PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF MEDICINE

FELITOR (10 mg Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains escitalopram oxalate corresponding to 10 mg escitalopram.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off white, round, biconvex, film coated tablets debossed with break line on both sides, separating '11' and '36' on one side and '10' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes

4.2 Posology and method of administration

Posology

Adults

Major depressive episodes:

FELITOR should be administered as a single oral dose of 10 mg daily in otherwise healthy adults.

Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Usually 2-4 weeks are necessary for an antidepressant response.

Elderly patients (>65 years of age)

The maximum recommended dose for elderly patients is 10 mg daily. A longer half-life and a decreased clearance have been demonstrated in the elderly.

Reduced renal function

Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance <30 mℓ/min.).

Reduced hepatic function

The maximum recommended dose for adult patients with hepatic impairment is 10 mg.

When stopping FELITOR therapy, gradual dose reduction should be considered. Withdrawal symptoms (see section 4.8) when stopping treatment is common, particularly if discontinuation is abrupt.

FELITOR is administered as a single daily dose. FELITOR may be taken without regard to food intake.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to escitalopram or any of the other ingredients in FELITOR (see section 6.1).
- Children and adolescents under the age of 18 years (see section 4.4 and 4.8).
- Pregnancy and lactation (see section 4.6).
- ***Monoamine Oxidase Inhibitors***- Cases of serious reactions have been reported in patients receiving an SSRI such as FELITOR in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on an MAOI (see section 4.5).
- Some cases presented with features resembling serotonin syndrome (see section 4.8).
- FELITOR should not be used in combination with a MAOI. FELITOR may be started 14 days after discontinuing treatment with a MAOI. At least 7 days should elapse after discontinuing FELITOR treatment before starting a MAOI.
- Patients with known QT interval prolongation or congenital long QT syndrome (see section 4.4).
- Concomitant treatment with linezolid.
- Concomitant treatment with pimozide as the combination may lead to clinically significant QT_C prolongation.

4.4 Special warnings and precautions for use

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

FELITOR should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt, suicidal thoughts as well as suicidal ideation and self-harm), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently reported among children and adolescents treated with antidepressants including SSRIs such as FELITOR.

Mania – FELITOR should be discontinued in any patient entering a manic phase. FELITOR should be used with caution in patients with a history of mania/hypomania.

Paradoxical anxiety - Some patients with panic disorder may experience increased anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Seizures - FELITOR should be discontinued in any patient who develops seizures. FELITOR should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. FELITOR should be discontinued if there is an increase in seizure frequency.

Diabetes mellitus - In patients with diabetes mellitus, treatment with FELITOR may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Suicide/thoughts or clinical worsening - Patients with depression, may experience worsening of their depression and or the emergence of suicidal thoughts, ideation, self-harm and suicide (suicide-related events) whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. As improvement may not occur during the first weeks or more of treatment, patients being treated with FELITOR should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

It has been reported that antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany FELITOR 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.

The following symptoms have been reported in patients being treated with antidepressants such as FELITOR for major depressive disorder, 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 such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing FELITOR, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision is made to discontinue treatment, FELITOR should be tapered (See section 4.2 and section 4.4).

Akathisia/psychomotor restlessness - The use of SSRIs/SNRIs has been associated with the development of akathisia. In patients who develop symptoms, increasing the dose may be detrimental. A subjectively unpleasant or distressing restlessness and need to move often

accompanied by an inability to sit or stand still is indicative of akathisia. This is most likely to occur within the first few weeks of treatment.

Hyponatraemia - Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be taken with patients at risk, such as patients with cirrhosis or the elderly, or if used in combination with other medications which may cause hyponatraemia.

Haemorrhage - There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura with FELITOR. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking FELITOR, particularly in concomitant use with medicines known to affect platelet function (e.g. atypical anti-psychotics and phenothiazines, most tricyclic antidepressants, aspirin, non-steroidal anti-inflammatory medicines (NSAIDs), ticlopidine and dipyridamole), as well as in patients with a history of bleeding disorders.

ECT (electroconvulsive therapy) - There is limited published clinical experience of concurrent administration of FELITOR and ECT, therefore caution is advisable.

Monoamine oxidase inhibitor (MAOI) – Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on a MAOI. In some cases the patient developed serotonin syndrome (see section 4.8). FELITOR should not be used in combination with a MAOI (see section 4.3). FELITOR may be started 14 days after discontinuing treatment with an MAOI. At least 7 days should elapse after discontinuing FELITOR

treatment before starting a MAOI. The combination of escitalopram with MAO-A inhibitors is contraindicated.

Serotonin syndrome – Special care is advisable if escitalopram is used concurrently with medicinal products with serotonergic effects such as tramadol, tryptophan and sumatriptan or other triptans.
In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as hyperthermia, myoclonus, tremor and agitation may be indicative of the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

St. John's wort - Concomitant use of SSRIs and herbal remedies containing St. John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

Discontinuation symptoms seen when stopping treatment - Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (See section 4.8).
The risk of discontinuation symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. 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 FELITOR should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see Section 4.2).

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/SNRI.

Coronary heart disease - Due to limited clinical experience, caution is advised in patients with coronary heart disease.

QT interval prolongation - Escitalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly

in female patients with cardiac diseases, with hypokalaemia, or with pre-existing QT interval prolongation.

Electrolyte disturbances - Electrolyte disturbances such as hypomagnesaemia and hypokalaemia elevate the risk for malignant arrhythmias and should be corrected before treatment with escitalopram commence.

Bradycardia - Special care should be taken in patients with significant bradycardia; or in patients with uncompensated heart failure or recent acute myocardial infarction.

Cardiac disease and cardiac dysrhythmia - An ECG review should be considered before commencing treatment in patients with stable cardiac disease. If signs of cardiac dysrhythmia occur, the treatment with escitalopram should be withdrawn and an ECG should be performed.

Angle-Closure Glaucoma - SSRIs including escitalopram may have an effect on pupil size resulting in mydriasis. This mydriatic effect has, especially in patients pre-disposed, the potential to narrow the eye angle resulting in angle-closure glaucoma and an increase in intraocular pressure. FELITOR should therefore be used with care in patients with angle-closure glaucoma or history of glaucoma.

Excipients - This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Contraindicated combinations:

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective, irreversible monoamine oxidase inhibitor (MAOI), and in patients who have recently

discontinued SSRI treatment and have been started on such MAOI treatment (see section 4.3). In some cases, the patient developed serotonin syndrome (see section 4.8).

Escitalopram is contraindicated in combination with non-selective, irreversible MAOIs.

Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective, irreversible MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO-A inhibitor such as moclobemide is contraindicated (see section 4.3). If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.

Reversible, non-selective MAO-inhibitor (linezolid)

The antibiotic linezolid is a reversible non-selective MAO-inhibitor and should not be given to patients treated with escitalopram. If the combination proves necessary, it should be given with minimum dosages and under close clinical monitoring (see section 4.3).

Irreversible, selective MAO-8 inhibitor (selegiline)

In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome. Selegiline doses up to 10 mg/day have been safely co-administered with racemic citalopram.

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of escitalopram

and these medicinal products cannot be excluded. Therefore, co-administration of escitalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, hydroxyzine, mizolastine), is contraindicated.

Combinations requiring precautions for use:

Serotonergic medicinal products

Co-administration with serotonergic medicinal products (e.g. opioids (including tramadol), and triptans (including sumatriptan) may lead to serotonin syndrome (see section 4.4).

Medicinal products lowering the seizure threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquin, bupropion and tramadol).

Lithium, tryptophan

There have been reports of enhanced effects when SSRIs have been given together with lithium or tryptophan, therefore concomitant use of SSRIs with these medicinal products should be undertaken with caution.

St. John's wort

Concomitant use of SSRIs and herbal remedies containing St. John's wort (Hypericum perforatum) may result in an increased incidence of adverse reactions (see section 4.4).

Haemorrhage

Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped (see section 4.4). Concomitant use of non-steriodal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency (see section 4.4).

Alcohol

No pharmacodynamic or pharmacokinetic interactions are expected between escitalopram and alcohol. However, as with other psychotropic medicinal products, the combination with alcohol is not advisable.

Medicinal products inducing hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias (see section 4.4).

Pharmacokinetic interactions

Influence of other medicinal products on the pharmacokinetics of escitalopram

The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6. Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50 %) increase in the plasma concentrations of escitalopram. Co-administration of escitalopram with cimetidine 400 mg twice daily (moderately potent general enzyme-inhibitor) resulted in a moderate (approximately 70 %) increase in the plasma

concentrations of escitalopram. Caution is advised when administering escitalopram in combination with cimetidine. Dose adjustment may be warranted.

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment (see section 4.4).

Effect of escitalopram on the pharmacokinetics of other medicinal products

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine or metoprolol resulted in both cases in a twofold increase in the plasma levels of these two CYP2D6 substrates.

In vitro studies have demonstrated that escitalopram may also cause weak inhibition of CYP2C19. Caution is recommended with concomitant use of medicinal products that are metabolised by CYP2C19.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate) (single dose), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin. However, prothrombin time

was slightly increased after a single dose of 25 mg warfarin. The International Normalised Ratio (INR) needs to be carefully monitored in patients on the combination.

4.6 Fertility, pregnancy and lactation

Pregnancy: FELITOR should not be used during pregnancy, Using SSRIs like FELITOR in the third trimester may result in effects, including neurobehavioural disturbances, in the newborn infant.

Lactation: It is expected that escitalopram will be excreted into human milk. Breastfeeding is therefore not recommended during treatment with FELITOR.

Fertility: It has been reported that some SSRIs may affect sperm quality. Human case reports with some SSRs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

FELITOR can cause dizziness and somnolence. Patients may have an impaired ability to drive or operate machinery. They should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

Adverse reactions observed with FELITOR are most frequent during the first one or two weeks of treatment and may decrease in intensity and frequency with continued treatment.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and the lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Less frequent	Anaphylactic reaction, Angioedema
Endocrine disorders	Frequency unknown	Inappropriate ADH secretion
Metabolism and nutrition disorders	Frequent	Decreased appetite, increased appetite, increased weight
	Less frequent	Decreased weight
	Frequency unknown	Hyponatraemia, anorexia[1]
Psychiatric disorders	Frequent	Anxiety, restlessness, abnormal dreams Female and male: decreased libido Female: anorgasmia
	Less frequent	In children reports of hostility, suicidal ideation and self-harm Bruxism, agitation, nervousness, panic attack, confusional state, aggression, depersonalisation, hallucination
	Frequency unknown	Mania, suicidal ideation, suicidal behaviour[2]
Nervous system disorders	Frequent	Headache, insomnia, somnolence, dizziness, paraesthesia, tremor
	Less frequent	Taste disturbance, sleep disorder, syncope, serotonin syndrome

	Frequency unknown	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia[1]
Eye disorders	Less frequent	Mydriasis, visual disturbance
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Tachycardia, bradycardia
	Frequency unknown	Electrocardiogram QT prolonged ventricular dysrhythmia including torsade de pointes
Vascular disorders	Frequency unknown	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Sinusitis, yawning
	Less frequent	Epistaxis
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, constipation, vomiting, dry mouth
	Less frequent	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepato-biliary disorders	Frequency unknown	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Frequent	Increased sweating
	Less frequent	Urticaria, alopecia, rash, pruritus
	Frequency unknown	Ecchymosis, angioedemas
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia, myalgia
Renal and urinary disorders	Frequency unknown	Urinary retention
Reproductive system and breast disorders	Frequent	Male: ejaculation disorder, impotence
	Less frequent	Female: metrorrhagia, menorrhagia

	Frequency unknown	Galactorrhoea, Female: postpartum haemorrhage[3] Male: priapism
General disorders and administrative site conditions	Frequent	Fatigue, pyrexia
	Less frequent	Oedema

[1] These events have been reported for the therapeutic class of SSRIs.

[2] Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4).

[3] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

QT interval prolongation:

Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

Class effects:

Epidemiological studies, mainly conducted in patients 50 years of age and older, reported an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Discontinuation symptoms seen when stopping treatment:

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock

sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the frequently reported reactions.
Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when escitalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and 4.4).

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

Symptoms

Symptoms and signs as described under section 4.8 may occur.

Treatment

There is no specific antidote. Treatment is supportive and symptomatic. The use of activated charcoal should be considered.
Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures. ECG monitoring is advised in case of overdose in patients with congestive heart

failure/bradydysrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

ATC-code: N 06 AB 10

Biochemical and behavioural studies have shown that escitalopram is a potent and selective inhibitor of serotonin (5-HT)-uptake.

Escitalopram has minimal effect of noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

Escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine and opioid receptors.

Escitalopram has high affinity for the primary binding site, and an allosteric modulating effect on the serotonin transporter. Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

5.2 Pharmacokinetic properties

Absorption: Absorption is independent of food intake (mean Tmax is 4 hours after multiple dosing).

Distribution: The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is approximately 55 %.

Biotransformation: Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolite. Alternatively the nitrogen may be oxidised to form N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the prominent compound in plasma. After multiple dosing the mean concentration of the dimethyl and didemethyl metabolites are usually 28-31 % and <5 % of the escitalopram concentration, respectively. Biotransformation of escitalopram to demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Elimination: The elimination half-life ($t_{1/2\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0,6 L/min. Escitalopram and major metabolites are- like racemic citalopram- assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolite in urine. Hepatic clearance is mainly by the P450 enzyme system. CYP2C19 is the primary isoenzyme involved in the demethylation of escitalopram, followed by CYP3A4 and CYP2D6.

There is linear pharmacokinetics. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (range 20 to125 nmol/L) are achieved at a dose of 10 mg.

Elderly patients (>65 years of age)

A longer half-life (about 50 %) and decreased clearance values, due to reduced rate of metabolism, have been demonstrated in elderly.

Reduced hepatic function

Escitalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of escitalopram is about twice as long and steady state escitalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

Reduced renal function

Escitalopram is eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on escitalopram concentrations in serum. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <30 mℓ/min).

Polymorphism

It has been reported that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was reported in poor metabolisers with respect to CYP2D6 (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Colloidal silicon dioxide (anhydrous)

Croscarmellose sodium (Ac-Di-Sol)

Isopropyl alcohol

Magnesium stearate

Microcrystalline cellulose

Povidone K-30

Talc

Tablet coating

Hypromellose

Polyethylene glycol 400

Titanium dioxide

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the outer carton until required for use

6.5 Nature and contents of container

Cold Forming Blister foil (OPA/ALU/PVC) sealed with aluminium foil with heat seal lacquer coating.

Printed carton containing 10 tablets, 30 tablets or 100 tablets. Each blister contains 10 tablets.

Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

TRINITY PHARMA (PTY) LTD.

18 NORMA JEAN SQUARE, 244 JEAN AVENUE, CENTURION,

SOUTH AFRICA

8. REGISTRATION NUMBER(S)

45/1.2/1032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 May 2019

10. DATE OF REVISION OF THE TEXT

27 September 2024