SCHEDULING STATUS **S5**

1 NAME OF THE MEDICINE

CITRAZ 5, 5 mg, film-coated tablets

CITRAZ 10, 10 mg, film-coated tablets

CITRAZ 20, 20 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CITRAZ 5: Each film-coated tablet contains escitalopram oxalate equivalent to escitalopram 5 mg.

Contains 12,41 mg lactose monohydrate (sugar) per tablet.

CITRAZ 10: Each film-coated tablet contains escitalopram oxalate equivalent to escitalopram 10 mg.

Contains 24,825 mg lactose monohydrate (sugar) per tablet.

CITRAZ 20: Each film-coated tablet contains escitalopram oxalate equivalent to escitalopram 20 mg.

Contains 49,65 mg lactose monohydrate (sugar) per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

CITRAZ 5: White, round, biconvex, film-coated tablets debossed ‘RDY’ on one side and ‘462’ on the other side.

CITRAZ 10: White, round, biconvex, film-coated tablets debossed ‘RDY 463’ on one side

and break-line on the other side.

CITRAZ 20: White, round, biconvex, film-coated tablets debossed ‘RDY 464’ on one side and break-line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes and panic disorders.

4.2 Posology and method of administration

Posology

Adults

Major depressive episodes

The initial dose is 10 mg once daily, with or without food, in otherwise healthy adults. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Safety of doses above 20 mg has not been shown.

Usually 2 to 4 weeks are necessary for an antidepressant response. After resolve of symptoms, treatment for at least 6 months is required for consolidation of the response.

Panic disorder

A single oral dose of 5 mg once daily, with or without food, is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response.

Elderly patients (> 65 years of age)

A lower initial and maximum dose is recommended. (See section 5.2).

The initial dose is 5 mg once daily, with or without food. Depending on the individual patient response, the dose may be increased to a maximum of 10 mg daily in otherwise healthy patients.

Reduced renal function

Dosage adjustment is not necessary in patients with mild or moderate renal impairment.

Caution is advised as no information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min).

Reduced hepatic function

An initial single oral dose of 5 mg once daily, with or without food, is recommended for the first two weeks of treatment in patients with mild to moderate hepatic impairment.

The dose may be further increased, up to a maximum of 10 mg daily, dependent on individual patient response.

Caution and extra careful dose titration is advised in patients with severely reduced hepatic function.

Poor metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg once daily, with or without food, during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg once daily. See “Polymorphism” (under section 5.2).

Discontinuing treatment with CITRAZ

Abrupt discontinuation of CITRAZ should be avoided.

Gradual discontinuation by dose tapering, is recommended, over a period of several weeks or months, according to the patient's needs.

The dose should be reduced gradually over a period of at least one to two weeks in order to reduce the risk of discontinuation symptoms which are generally mild to moderate and self-limiting (usually resolve within 2 weeks), however in some patients they may be severe and/ or prolonged (2 to 3 months or more).

(See section 4.8, “Discontinuation symptoms”).

They usually occur within the first few days of discontinuing treatment, but there have been reports of such symptoms in patients who have inadvertently missed a dose.

If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, (see sections 4.8 and 4.4) then resuming the previously prescribed dose may be considered. Subsequently, the doctor may continue decreasing the dose, but at a more gradual rate.

Method of administration

Oral administration.

4.3 Contraindications

-Hypersensitivity to escitalopram or any of the excipients of CITRAZ.

-Children and adolescents under 18 years of age, as safety and efficacy have not been established in these populations. (See section 4.4).

-Patients with ECG QT prolongation or congenital long QT syndrome

CITRAZ is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome. (See section 4.4).

-Co-administration of CITRAZ with the following medicines are contraindicated

-Medicines that prolong the QT Interval (ECG)

(See section 4.5).

Concomitant treatment with pimozide is contraindicated as the combination may lead to clinically significant QTc prolongation.

-Monoamine oxidase inhibitors (**MAOIs)**

CITRAZ should not be used in combination with MAOIs (e.g. linezolid).

Cases of serious reactions have been reported in patients receiving SSRIs such as CITRAZ in combination with monoamine oxidase inhibitors (MAOIs), and in patients who have recently discontinued an SSRI and have been started on MAOIs.

In some cases the patient developed serotonin syndrome.

(See sections 4.5, 4.8 and 4.4).

CITRAZ should not be started for at least 14 days after discontinuing treatment with a MAOI.

At least 7 days should elapse after discontinuing CITRAZ treatment before starting a MAOI.

4.4 Special warnings and precautions for use

Not to be used in children and adolescents under 18 years of age.

Suicide related behaviour and hostility were more frequent in these populations treated with antidepressants in clinical trials, compared to those receiving placebo. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Mania

CITRAZ should be used with caution in patients with a history of mania/ hypomania.

CITRAZ should be discontinued in any patient entering a manic phase.

Paradoxical anxiety

Some patients with panic disorder may experience increased anxiety symptoms at the start of treatment with CITRAZ. 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

CITRAZ should be discontinued in any patient who develops seizures for the first time, or if there is an increase in seizure frequency in patients with known epilepsy. CITRAZ should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored.

Diabetes mellitus

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

Suicide/suicidal thoughts or clinical worsening

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. This 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 CITRAZ 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 CITRAZ, 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, CITRAZ should be tapered (See section 4.2).

As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until improvement and after dose changes. The risk of suicide may increase in the early stages of recovery.

Patients with a history of these events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk.

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.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with CITRAZ.

Caution is advised in patients taking CITRAZ, particularly in concomitant use with oral anticoagulants, with medicines known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

Akathisia/psychomotor restlessness

The use of CITRAZ 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.

Hyponatraemia

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

Coronary heart disease

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

QT interval prolongation

CITRAZ has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular dysrhythmia, including torsade de pointes, have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases.

(See sections 4.3 and 4.5).

Caution is advised in patients with significant bradycardia and in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk of malignant dysrhythmias and should be corrected before treatment with CITRAZ is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac dysrhythmia occur during treatment with CITRAZ, the treatment should be withdrawn and an ECG should be performed.

ECT (Electroconvulsive therapy)

There is limited published clinical experience of concurrent administration of CITRAZ and ECT, therefore caution is advisable.

Discontinuation symptoms seen when stopping treatment

Discontinuation of CITRAZ (particularly when abrupt) commonly leads to discontinuation symptoms. (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.

Combinations requiring precautions for use – Serotonin syndrome

Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan), as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome.

Serotonin syndrome has been reported in patients using CITRAZ concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with CITRAZ and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

Medicinal products lowering the seizure threshold

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

Lithium, tryptophan

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

Anticoagulants - Haemorrhage.

Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when CITRAZ is started or stopped. Concomitant use of non-steriodal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency.

St. John´s Wort

Concomitant use of SSRIs like CITRAZ and herbal remedies containing St. John´s Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

Alcohol

No pharmacodynamic or pharmacokinetic interactions are expected between CITRAZ and alcohol. However, the combination with alcohol is not advisable.

Lactose

CITRAZ 5, 10 and 20 contain lactose. Patients with the rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take CITRAZ**.**

4.5 Interaction with other medicines and other forms of interaction

Contraindicated combinations – see also section 4.3

Monoamine Oxidase Inhibitors (MAOIs)

Starting CITRAZ in a patient who is being treated with MAOIs such as linezolid (a reversible non-selective MAO-inhibitor) is contraindicated because of an increased risk of serotonin

syndrome. (See section 4.3).

QT Interval prolongation

Pharmacokinetic and pharmacodynamic studies of CITRAZ combined with other medicines that prolong the QT interval have not been performed, but an additive effect of CITRAZ and these medicines cannot be excluded. Examples include

- Class IA and III antidysrhythmics
- antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol)
- tricyclic antidepressants
- certain antimicrobial agents (e.g. moxifloxacin, erythromycin, anti-malarial treatment particularly halofantrine)
- certain antihistamines (astemizole, mizolastine)

See section 4.3.

Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome (See section 4.4).

There have been reports of enhanced effects when CITRAZ has been given with lithium or tryptophan (See section 4.4).

SSRIs like CITRAZ can lower the seizure threshold. Caution is advised when concomitantly using other medicines capable of lowering the seizure threshold. (See section 4.4).

Pharmacokinetic interactions

Influence of other medicinal products on the pharmacokinetics of CITRAZ.

The metabolism of CITRAZ 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. Caution should be exercised when CITRAZ is used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of CITRAZ may be necessary based on monitoring of side-effects

during concomitant treatment.

CITRAZ is an inhibitor of the enzyme CYP2D6. Caution is recommended when CITRAZ is co-administered with medicines 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 medicines 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.

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

The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with CITRAZ.

Racemic citalopram increased the AUC of selegiline by 29 %.

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

The safety of CITRAZ in pregnant and lactating women has not been established.

Pregnancy

Only limited clinical data are available regarding exposed pregnancies.

Neonates should be observed if maternal use of CITRAZ continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonate after maternal use of SSRIs like CITRAZ in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (< 24 hours) after delivery.

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).

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).

Lactation

It is expected that CITRAZ will be excreted into human milk.

Consequently, breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

CITRAZ has not been shown to impair intellectual function or psychomotor performance. Nevertheless, any psychoactive medicines may potentially impair judgement or skills and cause drowsiness and fatigue. Patients should be cautioned about the potential risk on their ability to drive or operate machinery.

4.8 Undesirable effects

Adverse reactions with CITRAZ are most frequent during the first or second week of treatment and may decrease in intensity and frequency with continued treatment.

Adverse reactions known for selective serotonin reuptake inhibitors (SSRIs) and also reported for escitalopram containing products like CITRAZ in either placebo-controlled clinical studies or as spontaneous post-marketing events are listed below by system organ class and frequency.

Blood and lymphatic system disorders

Frequency unknown: Thrombocytopenia

Immune system disorders

Less frequent: Anaphylactic reaction

Frequency unknown: Angioedema

Endocrine disorders

Frequency unknown: Inappropriate ADH secretion

Metabolism and nutrition disorders

Frequent: Decreased appetite, increased appetite, weight increased

Less frequent: Weight decreased

Frequency unknown: Hyponatraemia, anorexia

Psychiatric disorders

Frequent: Anxiety, restlessness, abnormal dreams

Less frequent: Bruxism, agitation, nervousness, panic attack, confusional state, aggression, depersonalisation, hallucinations

Frequency unknown: Mania, suicidal ideation, suicidal behaviour

Nervous system disorders

Frequent: Insomnia, somnolence, dizziness, paraesthesia, tremor, drowsiness

Less frequent: Taste disturbance, sleep disorder, syncope.

Serotonin syndrome (typically characterised by a rapid onset of changes in mental state with confusion, mania, agitation, hyperactivity, shivering, fever, ocular movements, myoclonus, hyperreflexia and incoordination)

Frequency unknown: Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia

Eye disorders

Less frequent: Mydriasis, visual disturbance (abnormal vision)

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)

Hepatobiliary disorders

Frequency unknown: Hepatitis, liver function test abnormal

Skin and subcutaneous tissue disorders

Frequent: Sweating increased

Less frequent: Urticaria, alopecia, rash, pruritus

Frequency unknown: Ecchymosis

Musculoskeletal and connective tissue disorders

Frequent: Arthralgia, myalgia

Frequency unknown: Bone fractures

Renal and urinary disorders

Frequency unknown: Urinary retention

Reproductive system and breast disorders

Frequent: Decreased libido, ejaculation disorder and impotence (male)

Less frequent: Metrorrhagia, menorrhagia, anorgasmia

Frequency unknown: Galactorrhoea, priapism, postpartum haemorrhage*

General disorders and administration site conditions

Frequent: Fatigue, pyrexia

Less frequent: Oedema

- Discontinuation symptoms when stopping treatment (particularly when abrupt): (See "Discontinuing treatment with CITRAZ" under section 4.2)

Frequent: 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, visual disturbances

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

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 provders 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 seen in reported overdose of CITRAZ include symptoms mainly related to the central nervous system (ranging from dizziness, tremor, and agitation to rare cases of serotonin syndrome, convulsion, and coma), the gastrointestinal system (nausea/vomiting), and the cardiovascular system (hypotension, tachycardia, QT interval prolongation, and dysrhythmia) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia).

Treatment

There is no specific antidote. Treatment is supportive and symptomatic. Gastric lavage and the use of activated charcoal should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

ECG monitoring is advisable 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

Pharmacological classification

A 1.2 Psychoanaleptics (antidepressants)

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake.

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

Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT_2, DA, D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarinic receptors, benzodiazepine and opioid receptors.

*Effect on the hear*t

In a double-blind placebo controlled ECG study in healthy subjects, it was reported that the change from baseline in QTc (Fridericia-correction) was 4,3 ms. (90 % CI: 2,2; 6,4) at the 10 mg/day dose and 10,7 ms. (90 % CI: 8,6; 12,8) at the supratherapeutic dose of 30 mg/day). See also sections 4.3, 4.4, 4.5 and 4.8.

5.2 Pharmacokinetic properties

Absorption

Absorption is almost complete and independent of food intake. Mean time to maximum concentration (mean T_{max}) 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 plasma protein binding of escitalopram is approximately 55 %.

Biotransformation

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites both pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28 to 31 % and < 5 % of the escitalopram concentration, respectively.

Biotransformation of escitalopram to the demethylated metabolite is mediated by primarily CYP2C19 with some contribution by the enzymes CYP3A4 and CYP2D6.

Elimination

The elimination half-life ($t_{l/2}\,\beta$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0,6 l/min. The major metabolites have a significantly longer half-life.

Escitalopram and the 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 metabolites in urine. Hepatic clearance is mainly by the P450 enzyme system.

There is linear pharmacokinetics. Steady state plasma levels are achieved in about one week. Average steady state concentrations of 50 nmol/l (range 20 to 125 nmol/l) are achieved at a daily dose of 10 mg.

Elderly patients (> 65 years of age)

Escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients. Systemic exposure (AUC) is about 50 % higher in elderly patients compared to young healthy volunteers. (See section 4.2).

Reduced hepatic function

In patients with mild to moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram is about twice as long and the exposure is about 60 % higher than in subjects 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 the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min).

Polymorphism

It has been observed 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 observed in poor metabolisers with respect to CYP2D6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Tablet

Colloidal silicon dioxide

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Talc

Film-coating

Opadry white OY-58900 consisting of:

Hypromellose

Macrogol 400

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the tablets in the original container and keep tightly closed.

Keep the tablets in the blister and the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

CITRAZ 5: 30 film-coated tablets in white opaque HDPE bottles or 7 or 10 film-coated tablets in aluminium foil/PVC/PVdC blisters.

CITRAZ 10: 30 film-coated tablets in white opaque HDPE bottles or 7 or 10 film-coated tablets in aluminium foil/PVC/PVdC blisters.

CITRAZ 20: 30 film-coated tablets in white opaque HDPE bottles or 7 or 10 film-coated tablets in aluminium foil/PVC/PVdC blisters.

Not all pack sizes may be marketed.

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

Dr. Reddy's Laboratories (Pty) Ltd

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER(S)

CITRAZ 5: 41/1.2/0843

CITRAZ 10: 41/1.2/0844

CITRAZ 20: 41/1.2/0845

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/08/2008

10 DATE OF REVISION OF TEXT

24/02/2021