

**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 20 mg** 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.

### 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.

### 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:* 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. **CILORAM 20 mg** should be gradually withdrawn over a couple of weeks when stopping therapy (see section 4.4).

**CILORAM 20 mg** 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.
- Concurrent use with monoamine oxidase inhibitors (MAOIs). At least 14 days should elapse between discontinuing the MAOI and initiating therapy with **CILORAM 20 mg**. MAOIs should not be introduced for 7 days after discontinuation of **CILORAM 20 mg** (see section 4.5).
- Severe renal impairment (creatinine 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).
- **CILORAM 20 mg** is contraindicated in patients with congenital long QT syndrome (see section 4.4 and section 4.5).
- Concomitant use with products that prolong QT interval e.g. pimozide (see section 4.5).
- Concomitant use with Linezolid (see section 4.5).

#### 4.4 Special warnings and precautions for use

**CILORAM 20 mg** should be used with caution in:

- 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 20 mg** is reduced. Cautious dosage titration and a lower maximum dose are recommended.
- Renal impairment – Elimination is decreased. If creatinine clearance is less than 20 ml/min **CILORAM 20 mg** should not be used (see section 4.3).
- Seizures or history thereof – There is an increased risk of seizures. **CILORAM 20 mg** should be used with caution in patients with controlled epilepsy and avoided in patients who are poorly controlled epileptics. Care is advised in patients receiving electroconvulsive therapy.
- Mania or history of mania – Condition may be re-activated. **CILORAM 20 mg** should be discontinued if the patient enters the manic phase.
- **CILORAM 20 mg** may cause a reduction in heart rate. Caution is advised in patients with a pre-existing slow heart rate.
- Diabetes mellitus – Rare occurrences of hypoglycaemia have been reported.
- **CILORAM 20 mg** should not be used with monoamine oxidase inhibitors; imipramine; other serotonergic medicines; moclobemide; alcohol; warfarin; and cimetidine (see section 4.5).

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 20 mg** 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 20 mg** 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 20 mg** 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).

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in Major Depressive Disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see section 4.3).

### **QT-Prolongation and torsades de pointes**

Clinical experience with **CILORAM 20 mg** in patients with certain concomitant systemic illnesses is limited.

**CILORAM 20 mg** causes dose-dependent QT prolongation and should not be dosed above 40 mg/day. **CILORAM 20 mg** should not be used in patients with congenital long QT syndrome. Caution is advised in treating patients with diseases or conditions that cause hypokalaemia or hypomagnesaemia. Hypokalaemia and hypomagnesaemia should be corrected prior to initiation of treatment and periodically monitored. ECG monitoring is recommended in patients

with congestive heart failure, bradydysrhythmias, or patients on concomitant medications that prolong the QT interval. Dose escalations over 20 mg/day in CYP2C19 poor metabolisers or patients taking concomitant cimetidine or another CYP2C19 inhibitor is not recommended.

Serotonin syndrome is more likely to occur after an increase in dose.

**CILORAM 20 mg** may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8).

**CILORAM 20 mg** 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**

- **Monoamine oxidase inhibitors (MAOI)** – Concurrent use is contraindicated. Serious and potentially fatal reactions have occurred such as: 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).
- **Imipramine** – An increase in the concentration of desimipramine (the active metabolite of imipramine) may occur. It appears that **CILORAM 20 mg** does not cause a marked increase in plasma levels of some tricyclic antidepressants.
- **Other serotonergic medicines or medicines with serotonergic activity** – Increased risk of developing the serotonin syndrome, a rare but potentially fatal hyperserotonergic state, may occur when **CILORAM 20 mg** is co-administered with other medicines that may affect the serotonergic neurotransmitter systems such as linezolid or St. John's Wort (see section 4.3).
- **Moclobemide** - Serotonin syndrome has developed after taking overdoses of moclobemide and **CILORAM 20 mg**.
- **Alcohol** – The effects of alcohol may be increased.
- **Warfarin** – The anticoagulant activity of warfarin may be increased.

- **Cimetidine** – The AUC and the maximum plasma concentration of **CILORAM 20 mg** are increased when **CILORAM 20 mg** is administered concurrently with cimetidine.
- **Medicines that prolong the QT Interval** – Concomitant use is contraindicated (see section 4.3).
- **Pimozide** – concurrent administration of pimozide with **CILORAM 20 mg** has been associated with a mean increase in QTc values compared to when pimozide was given alone (see section 4.3).

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

Safety and efficacy in pregnancy has not been established.

Neonates should be observed if maternal use of **CILORAM 20 mg** 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 20 mg**) 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 20 mg** exposure within the month prior to birth (see sections 4.4, 4.8).

### Breastfeeding

Safety and efficacy in lactation has not been established. **CILORAM 20 mg** is excreted into the breast milk.

### Fertility

No data on fertility is currently available.

#### **4.7 Effects on ability to drive and use machines**

**CILORAM 20 mg** may impair performance of skilled tasks. The potential for dizziness, impaired concentration, confusion and headache should be taken into account before patients on **CILORAM 20 mg** drive or use machinery.

#### **4.8 Undesirable effects**

##### **Immune system disorders:**

*The following side effects have been reported and frequencies are unknown:* Anaphylaxis, angioedema.

##### **Endocrine disorders:**

*Less frequent:* Weight changes.

##### **Nervous system disorders:**

*Frequent:* Sleep disturbances, somnolence.

*Less frequent:* Paraesthesia, agitation, fatigue, mania, serotonin syndrome.

*The following side effects have been reported and frequencies are unknown:* Restlessness, headache, dizziness, confusion, impaired concentration, malaise, convulsions, neuroleptic malignant syndrome.

##### **Eye disorders:**

*The following side effects have been reported and frequencies are unknown:* Accommodation disturbances, mydriasis.

##### **Cardiac disorders:**

*Less frequent:* Bradycardia, tremor, QT prolongation, torsades de pointes.

*The following side effects have been reported and frequencies are unknown:* Palpitations.

**Respiratory, thoracic and mediastinal disorders:**

*The following side effects have been reported and frequencies are unknown:* Nasal congestion.

**Gastrointestinal disorders:**

*Frequent:* Nausea, dry mouth.

*Less frequent:* Diarrhoea, dyspepsia, salivation.

*The following side effects have been reported and frequencies are unknown:* Constipation.

**Hepato-biliary disorders:**

*The following side effects have been reported and frequencies are unknown:* Hepatitis.

**Skin and subcutaneous tissue disorders:**

*Less frequent:* Sweating, rash.

**Musculoskeletal, connective tissue and bone disorders:**

*Less frequent:* Asthenia.

**Renal and urinary disorders:**

*Less frequent:* Micturition disorders.

**Reproductive system and breast disorders:**

*Frequent:* Sexual dysfunction including ejaculation disorder, decreased libido, anorgasmia.

*The following side effects have been reported and frequencies are unknown:* Postpartum haemorrhage\*.

**General disorders and administration site conditions:**

*Less frequent:* Yawning, hostility, suicidal ideation and self-harm have been reported in children.

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

## **4.9 Overdose**

### **Symptoms of overdose:**

Tiredness, weakness, sedation, dizziness, tremor, nausea, somnolence, and sinus tachycardia.

### **Treatment of overdose:**

Treatment is symptomatic and supportive.

There is no specific antidote to **CILORAM 20 mg**.

The stomach should be emptied as soon as possible by emesis or gastric lavage. Monitoring of cardiac and vital signs is necessary and medical surveillance is advisable for about 24 hours.

## **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, 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 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.

**KEEP OUT OF THE REACH OF CHILDREN.**

## **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**

Revision date: 03 December 2021