SCHEDULING STATUS

S5

1. **NAME OF MEDICINE:**

   DUELOKS 30 (Capsules)

   DUELOKS 60 (Capsules)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

DUELOKS 30: Each delayed-release capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg duloxetine

Contains: sugar (sucrose 51.5 mg)

DUELOKS 60: Each delayed-release capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 60 mg duloxetine

Contains: sugar **(**sucrose 103 mg)

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

3. **PHARMACEUTICAL FORM**

Delayed released capsules

DUELOKS 30 (Capsules):

Opaque Blue/ Opaque White Hard Gelatin Capsules size “3” having imprinting “157” on body with green ink and “A” on cap with green ink filled with white to off-white coloured pellets.

DUELOKS 60 (Capsules):

Opaque Blue/ Opaque Green Hard Gelatin Capsules size “1” having imprinting “158” on body with white ink and “A” on cap with white ink filled with white to off-white coloured pellets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

DUELOKS is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).

4.2 Posology and method of administration

Posology

Depression: DUELOKS should be initiated and maintained at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per a day have been used the efficacy of the 120 mg dose was not statistically significant different from that of the 60mg once daily dose and the adverse event rate was higher with the 120 mg dose.

Diabetic peripheral neuropathic pain: DUELOKS should be administered at a dose of 60 mg once daily without regard to meals. Although doses up to 120 mg per a day have been used the efficacy of the 120 mg dose was not statistically 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 **DUELOKS** should be avoided. When stopping treatment with **DUELOKS** the dose should be gradually reduced over a period of at least two weeks 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. Initial dose should be 30 mg once daily in patients with mild moderate impairment of renal function. **DUELOKS** must not be used in patients with severe renal impairment. (See **sections 4.4, 5.2** and **4.3**).

Hepatic impairment: Initial dose should be lower or less frequent in patients with mild to moderate impairment of hepatic function. **DUELOKS** must not be used in patients with severe hepatic impairment. (See **sections 4.4, 5.2** and **4.3**).

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

Paediatric population:

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

Method of administration

For oral use

4.3 Contraindications:

- **DUELOKS** is contraindicated in patients with a known hypersensitivity to duloxetine or to any the excipients.
- Pregnancy and lactation.
- Severe impairment of hepatic function.
- Advanced renal impairment (creatinine clearance < 30 ml/min.)
- Concomitant use of monoamine oxides inhibitors (MAOIs). (See also “section 4.5”).

- Children under 18 years as the safety in children has not been established.

4.4 Special warnings and precautions for use

SUICIDE:

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial medicine therapy. Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine, as contained in **DUELOKS**, therapy and early after the treatment discontinuation.

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 they are taking antidepressant medicines. This risk may persist until significant remission occurs. A casual role, however, for antidepressant medicine in inducing such behaviour has not been established.

Patients being treated with **DUELOKS** 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.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non- psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania, and mania. Although a causal link between the emergence of suicidal impulses has not been established,

consideration should be given to changing the therapeutic regimen, including possibly discontinuing **DUELOKS**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Diabetic Peripheral Neuropathic Pain:

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

Use in children and adolescents under 18 years of age.

DUELOKS has not been studied in patients under the age of 18 and is not intended for use in this age group as safety and efficacy have not been established (see section 4.3). However pooled and some individual data analyses from the studies of some antidepressants in psychiatric conditions indicate a potential increased risk for hostility, self-harm, suicidal ideation and suicidal behaviours in paediatric patients compared to placebo. Medical practitioners should encourage patients to report any distressing thoughts or feelings at any time.

MOAIs (Monoamine Oxidase Inhibitors): **DUELOKS** should not be used within at least 14 days of discontinuing treatment with MAOI. Based on the half-life of **DUELOKS**, at least 5 days should be allowed after stopping **DUELOKS**, before starting a MAOI (see sections 4.3 and 4.5).

Activation of mania/hypomania:

DUELOKS should be used cautiously in patients with history of mania.

Seizures:

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

Mydriasis:

Mydriasis has been reported in association with duloxetine; therefore, caution should be used when prescribing **DUELOKS** in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Renal or hepatic impairment:

Increased plasma concentrations of **DUELOKS** occur in patients with renal impairment or hepatic impairment. A Lower starting dose should be used in such patients (see **sections 4.2, '5.2;** and **"4.3".**)

Elevated liver enzymes: DUELOKS is associated with an increased in blood pressure in some patients. In patients with known hypertension and or other cardiac diseases blood pressure monitoring is recommended as appropriate.

Increased blood pressure: elevations in the liver enzymes were seen in some patients treated with **DUELOKS**. These are usually transient and self-limiting or resolved upon discontinuation of **DUELOKS.** Severe elevations of the liver enzymes (> 10 x upper limit of normal) or liver injury with cholestatic or mixed pattern have been rarely reported, in some cases associated with excessive alcohol use.

DUELOKS should be used with caution in patients with substantial alcohol use.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with **DUELOKS** 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 **DUELOKS** 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 **DUELOKS** 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. **DUELOKS** 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 **DUELOKS**, 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.

Akathisia/psychomotor restlessness:

The use of **DUELOKS** 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:

DUELOKS is used under different product names in several indications.

The use of more than one of these medicines concomitantly should be avoided.

Sexual dysfunction

DUELOKS may cause symptoms of sexual dysfunction (see section 4.8). These symptoms may continue despite discontinuation of **DUELOKS**

Elderly

Data on the use of **DUELOKS** 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).

Sucrose

DUELOKS contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **DUELOKS**

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOI's):

Due to the risk of serotonin syndrome, **DUELOKS** should not be used in combination with monoamine oxidase inhibitors or within at least 14 days of discontinuation of treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping **DUELOKS** before starting an MAOI (see sections 4.3 and 4.4).

Serotonergic medicines:

Serotonin syndrome has been reported in patients using SSRI/SNRI concomitantly with serotonergic medicines. Caution is advised if **DUELOKS** is used concomitantly with serotonergic medicines like SSRI/SNRI, tricyclic antidepressants like clomipramine or amitriptyline, St John's Wort or triptans, tramadol, pethidine, and tryptophan. Concomitant use with MAOI's like moclobemide or linezolid is contraindicated (see above and section 4.3).

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

Inhibitors of CYP1A2: Because CYP1A2 is involved in **DUELOKS** metabolism concomitant use of **DUELOKS** with inhibitors of CYP1A2 will result in higher concentrations of **DUELOKS**. Fluvoxamine (100 mg once daily), an inhibitor of CYP1A2, decreased the apparent plasma clearance of **DUELOKS** by about 77 %. Caution is advised if administering **DUELOKS** with inhibitors of CYP1A2 (e.g. quinolone antibiotics) and the lower **DUELOKS** dose should be used.

Medicines metabolised by CYP2D6: DUELOKS is a moderator inhibitor of **CYP2D6**. When **DUELOKS** was administered at the 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 **DUELOKS** (40 mg twice daily) increase steady - state AUC of tolterodine (2 mg twice daily) by 71 % but did not affect the pharmacokinetics of the 5-hydroxl metabolite. Therefore, caution should be used if **DUELOKS** is co-administered with medications that are predominantly metabolised by CYP2D6 system and which have a narrow therapeutic index.

Inhibitors of CYP2D6 : Because CYP2D6 is involved in **DUELOKS** metabolism, concomitant use of **DUELOKS** with the inhibitors of CYP2D6 is involved will result in higher concentrations of **DUELOKS** Paroxetine (20mg once daily) decreased the apparent plasma clearance of **DUELOKS** by about 37 % caution is advised if administering **DUELOKS** with inhibitors of CYP2D6 (e.g. SSRI's).

CNS medicines:

Caution is advised when **DUELOKS** is taken in combination with other centrally acting medicines and substances including alcohol.

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

Oral contraceptives and other steroidal medicines*:* Results of *in vitro* studies demonstrate that **DUELOKS** does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet medicines*:* Caution should be exercised when **DUELOKS** 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnant women has not been established (see section 4.3).

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late

pregnancy may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

Discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine, as is contained in **DUELOKS,** 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. Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth).

Breast feeding

The use of **DUELOKS** while breast feeding is contraindicated (see section 4.3)

Duloxetine and /or its metabolites are excreted into human breast milk.

Fertility

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

4.7 Effects on ability to drive and use machines

DUELOKS may be associated with undesirable effects such as sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, while taking **DUELOKS.**

4.8 Undesirable effects

Infections and infestations

Less frequent: Laryngitis

Immune system disorder

Less frequent: Anaphylactic reaction, hypersensitivity disorders

Endocrine disorders:

*Less frequent***:** Hypothyroidism

Metabolism and nutrition disorders

Frequent: Decreased appetite

Less Frequent: Dehydration, hyponatremia, SIADH, hyperglycaemia (reported especially in diabetic patients).

Psychiatric disorders:

Frequent: Insomnia, anorgasmia, libido decreased, anxiety, sleep disorder, abnormal dreams.

Less Frequent: Agitation, bruxism, disorientation, apathy, suicidal ideation, mania, hallucinations, aggression, and anger.

Frequency unknown: Hostility, suicidal ideation and self-harm have been reported in children treated with SSRIs or SNRIs like **DUELOKS**

Nervous system disorders:

Frequent: Dizziness, headache, lethargy, somnolence (hypersomnia, sedation), tremor and paraesthesia

Less Frequent: Dysgeusia, myoclonus, akathisia, nervousness, disturbance in attention, dyskinesia, restless legs syndrome, poor quality sleep, serotonin syndrome, convulsion, psychomotor restlessness, extra-pyramidal symptoms

Eye disorders:

Frequent: Vision blurred

Less Frequent: Mydriasis, Visual disturbance, glaucoma

Ear and labyrinth disorders:

Frequent: Blurred vision

Less frequent: Vertigo, ear pain

Cardiac disorders:

Frequent: Palpitations

Less Frequent: Tachycardia, supra-ventricular arrhythmia, mainly atrial fibrillation

Vascular disorder:

Frequent: Hot flush, blood pressure increase.

Less Frequent: Flushing, peripheral coldness, syncope, orthostatic hypotension, hypertensive crisis.

Respiratory, thoracic and mediastinal disorders:

Frequent: Yawning

Less Frequent: Throat tightness, epistaxis, interstitial lung disease, eosinophilic pneumonia.

Gastrointestinal disorders:

Frequent: Constipation, dry mouth, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, flatulence

Less Frequent: Eructation, gastroenteritis, stomatitis, gastritis, dysphagia, gastrointestinal haemorrhage, stomatitis, haematochezia, breath odour, microscopic colitis.

Hepatobiliary disorder

Less frequent: Hepatitis, jaundice,

elevated liver enzymes (ALT, AST, alkaline phosphatase), acute liver injury, hepatic failure

Skin and subcutaneous tissue disorder:

Frequent: Hyperhidrosis, rash

Less Frequent: Night sweats, photosensitivity, urticaria, dermatitis contact, cold sweat, Stevens-Johnson syndrome, angio-neurotic oedema, cutaneous vasculitis

Musculoskeletal and connective tissue disorders:

Frequent: Musculo-skeletal pain, muscle spasm

Less Frequent: Muscle tightness, muscle twitching, trismus

Renal and urinary disorders:

Frequent: Dysuria, pollakiuria

Less Frequent: Nocturia, urinary hesitation, urinary retention, nocturia, polyuria, urine flow decreased, urine odour abnormal.

Reproductive system and breast disorders:

Frequent: Ejaculation disorder, erectile dysfunction, ejaculation delayed.

Less Frequent: Gynaecological haemorrhage, menstrual disorder, sexual dysfunction, testicular pain, menopausal symptoms, galactorrhoea, hyperprolactinaemia, postpartum haemorrhage.

General disorders and administration site conditions:

Frequent: Fatigue, rigors, falls

Less Frequent: Feeling abnormal, feeling hot and or cold, malaise, thirst, gait disturbance, chest pain, chills.

Investigations:

Frequent: Weight decreased

Less Frequent: Blood pressure increased, hepatic lab related findings, weight increased, blood cholesterol increased, blood creatine phosphokinase increased, blood potassium increased

Description of selected adverse reactions:

Discontinuation of duloxetine, as contained in **DUELOKS**, 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 **DUELOKS** 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. Health care 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://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Treatment should be symptomatic and supportive.

Cases of overdoses, alone or in combination with other medicines, with duloxetine doses of
5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with
duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms 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 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: A1.2 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 tricycle 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 the various brain areas of animals.

Neurochemical and behavioural studies in the 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 pathways with 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.

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 neurotransmission in the CNS.

5.2 Pharmacokinetic properties

Absorption: Duloxetine is well absorbed after oral administration with the Cmax occurring 6 hours post-dose. Food delays the time to reach a 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 the plasma proteins, primarily to albumin and acid glycoprotein. Protein binding is not affected by the renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised, and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse 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 hour. 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 Cmax 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 "**sections 4.2** and **4.3)**

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DUELOKS 30

(Colourants: FD and C Blue 2 aluminium lake, yellow iron oxide), gelatin, hypromellose, hypromellose phthalate, propylene glycol, shellac, starch, talc, titanium dioxide triethyl citrate.

Contains: sugar **(**sucrose 51.5mg)

DUELOKS 60

(Colourants: FD and C Blue 2 aluminium lake, yellow iron oxide), hypromellose, hypromellose phthalate, iron oxide yellow, propylene glycol, potassium hydroxide, methylene chloride, shellac, talc, titanium dioxide triethyl citrate.

Contains: sucrose 103 mg

6.2 Incompatibilities

None

6.3 Shelf life

DUELOKS 30 mg: 36 months

DUELOKS 60 mg: 36 months

6.4 Special Precautions for storage

Store at or below 25 °C. Protect from moisture and light

6.5 Nature and contents of container

DUELOKS 30 mg: 28 capsules in Alu/Alu blister pack (Aluminium foil and cold form blister foil) or Aluminium foil and clear transparent PVC/ Aclar film blister pack.

DUELOKS 60 mg: 28 capsules in Alu/Alu blister pack (Aluminium foil and cold form blister foil) or Aluminium foil and clear transparent PVC/ Aclar film blister pack.

Strips with a package insert are placed in a unit carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

REGISTRATION NUMBERS

DUELOKS 30: 52/1.2/0921

DUELOKS 60: 52/1.2/0922

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/01/2021

DATE OF REVISION OF THE TEXT

TBI