APPROVED PROFESSIONAL INFORMATION

October 2024

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

CIPRAMIL 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains citalopram hydrobromide corresponding to 20 mg citalopram.
Contains sugar: Lactose monohydrate 23,1 mg per tablet.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oval (8 x 5,5 mm), white, scored, film-coated and marked “C” and “N” symmetrically around the score.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of depression and prevention of relapse.
Treatment of panic disorder with or without agoraphobia.
Treatment of obsessive compulsive disorder (OCD).

4.2 Posology and method of administration

Posology
Adults

Treating depression
CIPRAMIL should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response, this may be increased to a maximum of 40 mg daily.

Duration of treatment - The antidepressant effect usually sets in after 2 to 4 weeks. Treatment with CIPRAMIL 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.

Treating panic disorder
A single dose of 10 mg is recommended for the first week before increasing the dose to 20 mg daily. The dose may be further increased, up to a maximum of 40 mg daily, dependent on individual patient response.

Treating obsessive compulsive disorder (OCD)
An initial dose of 20 mg is recommended. Dependent on individual patient response, the dose may be increased to a maximum of 40 mg daily.

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

Special populations

Elderly patients (> 65 years of age)

For elderly patients the dose should be decreased to half of the recommended dose, e.g. 10 - 20 mg daily. The recommended maximum dose for the elderly is 20 mg daily.

Children and adolescents (< 18 years)

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

Reduced renal function

Dosage adjustment is not necessary in cases of mild or moderate renal impairment. CIPRAMIL is contra-indicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see sections 4.3 and 5.2).

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.

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 CIPRAMIL 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.

Method of administration

CIPRAMIL tablets are administered as a single daily dose.
CIPRAMIL tablets can be taken any time of the day without regard to food intake.

4.3 Contraindications

Hypersensitivity to citalopram or to any of the excipients.

CIPRAMIL is contraindicated in children and adolescents under 18 years of age.

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.

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

Treatment with CIPRAMIL 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).

Concomitant treatment with pimozide (See section 4.5).

CIPRAMIL is contraindicated in combination with linezolid.

Severely impaired renal function (creatinine clearance less than 30 ml/min) (see section 5.2).

CIPRAMIL 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

Use in children and adolescents under 18 years of age - CIPRAMIL 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.

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 CIPRAMIL in inducing such behaviour has not been established. Patients being treated with CIPRAMIL 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 CIPRAMIL 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 CIPRAMIL, 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, CIPRAMIL should be tapered (see sections 4.4 and 4.8 WITHDRAWAL SYMPTOMS).

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 CIPRAMIL 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 CIPRAMIL 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 CIPRAMIL may be detrimental.

Mania - In patients with manic-depressive illness a change towards the manic phase may occur. CIPRAMIL should be discontinued if the patient enters a manic phase.

Seizures - Seizures are a potential risk with antidepressant medicines. CIPRAMIL should be discontinued in any patient who develops seizures. CIPRAMIL should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. CIPRAMIL should be discontinued if there is an increase in seizure frequency.

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

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 CIPRAMIL should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines - CIPRAMIL should not be used concomitantly with medicinal products with serotonergic effects such as triptans (including sumatriptan and oxitriptan), opioids (including tramadol) 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). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking CIPRAMIL, 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).

ECT (electroconvulsive therapy) - There is limited clinical experience of concurrent administration of CIPRAMIL and ECT; therefore caution is advisable.

St. John´s Wort - Undesirable effects may be more common during concomitant use of CIPRAMIL and herbal preparations containing St John's wort (*Hypericum perforatum*). Therefore CIPRAMIL 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 - CIPRAMIL 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 CIPRAMIL 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 CIPRAMIL, the treatment should be withdrawn, and an ECG should be performed.

Withdrawal symptoms - After prolonged administration, abrupt cessation of CIPRAMIL 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.

Special precaution - Treatment of elderly patients and patients with reduced kidney and liver function (see section 4.2).

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.

Excipients - CIPRAMIL 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 CIPRAMIL and moclobemide and buspirone have been reported.

Contraindicated combinations:

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 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 CIPRAMIL 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide. The co-administration of pimozide and CIPRAMIL 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 CIPRAMIL and pimozide is contraindicated (see section 4.3).

Combinations requiring precaution for use:

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

Serotonergic medicinal products

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

Co-administration with serotonergic medicinal products e.g. opioids (including tramadol, and triptans (including sumatriptan and oxitriptan) may lead to enhancement of 5-HT associated effects. The simultaneous use of CIPRAMIL 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 CIPRAMIL 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, 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 CIPRAMIL (see section 4.4).

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

Medicinal products lowering the seizure threshold
CIPRAMIL 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], 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 CIPRAMIL 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 CIPRAMIL and other medicines that prolong the QT interval have not been performed. An additive effect of CIPRAMIL and these medicines cannot be excluded. Therefore, co-administration of CIPRAMIL with medicines that prolong the QT interval, 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), 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 CIPRAMIL 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 CIPRAMIL
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 CIPRAMIL in combination with cimetidine. Dose adjustment may be warranted.

Effects of CIPRAMIL 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 CIPRAMIL 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 CIPRAMIL 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 CIPRAMIL and levomepromazine, or digoxin, (indicating that CIPRAMIL neither induces nor inhibits P-glycoprotein).

4.6 Fertility, pregnancy and lactation

Safety 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 CIPRAMIL 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).

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

Breastfeeding
Citalopram is excreted into 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

CIPRAMIL does not impair intellectual function or psychomotor performance. Nevertheless, patients who are depressed and require treatment may have an impaired ability to drive or operate machinery. They should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects

Adverse events observed with CIPRAMIL 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.

The tables show the percentage of adverse reactions associated with SSRIs and/or CIPRAMIL seen in either ≥ 1% of patients in double-blind placebo-controlled trials or in the post-marketing period. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from available data).

Adverse reactions from clinical trials

System organ class	**Frequency**	**Undesirable Effect**
Psychiatric disorders	Common	Female and male: libido decreased
Nervous system disorders	Very common	Insomnia, somnolence
	Common	Tremor
Gastrointestinal disorders	Very common	Dry mouth, nausea
	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Very common	Sweating increased
Reproductive system and breast disorders	Common	Male: ejaculation disorder
General disorders and administration site conditions	Common	Fatigue

Number of patients: CIPRAMIL / placebo = 1346/ 545

Adverse reactions from post marketing data

System organ class	**Undesirable Effect**
Blood and lymphatic disorders	Thrombocytopenia
Immune system disorders	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Inappropriate ADH secretion Hyperprolactinaemia[3]
Metabolism and nutrition disorders	Appetite decreased, weight decreased
	Increased appetite, weight increased
	Hyponatraemia
	Hypokalaemia
Psychiatric disorders	Agitation, anxiety, nervousness, confusional state, abnormal orgasm (female), sleep disturbances including abnormal dreams

	Aggression, depersonalization, hallucination, mania
	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[1]
Nervous system disorders	Restlessness
	Paraesthesia, dizziness, disturbance in attention
	Syncope
	Convulsion, dyskinesia, taste disturbance
	Serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	Mydriasis
	Visual disturbance
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Bradycardia, tachycardia, palpitations
	Electrocardiogram QT prolonged, ventricular dysrhythmia including torsade de pointes
Vascular disorders	Haemorrhage
	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Yawning
	Nose congestion
	Epistaxis
Gastrointestinal disorders	Dyspepsia
	Vomiting, constipation
	Salivation
	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Hepatitis
	Liver function test abnormal
Skin and subcutaneous tissue disorders	Pruritus
	Urticaria, alopecia, rash, purpura, photosensitivity
	Ecchymosis, angioedema
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia
Renal and urinary disorders	Micturition disorder including urinary retention
Reproductive system and breast disorders	Impotence, ejaculation failure
	Female: Menorrhagia
	Galactorrhoea Female: Metrorrhagia, postpartum haemorrhage[2] Male: Priapism
General disorders and administration site conditions	Asthenia, headache, malaise, yawning
	Oedema
	Pyrexia
	Neuroleptic malignant syndrome

[1] Cases of suicidal ideation and suicidal behaviours have been reported during CIPRAMIL therapy or early after treatment discontinuation (see section 4.4).
[2]This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).
[3] This event has been reported for the therapeutic class of SSRIs/SNRIs

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. The mechanism leading to this 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 - Discontinuation of CIPRAMIL (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 CIPRAMIL 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Toxicity

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

Symptoms

The following symptoms have been seen in reported overdose of CIPRAMIL: tiredness, weakness, sedation, convulsion, tachycardia, somnolence, 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.

Management

There is no known specific antidote to CIPRAMIL. Treatment should be symptomatic and supportive. Activated charcoal, osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered. If consciousness is impaired the patient should be

intubated. ECG and vital signs should be monitored. Medical surveillance for about 24 hours is advisable.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class

A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Citalopram is a bicyclic phthalane derivative with antidepressant effect. The substance is a racemate, in which one of the enantiomers is responsible for the effect. The pharmacodynamic effect is specifically related to a selective inhibition of serotonin (5-HT) uptake. Citalopram has no effect on the uptake of noradrenaline, dopamine or GABA. Moreover neither citalopram nor its metabolites have antidopaminergic, antiadrenergic, antiserotoninergic, antihistaminergic or anticholinergic (antimuscarinic) properties. After prolonged treatment, the 5-HT- uptake inhibitory efficacy is unchanged and citalopram does not induce changes in the density of neurotransmitter receptors at the recommended dosages.

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 7,5 (90 % CI 5,9 - 9,1) ms at the 20 mg/day dose and 16,7 (90 % CI 15,0 - 18,4) ms at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Pharmacokinetic data are based on the racemate. The oral bioavailability is high (>80 %). Maximum plasma levels are reached within 4 hours (interval 1 - 6 hours) after administration. A linear relationship has been demonstrated between steady-state plasma levels and administered dose and varies four-fold between individuals treated with the same dose. Steady state levels are reached within 1 - 2 weeks. The volume of distribution is about 14 L/kg. The protein binding is about 80 %.

Unchanged citalopram is a predominant compound in plasma. The metabolites have the same pharmacological effect as citalopram, but are less potent. It is not known whether the kinetics of the active enantiomer differs in patients, who are slow metabolisers of spartein/debrisoquine or mephenytoin. The biological half-life is about 36 hours (interval 28 - 42 hours). The systemic plasma clearance is about 0,4 L/min.

Longer half-lives and decreased clearance value due to a reduced rate of metabolism have been demonstrated in elderly patients, and therefore these patients should be given a lower dose.

Patients with reduced liver function have a slower elimination.
Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min) (see section 4.2 and 4.3).

The excretion proceeds with the urine. In steady-state about 30 % of the administered dose is identified in the urine, 12 % as unchanged substance.

Citalopram is a weak inhibitor of the cytochrome P450 IID6 metabolic pathway with a consequent reduction in potential for adverse events and interactions.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Maize starch
Lactose monohydrate
Cellulose, microcrystalline
Copovidone
Glycerol 85%
Croscarmellose sodium
Magnesium stearate

Coating:
Hypromellose 5
Macrogol 400
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 25 ºC. Keep out of reach of children.

6.5 Nature and contents of container

Blister packs containing 28 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

H. Lundbeck (Pty) Ltd
Office A1002, First Floor, Knightsbridge,
33 Sloane Street, Bryanston
2190
South Africa

8 REGISTRATION NUMBER

29/1.2/0232

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