Applicant: Oethmaan Biosims (Pty) Ltd	**SAHPRA approval date:** 09 June 2022
Product: CITALOPRAM 20 OETHMAAN	**Dosage form and strength:** Each tablet contains citalopram hydrobromide equivalent to 20 mg citalopram

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

CITALOPRAM 20 OETHMAAN (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each CITALOPRAM 20 OETHMAAN film-coated tablet contains: citalopram hydrobromide equivalent to 20 mg citalopram.

Contains sugar (23,0 mg lactose monohydrate).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, oblong, biconvex film-coated tablets with a one-sided notch and embossment C20.

Initial:	09/06/2022

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

CITALOPRAM 20 OETHMAAN is indicated for the treatment of:

- Depression and prevention of relapse
- Panic disorders with or without agoraphobia
- Obsessive-compulsive disorder (OCD)

4.2 Posology and method of administration

Posology

Depression:

20 mg a day as a single dose. Dosage may be increased by 20 mg a day at intervals of at least one week to a maximum of 60 mg depending on the patient's response.

Panic disorder:

10 mg a day as a single dose for the first week then increasing to 20 mg a day. The dose may be increased thereafter as required to a maximum of 60 mg a day depending on the patient's response.

Obsessive compulsive disorder:

20 mg a day as a single dose. This dose can be increased by 20 mg increments to a maximum of 60 mg a day depending on the patient's response.

Special populations:

Elderly:

20 mg a day as a single dose. Depending on the patient's response, the dose can be increased to a maximum of 30 mg a day.

Reduced hepatic function:

Dose should be halved.

Reduced renal function:

Dose adjustment is not necessary in cases of mild or moderate renal impairment.

The onset of action is seen within 2 to 4 weeks. Treatment should be continued for an appropriate length of time (up to six months) after recovery in order to prevent relapse. The medicine should be gradually withdrawn during a couple of weeks when stopping therapy (see section 4.8).

Method of administration

CITALOPRAM 20 OETHMAAN may be taken with or without food in the morning or evening.

4.3 Contraindications

- Hypersensitivity to citalopram or any of the ingredients in the formulation.

- MAOIs (monoamine oxidase inhibitors):

  Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAO-B inhibitor selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

  Some cases presented with features resembling serotonin syndrome.

  ClTALOPRAM 20 OETHMAAN must not be used in combination with a MAOI, including selegiline in doses above 10 mg daily.

  Treatment with CITALOPRAM 20 OETHMAAN may be instituted 14 days after discontinuation of non-selective MAOIs and minimum one day after discontinuation of moclobemide. Treatment with MAOIs may be introduced 7 days after discontinuation of citalopram (See section 4.5).
- Severe renal impairment (creatine clearance less than 20 ml/min).
- Safety and efficacy in pregnancy and lactation has not been established.
- Children under the age of 18 years (see section 4.4 and 4.8).
- Concomitant treatment with pimozide (See section 4.5).

- CITALOPRAM 20 OETHMAAN is contraindicated in combination with linezolid (See section 4.5).
- CITALOPRAM 20 OETHMAAN is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome (see sections 4.4, 4.8 and 5.1).

4.4 Special warnings and precautions for use

CITALOPRAM 20 OETHMAAN should be used with caution in:

Use in children and adolescents under 18 years of age – CITALOPRAM 20 OETHMAAN should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. (See section 4.3).

In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Elderly patients - longer half-life and decreased clearance due to a reduced rate of metabolism. A lower dose is recommended in the elderly.

Hepatic impairment - clearance of CITALOPRAM 20 OETHMAAN is reduced. Cautious dosage titration and a lower maximum dose are recommended.

Renal impairment - elimination is decreased. If creatine clearance is less than 20 ml/min CITALOPRAM 20 OETHMAAN should not be used (see section 4.3).

Seizures or history thereof - there is an increased risk of seizures. CITALOPRAM 20 OETHMAAN should be discontinued in any patient who develops seizures.

CITALOPRAM 20 OETHMAAN should be used with caution in patients with controlled epilepsy and avoided in patients who are poorly controlled epileptics. CITALOPRAM 20 OETHMAAN should be discontinued if there is an increase in seizure frequency.

ECT (electroconvulsive therapy) - Care is advised in patients receiving electroconvulsive therapy.

Mania or history of mania - condition may be re-activated.

CITALOPRAM 20 OETHMAAN should be discontinued if the patient enters the manic phase.

CITALOPRAM 20 OETHMAAN may cause a reduction in heart rate. Caution is advised in patients with a pre-existing slow heart rate.

Diabetes mellitus - In patients with diabetes, treatment with an SSRI including CITLOPRAM 20 OETHMAAN may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Use with other medicines - CITALOPRAM 20 OETHMAAN should not be used with monoamine oxidase inhibitors, imipramine, other serotonergic medicines, moclobemide, alcohol, warfarin, and cimetidine (see section 4.5).

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 medicine. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with CITALOPRAM 20 OETHMAAN 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 disorder 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 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 CITALOPRAM 20 OETHMAAN, 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, CITALOPRAM 20 OETHMAAN should be tapered (see section 4.4 and 4.8 WITHDRAWAL SYMPTOMS).

Paradoxical anxiety- Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose of CITALOPRAM 20 OETHMAAN is advised to reduce the likelihood of a paradoxical anxiogenic effect (see section 4.2).

Hyponatraemia - Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as an adverse reaction with the use of SSRIs and generally reverses on discontinuation of therapy. Elderly female patients seem to be at higher risk.

Akathisia/psychomotor restlessness - The use of SSRIs/SNRIs 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 of CITALOPRAM OETHMAAN may be detrimental.

Serotonin syndrome - Serotonin syndrome has been reported in patients using SSRIs. Serotonin syndrome is more likely to occur after an increase in dose. A combination of symptoms such as agitation, tremor, myoclonus, and hyperthermia may indicate the development of this condition. Treatment with CITALOPRAM 20 OETHMAAN should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines - CITALOPRAM 20 OETHMAAN should not be used concomitantly with medicines with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan, and tryptophan (see section 4.5).

Haemorrhage - There have been reports of cutaneous bleeding time and/or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings with SSRIs (see section 4.8). Caution is advised in patients taking ClTALOPRAM 20 OETHMAAN, particularly with concomitant use of active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see section 4.5).

Post-partum haemorrhage - There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2- fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy. Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

St. John's Wort- Undesirable effects may be more common during concomitant use of CITALOPRAM 20 OETHMAAN and herbal preparations containing St John's wort *(Hypericum perforatum).* Therefore CITALOPRAM 20 OETHMAAN and St John's wort preparations should not be taken concomitantly (see section 4.5).

Psychosis - Treatment of psychotic patients with depressive episodes may increase psychotic symptoms.

QT interval prolongation - CITALOPRAM 20 OETHMAAN 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 prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1).

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

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant dysrhythmias and should be corrected before treatment with ClTALOPRAM 20 OETHMAAN 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 CITALOPRAM 20 OETHMAAN, the treatment should be withdrawn, and an ECG should be performed.

Withdrawal symptoms - After prolonged administration, abrupt cessation of CITALOPRAM 20 OETHMAAN may produce withdrawal symptoms such as dizziness, sensory disturbances (including paraesthesia), 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 in some patients. These symptoms are not indicative of addiction.

It is recommended that withdrawal of treatment should proceed by gradually tapering off the dosage over a period of several weeks or months, according to the patient's needs to avoid occurrence of discontinuation symptoms.

Angle-Closure Glaucoma

SSRIs including citalopram may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Citalopram should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Alcohol - Avoid alcohol (see section 4.5).

Excipients - CITALOPRAM 20 OETHMAAN tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

At the pharmacodynamic level, cases of serotonin syndrome with CITALOPRAM 20 OETHMAAN and moclobemide and buspirone have been reported.

Contraindicated combinations:

Monoamine Oxidase Inhibitors (MAO/s) - Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline, the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued SSRI and have been started on a MAOI. Some cases presented with features resembling serotonin syndrome.

Symptoms of citalopram interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma (see section 4.3).

Pimozide - Co-administration of a single dose of pimozide 2 mg to subjects treated with CITALOPRAM 20 OETHMAAN 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide. The coadministration of pimozide and CITALOPRAM 20 OETHMAAN resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of CITALOPRAM 20 OETHMAAN and pimozide is contraindicated (see section 4.3).

Combinations requiring precaution for use:

Selegiline (selective MAO-B inhibitor) - A pharmacokinetic *I* pharmacodynamic interaction study with concomitantly administered CITALOPRAM 20 OETHMAAN (20 mg daily) and selegiline (10 mg daily) (a selective MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of CITALOPRAM 20 OETHMAAN and selegiline (in doses above 10 mg daily) is not recommended. (See section 4.3).

Serotonergic medicines

Lithium and tryptophan: No pharmacodynamic interactions have been found in clinical studies in which CITALOPRAM 20 OETHMAAN has been given concomitantly with lithium. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of CITALOPRAM 20 OETHMAAN with these medicines should be undertaken with caution.

Routine monitoring of lithium levels should be continued as usual.

Co-administration with serotonergic medicines (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects. The simultaneous use of CITALOPRAM 20 OETHMAAN and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

St. John's Wort - Pharmacodynamic interactions between SSRIs such as CITALOPRAM 20 OETHMAAN and herbal remedy St John's wort *(Hypericum perforatum)* can occur, resulting in an increase in undesirable effects (see section 4.4).

Pharmacokinetic interactions have not been investigated.

Haemorrhage - Simultaneous treatment with anticoagulants, medicines that affect the platelet function, such as non-steroidal anti-inflammatory medicines (NSAIDs), acetylsalicylic acid, dipyridamol, and ticlopidine or other medicines (e.g. atypical antipsychotics, phenothiazines, tricyclic antidepressants) can increase the risk of haemorrhage (see section 4.4).

ECT (electroconvulsive therapy) - There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and CITALOPRAM 20 OETHMAAN (see section 4.4).

Alcohol - No pharmacodynamic or pharmacokinetic interactions have been demonstrated between CITALOPRAM 20 OETHMAAN and alcohol. However, the combination of CITALOPRAM 20 OETHMAAN and alcohol is not advisable.

Medicines lowering the seizure threshold

CITALOPRAM 20 OETHMAAN can lower the seizure threshold. Caution is advised when concomitantly using other medicines capable of lowering the seizure threshold (e.g. antidepressants [tricyclics, other SSRIs], neuroleptics [phenothiazines, thioxanthenes, and butyrophenones], mefloquin, bupropion and tramadol).

Desipramine, imipramine - In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased. When desipramine is combined with citalopram, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

Neuroleptics - Experience with CITALOPRAM 20 OETHMAAN has not revealed any clinically relevant interactions with neuroleptics. However, the possibility of a pharmacodynamic interaction cannot be excluded.

QT interval prolongation - Pharmacokinetic and pharmacodynamic studies between CITALOPRAM 20 OETHMAAN and other medicines that prolong the QT interval have not been performed. An additive effect of CITALOPRAM 20 OETHMAAN and these medicines cannot be excluded. Therefore, co-administration of CITALOPRAM 20 OETHMAAN with medicines that prolong the QT interval, such as Class IA and Ill antidysrhythmics, antipsychotic (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial medicines (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), should only be prescribed after careful consideration.

Pharmacokinetic interactions

Biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38 %), CYP3A4 (approx. 31 %) and CYP2D6 (approx. 31 %) isozymes of the cytochrome P450 system. Therefore, co-administration of CITALOPRAM 20 OETHMAAN with other medicines may result in pharmacokinetic medicine interactions.

Food - The absorption and other pharmacokinetic properties of citalopram have not been reported to be affected by food.

Influence of other medicines on the pharmacokinetics of CITALOPRAM 20 OETHMAAN

Co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of citalopram.

A pharmacokinetic interaction study of lithium and citalopram did not reveal any pharmacokinetic interactions (see also above).

Cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram. Caution is advised when administering CITALOPRAM 20 OETHMAAN in combination with cimetidine. Dose adjustment may be warranted.

Effects of CITALOPRAM 20 OETHMAAN on other medicines

A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram and metoprolol (a CYP2D6 substrate) showed a twofold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and cardiac rhythm in healthy volunteers. Caution is recommended when metoprolol and CITALOPRAM 20 OETHMAAN are co-administered. Dose adjustment may be warranted.

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6.

No change or only very small changes of clinical importance were observed when CITALOPRAM 20 OETHMAAN was given with CYP1A2 substrates (clozapine and theophylline), CYP2C9

(warfarin), CYP2C19 (imipramine and mephenytoin}, CYP2D6 (sparteine, imipramine, amitriptyline, risperidone) and CYP3A4 (warfarin, carbamazepine (and its metabolite carbamazepine epoxide) and triazolam).

No pharmacokinetic interaction was observed between CITALOPRAM 20 OETHMAAN and levomepromazine, or digoxin, (indicating that CITALOPRAM 20 OETHMAAN neither induces nor inhibits P-glycoprotein).

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established.

Pregnancy

The following symptoms may occur in neonates after maternal SSRI use 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 such as CITALOPRAM 20 OETHMAAN in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

Neonates should be observed if maternal use of CITALOPRAM 20 OETHMAAN continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

Breastfeeding

CITALOPRAM 20 OETHMAAN is excreted into the breast milk.

Fertility

Animal data have shown that citalopram may affect sperm quality. Human case reports with some SSRIs 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

CITALOPRAM 20 OETHMAAN may impair performance of skilled tasks. If affected these patients should not operate machinery or drive.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse events observed with CITALOPRAM 20 OETHMAAN are most frequent during the first one or two weeks of treatment, and usually decrease in intensity and frequency as the depressive state improves.

For the following reactions a dose-response was discovered: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue.

b. Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Frequency not known
Immune system disorders	Hypersensitivity Anaphylactic reaction	Frequency not known
Endocrine disorders	Inappropriate antidiuretic hormone secretion	Frequency not known
Metabolism and nutrition disorders	Appetite decreased Weight decreased Increased appetite Weight increased Hyponatraemia Hypokalaemia	Frequency not known
Psychiatric disorders	Female and male: Libido decreased	Frequent
	Agitation Anxiety Nervousness	Frequency not known

	Confusional state Abnormal orgasm (female) Sleep disturbances including abnormal dreams Aggression Depersonalization Hallucination Mania Panic attack Bruxism Restlessness Suicidal ideation Suicidal behaviour	
Nervous system disorders	Insomnia Somnolence Tremor	Frequent
	Paraesthesia Dizziness Disturbance in attention Syncope Convulsion Dyskinesia Taste disturbance	Frequency not known

	Serotonin syndrome Extrapyramidal disorder Akathisia Movement disorder	
Eye disorders:	Mydriasis Visual disturbance	Frequency not known
Ear and labyrinth disorders	Tinnitus	Frequency not known
Cardiac disorders	Bradycardia Tachycardia Palpitations Electrocardiogram QT prolonged Ventricular dysrhythmia including torsade de pointes	Frequency not known
Vascular disorders	Haemorrhage Orthostatic hypotension	Frequency not known
Respiratory, thoracic and mediastinal disorders	Nose congestion Epistaxis	Frequency not known
Gastrointestinal disorders	Diarrhoea Nausea Dry mouth	Frequent

	Dyspepsia Vomiting Constipation Salivation Gastrointestinal haemorrhage (including rectal haemorrhage)	Frequency not known
Hepatobiliary disorders:	Hepatitis	Frequency not known
Skin and subcutaneous tissue disorder	Sweating increased	Frequent
	Pruritus Urticaria Alopecia Rash Purpura Photosensitivity Ecchymosis Angioedema	Frequency not known
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia	Frequency not known
Renal and urinary disorders	Micturition disorder including urinary retention	Frequency not known

Reproductive system and breast disorders	Male: Ejaculation disorder	Frequent
	Impotence Ejaculation failure Female: Menorrhagia Galactorrhoea Female: Metrorrhagia Male: Priapism Postpartum haemorrhage	Frequency not known
General disorders and administrative site conditions	Fatigue	Frequent:
	Asthenia Headache Malaise Yawning Oedema Pyrexia Neuroleptic malignant syndrome	Frequency not known
Investigations	Liver function test abnormal	Frequency not known

c. Description of selected adverse reactions

Suicide/suicidal thoughts or clinical worsening

Cases of suicidal ideation and suicidal behaviour have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).

Bone fractures

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

QT interval prolongation

Cases of QT 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 of other cardiac diseases (see section 4.3, 4.4, 4.5, 4.9 and 5.1).

Withdrawal symptoms seen on discontinuation of citalopram treatments

Discontinuation of citalopram commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged (see section 4.4). It is therefore advised that when CITALOPRAM 20 OETHMAAN treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Children and adolescents under 18 years of age

In children reports of hostility and suicidal ideation (see sections 4.3 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

(See section 4.8).

Toxicity

Fatal cases of CITALOPRAM 20 OETHMAAN overdose have been reported with CITALOPRAM 20 OETHMAAN alone; however, the majority of fatal cases have involved overdose with concomitant medicines/alcohol.

Symptoms of overdose:

Tiredness, weakness, sedation, dizziness, tremor, nausea, somnolence, sinus tachycardia, sedation, convulsion, QT interval prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, and mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, and atrial- and ventricular dysrhythmia.

Treatment of overdose:

Treatment is symptomatic and supportive. There is no specific antidote to CITALOPRAM 20 OETHMAAN.

Activated charcoal, osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered. If consciousness is impaired the patient should be intubated. Monitoring of cardiac and vital signs necessary and medical surveillance is advisable for about 24 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

ATC Code: N06AB04

Citalopram is a bicyclic phthallane derivative with antidepressant effect. Its effect is linked to the selective inhibition of specific serotonin (5-HT) reuptake. Citalopram, primarily through its (S)-enantiomer, blocks 5-HT reuptake, leading to potentiation of serotonergic activity in the central nervous system (CNS), Neither citalopram nor its metabolites have an effect on noradrenaline, dopamine and GABA reuptake. Citalopram also has little or no antidopaminergic, antiadrenergic, antiserotonergic, antihistaminergic or anticholinergic properties.

5.2 Pharmacokinetic properties

Oral bioavailability is about 80 % with maximum plasma levels being reached in 4 hours (range 1 to 6 hours). Volume of distribution is about 14 L/kg (range 9 to 17 L/kg). Time to reach steady state concentration is 1 to 2 weeks. Protein binding is about 80 %. Elimination half-life is 36 hours (range 28 to 42 hours).

Citalopram undergoes hepatic metabolism primarily involving the cytochrome P450 (CYP3A4) and 2C19 (CYP2C19) isoenzymes and to a small extent cytochrome P450 2D6 (CYP2D6) isoenzymes. The metabolites inhibit the reuptake of serotonin, but are less potent than the parent molecule.

Citalopram is excreted mainly via the liver with the remainder via the kidneys (approximately 20 % of which 12 % is unchanged medicine). Longer half-lives and decreased clearance due to a reduced rate of metabolism have been demonstrated in the elderly.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Maize starch

Povidone K64

Lactose monohydrate

Glycerol

Microcrystalline cellulose

Sodium Starch Glycolate

Magnesium Stearate

Coating:

Hypromellose

Macrogol 6000

Titanium Dioxide (E171)

Talc.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 25 °C.

Store in the original package/container.

Do not remove the blister from the carton until required for use.

6.5 Nature and contents of container

Clear PVC/aluminium blister strips containing 10 or 14 tablets each. 3 (10) blister strips to be packed into a carton i.e. 30 tablets per carton or 2 (14's) blister strips to be packed into a carton i.e. 28 tablets per carton.

OR

Clear PVDC coated PVC/aluminium blister strips containing 10 or 14 tablets each. 3 (10) blister strips to be packed into a carton i.e. 30 tablets per carton or 2 (14's) blister strips to be packed into a carton i.e. 28 tablets per carton.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

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2195

8 REGISTRATION NUMBER(S):

36/1.2/0469

9 DATE OF FIRST AUTHORISATION

18 March 2005

10 DATE OF REVISION OF THE TEXT

09 June 2022