PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

CILORAM 20 mg (Film-coated Tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (lactose monohydrate 45,72 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White coloured, biconvex, capsule-shaped film coated tablets debossed with 'A' on one side and with a score-line in between '0' and '6' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CILORAM 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 40 mg depending on the patient's response.

Duration of treatment - The antidepressant effect usually sets in after 2 to 4 weeks. Treatment with CILORAM is symptomatic and must therefore be continued for an appropriate length of time, usually up to 6 months after recovery in order to prevent relapse.

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 40 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 40 mg a day depending on the patient's response.

Duration of treatment - The onset of action in treating OCD is 2 – 4 weeks with further improvement over time.

Special populations

Elderly

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

Reduced hepatic function

An initial dose of 10 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function.

Reduced renal function

Dose adjustment is not necessary in cases of mild or moderate renal impairment. CILORAM is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see sections 4.3 and 5.2).

Poor metabolisers of CYP2C19

An initial dose of 10 mg daily during the first two weeks of treatment is recommended for patients who are known to be poor metabolisers with respect to CYP2C19. The dose may be increased to a maximum of 20 mg daily depending on individual patient response.

Withdrawal symptoms seen on discontinuation

Abrupt discontinuation should be avoided. When stopping treatment with CILORAM the dose should be gradually reduced over a period of at least one or two weeks in order to reduce the risk of withdrawal symptoms (See sections 4.4 and 4.8).

If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the medical practitioner may continue decreasing the dose, but at a more gradual rate.

Paediatric population

CILORAM should not be used in the treatment of children and adolescents under the age of 18 years (See sections 4.3 and 4.4).

Method of administration

CILORAM may be taken with or without food in the morning or evening.

CILORAM is administered as a single daily dose.

4.3 Contraindications

- Hypersensitivity to citalopram or any of the excipients (see section 6.1).
- Concurrent use with monoamine oxidase inhibitors (MAOIs).

  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.

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

At least 14 days should elapse between discontinuing the MAOI and initiating therapy with CILORAM, and minimum one day after discontinuation of moclobemide. MAOIs should not be introduced for 7 days after discontinuation of CILORAM (see section 4.5).

- Severe renal impairment (creatinine clearance less than 30 ml/min).
- Safety and efficacy in pregnancy and lactation has not been established.
- Children and adolescents under the age of 18 years (see section 4.4).
- Concomitant use with pimozide (see section 4.5).
- CILORAM is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome (see sections 4.4, 4.8)
- Concomitant use with linezolid (see section 4.5).

4.4 Special warnings and precautions for use

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 CILORAM is reduced. Cautious dosage titration and a lower maximum dose are recommended (see section 4.2).

Renal impairment – Elimination is decreased. If creatinine clearance is less than 30 ml/min CILORAM should not be used (see section 4.2 and 4.3).

Seizures

Seizures are a potential risk with antidepressant medicines. CILORAM should be used with caution in patients with controlled epilepsy and avoided in patients who are poorly controlled epileptics. CILORAM should be discontinued in any patient who develops seizures or if there is an increase in seizure frequency.

ECT (electroconvulsive therapy)

There is limited clinical experience of concurrent administration of CILORAM and ECT therefor care is advised in patients receiving electroconvulsive therapy.

Mania or history of mania

Condition may be re-activated. In patients with manic-depressive illness a change towards the manic phase may occur. CILORAM should be discontinued if the patient enters the manic phase.

Diabetes mellitus

Rare occurrences of hypoglycaemia have been reported. In patients with diabetes, treatment with an SSRI including CILORAM may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

CILORAM should not be used with monoamine oxidase inhibitors; imipramine; moclobemide; alcohol; warfarin; and cimetidine (see section 4.5).

Serotonin syndrome

Serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus, and hyperthermia may indicate the development of this condition. Treatment with CILORAM should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines

CILORAM should not be used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan, and tryptophan (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 medicines. This risk may persist until significant remission occurs. Patients should be monitored during early therapy until

improvement in depression is observed because suicide is an inherent risk in depressed patients. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with CILORAM 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 disorders 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 disorders 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 CILORAM 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, CILORAM should be tapered. It is recommended that the dose is decreased gradually in order to prevent the possibility of a withdrawal syndrome (see section 4.2 and 4.8).

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

A meta-analysis of placebo-controlled clinical trials of antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants such as citalopram compared to placebo in patients less than 25 years old.

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 CILORAM 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 CILORAM may be detrimental.

Use in children and adolescents under 18 years of age

CILORAM should not be used in the treatment of children and adolescents under the age of 18 years. In clinical trials in Major Depressive Disorder, there were increased reports of hostility (predominantly aggression, oppositional behaviour and anger) and suicide-related adverse events such as suicidal ideation and self-harm (see section 4.3).

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

QT-Prolongation and torsades de pointes

CILORAM causes dose-dependent QT prolongation and should not be used in patients with congenital long QT syndrome. Cases of 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).

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 CILORAM 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 CILORAM, the treatment should be withdrawn, and an ECG should be performed.

Haemorrhage

CILORAM may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). 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 CILORAM, particularly with concomitant use of medicine known to affect platelet function or other medicine that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see section 4.5).

Withdrawal symptoms

After prolonged administration, abrupt cessation of CILORAM 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. CILORAM should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

St. John´s Wort

Undesirable effects may be more common during concomitant use of CILORAM and herbal preparations containing St John's wort (*Hypericum perforatum*). Therefore, CILORAM 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.

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.

CILORAM contains lactose and should not be given to patients with rare hereditary problems or a history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

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

Contraindicated combinations:

Monoamine oxidase inhibitors (MAOI) – Concurrent use is contraindicated. Serious and potentially 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 rapid fluctuation of vital signs and mental status changes including extreme agitation progressing to delirium and coma (see section 4.3).

Pimozide – concurrent administration of pimozide with CILORAM has been associated with a mean increase in

QTc values compared to when pimozide was given alone (see section 4.3).

Medicines that prolong the QT Interval – Concomitant use is contraindicated (see section 4.3) with medicine such as Class IA and III antidysrhythmics, antipsychotic (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 (astemizole, mizolastine).

Combinations requiring precaution for use:

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

Desipramine, Imipramine – An increase in the concentration of desipramine (the active metabolite of imipramine) may occur (see section 4.4). A reduction of the desipramine dose may be needed.

Serotonergic medicinal products

Lithium and tryptophan: No pharmacodynamic interactions have been found in clinical studies in which CILORAM 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 CILORAM with these medicinal products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

Other serotonergic medicines or medicines with serotonergic activity (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects. The simultaneous use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, is not recommended.

Increased risk of developing the serotonin syndrome, a rare but potentially fatal hyperserotonergic state, may occur when CILORAM is co-administered with other medicines that may affect the serotonergic neurotransmitter systems such as linezolid (see section 4.3).

St. John's Wort – Pharmacodynamic interactions between SSRIs such as CILORAM 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.

Alcohol – The effects of alcohol may be increased.

Haemorrhage - Simultaneous treatment with anticoagulants (e.g. warfarin), medicinal products 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 CILORAM (see section 4.4).

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

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

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 CILORAM with other medicinal products may result in pharmacokinetic medicinal product interactions.

Food – The absorption and other pharmacokinetic properties of citalopram have not been reported to be affected

by food.

Influence of other medicinal products on the pharmacokinetics of CILORAM

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 – Cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram. The AUC and the maximum plasma concentration of CILORAM are increased when CILORAM is administered concurrently with cimetidine. Dose adjustment may be warranted.

Influence of CILORAM on other medicinal products

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 CILORAM 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 CILORAMwas 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 CILORAM and levomepromazine, or digoxin, (indicating that CILORAM neither induces nor inhibits P-glycoprotein).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy has not been established (see section 4.3).

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

The following symptoms may occur in the neonates after maternal SSRI/SNRI (such as CILORAM) 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.

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

Breastfeeding

Safety and efficacy in lactation has not been established. CILORAM is excreted into the breast milk (see section 4.3).

Fertility

No data on fertility is currently available.

4.7 Effects on ability to drive and use machines

CILORAM may impair performance of skilled tasks. The potential for dizziness, impaired concentration, confusion and headache should be taken into account before patients on CILORAM drive or use machinery.

4.8 Undesirable effects

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Psychiatric disorders	*Frequent*	Female and male: libido decreased, sleep disorder, agitation, anxiety, nervousness, confusional state, abnormal orgasm (female), sleep disturbances including abnormal dreams, apathy
	Less frequent	Aggression, depersonalisation, hallucination, mania, libido increased
	Frequency unknown	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[1)]
Immune system disorders	*Frequency unknown*	Anaphylaxis, hypersensitivity
Endocrine disorders	*Frequency unknown*	Inappropriate ADH secretion
Nervous system disorders	*Frequent*	Sleep disturbances, somnolence. insomnia, tremor, headache, paraesthesia, dizziness, disturbance in attention, migraine, amnesia
	Less frequent	Serotonin syndrome, syncope, convulsion grand mal, dyskinesia, taste disturbance
	Frequency unknown	Neuroleptic malignant syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	*Less frequent*	Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4
	Frequency unknown	Accommodation disturbances, visual disturbances
Ear and labyrinth disorders	*Frequent*	Tinnitus
Cardiac disorders	*Frequent*	Palpitations
	Less frequent	Bradycardia, tachycardia.

	Frequency unknown	QT prolongation, ventricular arrhythmia including torsades de pointes
Vascular disorders	*Less frequent*	Haemorrhage
	Frequency unknown	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	*Frequent*	Yawning, rhinitis, nasal congestion
	Less frequent	Coughing
	Frequency unknown	Epistaxis
Gastrointestinal disorders	*Frequent*	Nausea, dry mouth, diarrhoea, constipation, dyspepsia, vomiting, abdominal pain, flatulence, salivary hypersecretion
	Frequency unknown	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	*Less frequent*	Hepatitis
	Frequency unknown	Liver function test abnormal
Skin and subcutaneous tissue disorders	*Frequent*	Sweating increased, pruritis
	Less frequent	Rash, urticaria, alopecia, purpura, photosensitivity reaction
	Frequency unknown	Ecchymosis, angioedema
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Myalgia, arthralgia
	Less frequent	Asthenia
Renal and urinary disorders	*Less frequent*	Micturition disorders, urinary retention
Reproductive system and breast disorders	*Frequent*	Sexual dysfunction including ejaculation disorder, decreased libido, anorgasmia, impotence, ejaculation failure
	Less frequent	Female: Menorrhagia
	Frequency	Female: Metrorrhagia, postpartum haemorrhage[2)],

	unknown	Male: Priapism Galactorrhoea
General disorders and administration site conditions	*Frequent*	Fatigue, asthenia
	Less frequent	Hostility, suicidal ideation and self-harm have been reported in children, oedema, pyrexia, malaise, neuroleptic malignant syndrome
Blood and lymphatic disorders	*Frequency unknown*	Thrombocytopenia
Metabolism and nutrition disorders	*Frequent*	Appetite decreased, weight decreased
	Less frequent	Increased appetite, weight increased, hyponatraemia
	Frequency unknown	Hypokalaemia

[1)] Cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early aftertreatment discontinuation (see section 4.4).

[2)] This event has been reported for the therapeutic class of SSRIs/SNRIs (see section 4.4 and 4.6).

Qt interval prolongation - Cases of QT-prolongation and ventricular arrhythmia 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, 4.4, 4.5, 4.9 and 5.1).

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 this risk is unknown.

Withdrawal symptoms seen on discontinuation

Discontinuation of CILORAM (particularly when abrupt) commonly leads to withdrawal symptoms. 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 are the most commonly reported reactions. In some patients they may be severe and/or prolonged. It is therefore advised that when CILORAM treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 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 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

Toxicity

Fatal cases of overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medication/alcohol.

Symptoms of overdose

Tiredness, weakness, sedation, dizziness, tremor, nausea, somnolence, sinus tachycardia, convulsion, QT interval prolongation, coma, vomiting, hypotension, cardiac arrest, serotonin syndrome, agitation, bradycardia, 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 CILORAM.

The stomach should be emptied as soon as possible by emesis or gastric lavage. Activated charcoal and osmotically working laxative (such as sodium sulphate) should be considered. If the consciousness is impaired the patient should be intubated. Monitoring of cardiac and vital signs is necessary and medical surveillance is advisable for about 24 hours.

ECG monitoring should be considered in all cases of overdose especially in congestive heart failure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants)

Citalopram is a bicyclic pthalane 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, anthistaminergic 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 has been demonstrated in the elderly.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Cellulose microcrystalline

Copovidone

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Maize starch

Coating

Hypromellose

Macrogol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool, dry place, at or below 25 °C.

6.5 Nature and contents of container

Blister Pack:

Tablets are packed in clear PVC (250 microns) coated with PVdC (60 gsm) as the forming material and aluminium foil (25 microns) as the lidding material.

Pack Size: 28's: Each carton contains 2 blisters of 14 tablets each.

30's: Each carton contains 3 blisters of 10 tablets each.

HDPE Container:

Tablets are packed in a HDPE container with a stock ribbed closure and induction sealing wad. The void space in the container is filled with a rayon coil.

Pack Size: 28's, 30's

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd.

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Road,

Irene, Pretoria

South Africa

8. REGISTRATION NUMBER(S)

CILORAM 20 mg: A40/1.2/0564

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 13 April 2007

10. DATE OF REVISION OF THE TEXT

05 April 2022