is likely to result in increased duloxetine concentrations. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreases the apparent plasma clearance of duloxetine by about 77 % and increased AUC_{0-t} 6-fold. Caution should be taken when administering DULTA with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3) and a lower DULTA dose is advised.

Inducers of CYP1A2:

Population pharmacokinetic analyses have shown that smokers have almost 50 % lower plasma concentrations of duloxetine, as in DULTA, compared with non-smokers.

Medicines metabolised by CYP2D6:

DULTA is a moderate inhibitor of CYP2D6 and should be used cautiously with medicines that have a narrow therapeutic index and are extensively metabolised by this isoenzyme. When DULTA is administered at a dose of 60 mg twice daily with a single dose of desipramine (a CYP2D6 substrate), the AUC of desipramine increases 3-fold.

Co-administration of DULTA (40 mg twice daily) and tolterodine (2 mg twice daily) increases steady-state AUC of tolterodine by 71 % but with no effect on the pharmacokinetics of the 5 - hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if DULTA is co-administered with medicines that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidrepressants (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 metabolism, concomitant use of DULTA with inhibitors of CYP2D6 may result in increased concentrations of DULTA. The apparent plasma clearance of DULTA is decreased by about 37 % when administered with paroxetine (20 mg once daily). Use with caution if administering DULTA with inhibitors of CYP2D6 (e.g. SSRIs, as this may require lower doses of DULTA).

CNS medicines:

Use DULTA with caution when taken in combination with other centrally acting medicines and substances, including alcohol and those with sedative properties. (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 DULTA is used concomitantly with serotonergic medicines like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's Wort (*Hypericum perforatum*) or triptans, tramadol, pethidine and trypotophan (see section 4.4).

Medicines highly bound to plasma protein:

DULTA is highly bound to plasma protein (> 90 %). Co-administration of DULTA to a patient with another medicine that is highly protein bound may cause an increase in free

concentrations of either medicine and adverse effects may occur.

Anticoagulants and anti-platelet medicines:

Caution should be exercised when DULTA is combined with oral anticoagulants such as warfarin or anti-platelet medicines due to a potential risk of bleeding (see section 4.4). However, concomitant administration of DULTA with warfarin under steady-state conditions, in healthy patients, does 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 DULTA:

Antacids and H_2 antagonists: Co-administration of DULTA with aluminium- and magnesium-containing antacids, or DULTA with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Additional information on special populations

Paediatric population

Safety and efficacy in children under 18 years of age have not been established (see section 4.3*).*

4.6 Fertility, pregnancy and lactation

Fertility

In animal studies, duloxetine had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

Pregnancy

DULTA is contraindicated in pregnancy and lactation (see section 4.3).

There was no evidence of teratogenicity in animal studies.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breastfeeding

Safety has not been established in breastfeeding women. DULTA and/or its metabolites are excreted into milk of lactating rats (see section 4.3). Mothers on DULTA should not breastfeed their infants.

4.7 Effects on ability to drive and use machines:

DULTA may cause sedation and dizziness. Patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking DULTA.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients treated with DULTA 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.

Tabulated list of adverse effects

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Laryngitis
Immune system disorders	Less frequent	Anaphylactic reaction, hypersensitivity disorder, angioedema
Endocrine disorders	Less frequent	Hypothyroidism
Blood and lymphatic system disorders	Less frequent	Increased tendency to bruise
Metabolism and nutrition disorders	Frequent Less frequent	Decreased appetite Dehydration, hyponatraemia, SIADH (syndrome of inappropriate anti-diuretic hormone secretion), hyperglycaemia (reported especially in diabetic patients)

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Psychiatric disorders	Frequent Less frequent	Insomnia, agitation, anxiety, abnormal dreams, anxiety orgasm abnormal, libido decreased Activation of mania or hypomania, bruxism, disorientation, sleep disorder, suicidal ideation, apathy, suicidal behaviour, hallucinations, aggression, anger
Nervous system disorders	Frequent Less frequent	Headache, somnolence, insomnia, sedation, dizziness, tremor, lethargy, paraesthesia Nervousness, restlessness, tension, dysgeusia, dyskinesia, convulsions, myoclonus akathisia, disturbance in attention, restless legs syndrome, poor quality sleep, Serotonin syndrome, convulsions, psychomotor restlessness, extrapyramidal symptoms
Eye disorders	Frequent Less frequent	Blurred vision Mydriasis, visual disturbance, glaucoma

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Ear and labyrinth disorders	Frequent Less frequent	Tinnitus Vertigo, ear pain
Cardiac disorders	Frequent Less frequent	Palpitations Tachycardia, supra-ventricular dysrhythmia, mainly atrial fibrillation
Vascular disorders	Frequent Less frequent	Hot flushes, increased blood pressure Peripheral coldness, orthostatic hypotension, syncope, hypertensive crisis
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Yawning Throat tightness, epistaxis, Interstitial lung disease, Eosinophilic pneumonia
Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting, constipation, diarrhoea, dry mouth, dyspepsia, abdominal pain, flatulence Gastroenteritis, eructation, stomatitis, gastrointestinal haemorrhage, gastritis, dysphagia, haematochezia, breath odour, microscopic colitis

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Hepato-biliary disorders	Less frequent	Increase in liver enzymes (AST, ALT, alkaline phosphatase, bilirubin), acute liver injury, jaundice, hepatitis, hepatic failure
Skin and subcutaneous tissue disorders	Frequent Less frequent	Increased sweating, rash Night sweats, urticaria, photosensitivity reactions, contact dermatitis, cold sweats, pruritus, Stevens-Johnson Syndrome,-cutaneous vasculitis
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Musculoskeletal pain, muscle spasm Muscle twitching, myalgia, muscle tightness, muscle cramps, trismus
Renal and urinary disorders	Frequent Less frequent	Pollakiuria, dysuria Urinary retention, urinary hesitation, nocturia, polyuria, decreased urine flow, abnormal urine odour

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Reproductive system and breast disorders	Frequent Less frequent Frequency unknown	Erectile dysfunction, ejaculation disorder, delayed ejaculation, decreased libido Abnormal orgasm, ejaculatory dysfunction, sexual dysfunction, gynaecological haemorrhage, menstrual disorder, menopausal symptoms, testicular pain, galactorrhoea, hyperprolactinaemia Postpartum haemorrhage
General disorders and administrative site conditions	Frequent Less frequent	Fatigue, asthenia, falls (in the elderly, over 65 years and older) Chest pain, feeling abnormal, feeling cold, chills, thirst, malaise, feeling hot, gait disturbance
Investigations	Frequent Less frequent	Weight decrease Increase in weight, blood creatine phosphokinase increased, blood potassium and blood cholesterol increased

a. Description of selected adverse reactions

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0,3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for

QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

Signs and symptoms of overdose (DULTA alone or in combination with other medicines) is related to the central nervous and gastrointestinal systems, such as tremors, clonic convulsions, ataxia, emesis and decreased appetite).

Management of overdose:

No specific antidote is known for DULTA. An open airway should be established. Monitor cardiac and vital signs, along with symptomatic and supportive measures. Activated charcoal may be useful in limiting the absorption of DULTA. Forced diuresis, haemoperfusion and exchange perfusion are unlikely to be beneficial due to DULTA

having a large volume of distribution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants.

ATC code: N06AX21

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Duloxetine is a serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline reuptake inhibitor (SNRI). Duloxetine is chemically unrelated to tricyclic and tetracyclic antidepressants. Duloxetine weakly inhibits dopamine uptake with no significant affinity for adrenergic, cholinergic, dopaminergic or histaminergic receptors. Duloxetine increased extracellular levels of serotonin and norepinephrine in various brain areas of animals, depending on the dose. 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 Central Nervous System (CNS). The inhibition of pain by duloxetine seems to be the result of potentiation of descending inhibitory pain pathways in the CNS.

5.2 Pharmacokinetic properties

Absorption:

Duloxetine is well absorbed after oral administration with C_{max} reached at 6 hours after oral administration. Food delays the time to reach C_{max} from 6 to 10 hours and marginally decreases the extent of absorption by approximately 11 %. Steady-state plasma concentrations are reached after 3 days of dosing.

Distribution:

Duloxetine is bound to human plasma proteins (more than 90 %); primarily to albumin and alpha 1-acid glycoprotein. Binding is not affected by renal or hepatic impairment.

Biotransformation:

Duloxetine is extensively metabolised by the cytochrome P450 isoenzymes CYP1A2 and CYP2D6. These and other metabolites are excreted principally in urine. Two major, but inactive metabolites are formed (glucoronide 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 with an average of about 12,1 hours. After an oral dose, the mean plasma clearance of duloxetine is 101 L/hr.

Pharmacokinetics in special patient groups

Gender:

Males and females have different pharmacokinetic profiles. The mean plasma clearance is approximately 9 % to 55 % lower in females, while the duloxetine half-life is similar in both genders. 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.

Smoking status:

Duloxetine's bioavailability is 34 % lower in smokers than in non-smokers (see section 4.5).

Age:

Pharmacokinetic differences have been identified between younger and older females (AUC increase by about 25 % and half-life is about 4,3 hours longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment:

Patients receiving chronic haemodialysis for End Stage Renal Disease (ESRD) had 2-fold higher duloxetine C_{max} and AUC values compared to healthy patients. A lower dose should therefore be used in patients with clinically significant renal impairment (see

section 4.3).

Hepatic impairment:

A lower dose should be used for patients with mild to moderate liver impairment. Studies showed that duloxetine's half-life was 34 hours longer in patients with cirrhosis of the liver. Clearance was 15 % of that for the age and gender-matched healthy patients (see section 4.2 and 4.3).

Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79 % lower, the apparent terminal half-life was 2,3 times longer, and the AUC was 3,7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Paediatric population

Safety and efficacy in children have not been established (see section 4.4 and 4.3).

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144

mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

Studies in juvenile rats reveal transient effects on neuro-behaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Hypromellose

Hypromellose phthalate

Lactose monohydrate

Magnesium stearate

Polysorbate 80

Pregelatinised starch

Talc

Triethyl citrate

Gelatine capsule shells.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove capsule from blister until required for use.

Keep the blister in the outer container until required for use.

Keep the HDPE container tightly closed.

Protect from light and moisture.

6.5 Nature and contents of container

DULTA: Blisters are packed in a PVC/PE/ACLAR aluminum strip pack containing 7, 10,14 or 15 capsules per strip, each packed in an outer carton containing 28, 30, 56, 60, 84, 90 or 100 capsules.

DULTA 30 mg: White, round HDPE bottle with a white child resistant cap containing 28, 30, 56, 60, 84, 90 or 100 capsules.

DULTA 60 mg: White, round HDPE bottle with a white child resistant cap containing 28, 30, 56, 60, 84, 90 or 100 capsules.

*Not all presentations are marketed

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBERS

DULTA 30 mg: A46/1.2/0889

DULTA 60 mg: A46/1.2/0890

9. DATE OF FIRST AUTHORISATION

29 September 2017

10. DATE OF REVISION OF THE TEXT

27 August 2021