CLEAN PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

CILATE 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

CILATE contains sugar:

Lactose monohydrate 45,72 mg per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

A white, biconvex, capsule shaped, film-coated tablet, 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

CILATE is indicated for the treatment of: -

Depression and prevention of relapse.

Panic disorder with or without agoraphobia.

Obsessive-compulsive disorder (OCD).

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4.2 Posology and method of administration

Adults

Treating depression

CILATE 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 **CILATE** 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.

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.

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Children and adolescents (< 18 years)

CILATE 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.

CILATE 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 are 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 of CILATE

Abrupt discontinuation should be avoided. The dose of **CILATE** should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 Special Warnings and Precautions for Use and section 4.8 Undesirable Effects).

If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered by the medical

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practitioner. Subsequently, the medical practitioner may continue reducing the dose, but at a more gradual rate.

Method of administration

CILATE must be administered as a single daily dose, and can be taken any time of the day without regard to food intake.

4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.

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

Monoamine Oxidase Inhibitors (MAOIs):
Some cases have been reported with features resembling serotonin syndrome.
CILATE should not be given to patients receiving MAOIs (including selegiline) in daily doses exceeding 10 mg/day.
CILATE should not be given for fourteen days after discontinuation of an irreversible MAOI or for the time specified after discontinuation of a reversible MAOI as stated in the professional information of the reversible MAOI. MAOIs should not be introduced for seven days after discontinuation of **CILATE** (see section 4.5).
CILATE is contraindicated in combination with linezolid (see section 4.5).

CILATE is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.

CILATE is contraindicated together with medicines that are known to prolong the QT-interval (see section 4.5).

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Concomitant treatment with pimozide (see section 4.5).

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

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide related events). Patients should be closely monitored as improvement may not occur during the first few weeks or more of treatment.

It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which **CILATE** is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those presenting with 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 be carefully monitored during treatment.

Patients and caregivers of patients should be advised to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age

CILATE should not be used in the treatment of children and adolescents under the age of 18 years.

In clinical trials, among children and adolescents treated with antidepressants compared to those treated with placebo, suicide related behaviours (suicide attempt and suicidal

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thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed.

If a decision is taken to treat with **CILIFT** (based on clinical need) the patient should be carefully monitored for the presence of suicidal symptoms. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Elderly patients

Caution should be used in the treatment of elderly patients (see section 4.2).

Reduced kidney and liver function

Caution should be used in the treatment of patients with reduced kidney and liver function (see section 4.2).

Paradoxical anxiety

At the start of treatment with antidepressants some patients with panic disorder may experience intensified anxiety symptoms. This paradoxical reaction usually subsides within the first two weeks of starting treatment. To reduce the likelihood of a paradoxical anxiogenic effect starting on a low starting dose is advised (see section 4.2).

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion, has been reported as a rare adverse reaction with the use of SSRIs and generally reverses on discontinuation of therapy. Elderly female patients appear to be at particularly high risk.

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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 may be detrimental.

Mania

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

Seizures

Developing seizures with the use of antidepressant medicines is a potential risk. **CILATE** should be discontinued in any patient who develops seizures, and if there is an increase in seizure frequency. **CILATE** should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored.

Diabetes

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

Angle-closure Glaucoma

CILATE should be used with caution in patients with angle-closure glaucoma or history of glaucoma since SSRIs including **CILATE** 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 pre-disposed patients.

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Serotonin syndrome

Serotonin syndrome has been reported (in rare cases) in patients using SSRIs. Symptoms of serotonin syndrome include agitation, tremor, myoclonus and hyperthermia. Treatment with **CILATE** should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines

CILATE should not be used concomitantly with medicines with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan and tryptophan.

Haemorrhage

There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleedings with SSSRIs (see section 4.8). SSRIs/SNRIs may increase the risk of postpartum haemorrhage, and this risk could potentially apply also to **CILATE** (see sections 4.6, 4.8). Caution is advised in patients taking SSRIs, particularly with concomitant use of active ingredients known to affect platelet function or other active ingredient 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)

Caution is advised with concurrent therapy of SSRIs and ECT as there is limited clinical experience.

Reversible, selective MAO-A inhibitors

For information on concomitant treatment with non-selective, irreversible MAO-inhibitors see section 4.5.

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St. John's wort

CILATE and St John's wort preparations should not be taken concomitantly (see section 4.5) as undesirable effects may be frequent during concomitant use of **CILATE** and herbal preparations containing St John's wort (*Hypericum perforatum*).

Withdrawal symptoms seen on discontinuation

Withdrawal symptoms when treatment is discontinued occur frequently, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects).

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The following are frequent reactions: 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. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. These usually occur within the first few days of discontinuing treatment, but there have been less frequent cases of such symptoms in patients who have missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, however in some patients they may be prolonged (2-3 months or more). It is therefore advised that **CILATE** should be gradually reduced over a period of several weeks or months when discontinuing treatment according to the patient's needs (see “Withdrawal symptoms seen on discontinuation of **CILATE**”, Section 4.2)

Psychosis

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

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QT-interval prolongation

CILATE may cause a dose dependent prolongation of the QT-interval. Cases of QT-interval prolongation and ventricular arrhythmia including torsade de pointes have been reported, mainly 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 arrhythmias should be corrected before treatment with **CILATE** is initiated.

Patients with stable cardiac disease should undergo an ECG review before treatment is started. ECG monitoring should be considered in case of overdose or conditions of altered metabolism with increased peak levels, such as liver impairment.

If signs of cardiac arrhythmia occur during treatment with **CILATE**, the treatment should be withdrawn and an ECG should be performed.

Excipients

CILATE contains 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 and moclobemide and buspirone have been reported.

Contraindicated combinations

MAO-inhibitors

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Concurrent use of **CILATE** and MAO-inhibitors (MAOIs) can result in severe undesirable effects, including serotonin syndrome (see section 4.3).

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a MAOI, including selegiline (irreversible MAOI), and linezolid and moclobemide (reversible MAOIs) and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome. Symptoms of an interaction with a MAOI include: agitation, tremor, myoclonus, and hyperthermia.

QT-interval prolongation

An additive effect of **CILATE** and medicines that prolong the QT-interval cannot be excluded. Therefore, co-administration of **CILATE** and medicines that prolong the QT-interval, such as Class IA and III antiarrhythmics, antipsychotics (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) etc., is contraindicated.

Pimozide

In a study the co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an inconsistent increase in AUC and Cmax of pimozide. The co-administration also caused a mean increase in the QTc interval of approximately 10 msec. Due to the interaction (albeit a low dose of pimozide) concomitant administration of **CILATE** and pimozide is contraindicated.

Combinations requiring precaution for use

Selegiline (selective MAO-B inhibitor)

No clinically relevant interactions occurred in a pharmacokinetic/pharmacodynamic

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interaction study with concomitantly administered citalopram 20 mg daily and selegiline 10 mg daily (a selective MAO B inhibitor). However, the concomitant use of citalopram and selegiline in doses above 10 mg daily is contraindicated.

Serotonergic medicines

Lithium and tryptophan

No pharmacodynamic interactions have been found in clinical studies in which citalopram 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 **CILATE** 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, therefore the simultaneous use of **CILATE** 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 and 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

Caution is advised for patients who are being treated simultaneously with anticoagulants, medicines that affect the platelet function, such as non-steroidal anti-inflammatory medicines (NSAIDs), acetylsalicylic acid, dipyridamole, and ticlopidine or other medicines (e.g. atypical antipsychotics) that can increase the risk of haemorrhage (see section 4.4).

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ECT (electroconvulsive therapy)

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and **CILATE** (see section 4.4).

Alcohol

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

Medicines inducing hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia-inducing medicines as these conditions increase the risk of malignant arrhythmias.

Medicines lowering the seizure threshold

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

Pharmacokinetic interactions

Biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38 %), CYP3A4 (approx. 31 %) and CYP2D6 (approx. 3 1%) isozymes of the cytochrome P450 system. The fact that citalopram is metabolised by more than one CYP means that inhibition of its biotransformation is less likely as inhibition of one enzyme may be compensated by another. Therefore, co-administration of **CILATE** with other medicines in clinical practice has a very low likelihood of producing pharmacokinetic medicine interactions.

Food

The absorption and other pharmacokinetic properties of **CILATE** are not affected by food.

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Effect of other medicines on the pharmacokinetics of CILATE

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

Cimetidine

Caution is advised when administering **CILATE** in combination with cimetidine, as cimetidine is a potent CYP2D6, 3A4 and 1A2 inhibitor causing a moderate increase in the average steady state levels of citalopram. Dose adjustment may be necessitated.

Co-administration of escitalopram (the active enantiomer of citalopram) with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50 %) increase in the plasma concentrations of escitalopram. Therefore, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g., omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine). A reduction in the dose of **CILATE** may be necessary based on the advent of undesirable effects during concomitant treatment.

Metoprolol

Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when **CILATE** is co-administered with medicines that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6 (e.g., antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol). Dosage adjustment may be necessitated.

A study demonstrated that the co-administration with metoprolol resulted in a twofold increase in the plasma levels of metoprolol, but did not statistically significant increase the

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effect of metoprolol on the blood pressure and cardiac rhythm.

Effects of CILATE on other medicines

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6 as compared to other SSRIs established as significant inhibitors.

Levomepromazine, digoxin, carbamazepine

No change or only very small changes of clinical importance were observed when citalopram 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 epoxid) and triazolam).

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

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.

A reduction of the desipramine dose may be necessitated, when desipramine is combined with citalopram as an increase of the desipramine plasma concentration has been observed in a study.

4.6 Fertility, pregnancy and lactation

Pregnancy

CILATE should not be used during pregnancy unless clearly necessary and only after

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careful consideration of risk/benefit.

Neonates should be observed if maternal use of **CILATE** 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 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.

The use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

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

Breastfeeding

CILATE is excreted into breast milk. It is estimated that the suckling infant will receive about 5 % of the weight related maternal daily dose (in mg/kg). No or only minor events have been observed in the infants. However, the existing information is insufficient for assessment of the risk to the child. If treatment with **CILATE** is considered necessary, discontinuation of breast feeding should be considered.

Fertility

Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

CILATE has minor or moderate influence on the ability to drive and use machines.

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Patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration due to the illness itself and psychoactive medicines can reduce the ability to make judgements and to react to emergencies. Patients should be informed of the above-mentioned effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 Undesirable effects

a) Summary of adverse reactions

Adverse effects observed with **CILATE** are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually diminish subsequently. Dose-response reactions were reported for the following reactions: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue.

System organ class	**Frequency**	**Undesirable effect**
Blood and lymphatic disorders	Unknown	Thrombocytopenia
Immune system disorders	Unknown	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Unknown	Inappropriate ADH secretion
Metabolism and nutrition disorders	Frequent	Appetite decreased; weight decreased
	Less frequent	Increased appetite, weight increased, hyponatraemia
	Unknown	Hypokalaemia
Psychiatric disorders	Frequent	Sleep disorder, agitation, libido decreased, anxiety, nervousness, confusional state, abnormal

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		orgasm (female), abnormal dreams, apathy
	Less frequent	Aggression, depersonalisation, hallucination, mania, libido increased
	Unknown	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[1]
Nervous system disorders	Frequent	Somnolence, insomnia, headache, tremor, paraesthesia, restlessness, dizziness, disturbance in attention, migraine, amnesia
	Less frequent	Syncope, convulsion grand mal, dyskinesia, taste disturbance
	Unknown	Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	Less frequent	Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4 Special warnings and precautions for use
	Unknown	Visual disturbance
Ear and labyrinth disorders	Frequent	Tinnitus
Cardiac disorders	Frequent	Palpitations
	Less frequent	Bradycardia, tachycardia
	Unknown	QT-prolongation, ventricular arrhythmia including torsade de pointes
Vascular disorders	Less frequent	Haemorrhage

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	Unknown	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Frequent	Yawning, rhinitis
	Less frequent	Nasal congestion coughing
	Unknown	Epistaxis
Gastrointestinal disorders	Frequent	Dry mouth, nausea, diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, flatulence, salivary hypersecretion
	Unknown	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepato-biliary disorders	Less frequent	Hepatitis
	Unknown	Liver function test abnormal
Skin and subcutaneous tissue disorders	Frequent	Sweating increased, pruritus
	Less frequent	Urticaria, alopecia, rash, purpura, photosensitivity reaction
	Unknown	Ecchymosis, angioedema
Musculoskeletal and, connective tissue disorders	Frequent	Myalgia, arthralgia
Renal and urinary disorders	Less frequent	Micturition disorders including urinary retention
Reproductive system and breast disorders	Frequent	Impotence, ejaculation disorder, ejaculation failure

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	Less frequent	Female: Menorrhagia
	Unknown	Galactorrhoea Female: Metrorrhagia, postpartum haemorrhage[2] Male: Priapism
General disorders and administration site conditions	Frequent	Asthenia, fatigue
	Less frequent	Oedema, pyrexia, malaise
	Unknown	Neuroleptic malignant syndrome

[1] Suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).

Cases of QT-prolongation and ventricular arrhythmia including torsade de pointes have been reported, 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).

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

Class effects

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 **CILATE** (particularly when abrupt) frequently leads to withdrawal symptoms. The following are the frequent reactions: dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams),

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agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances. Generally, these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged. It is therefore advised that when **CILATE** treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and section 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.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za.

4.9 Overdose

Fatal cases of citalopram overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medications. The fatal dose is unknown. Patients have survived ingestion of more than 2 g citalopram. The effects may be potentiated by alcohol taken at the same time.

Potential interaction with TCAs, MAOIs and other SSRIs.

Symptoms

The following symptoms have been seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block,

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QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, hyperpyrexia, and atrial and ventricular arrhythmia.

ECG changes including nodal rhythm, prolonged QT-intervals and wide QRS complexes may occur. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported.

Less frequent, features of the "serotonin syndrome" (which may include alteration of mental status, neuromuscular hyperactivity and autonomic instability) may occur in severe poisoning. There may be hyperpyrexia and elevation of serum creatine kinase.

Rhabdomyolysis is a less frequent occurrence.

Treatment of overdose

There is no known specific antidote to **CILATE** overdose.

Treatment should be symptomatic and supportive and includes the maintenance of a clear airway and monitoring of ECG and vital signs until stable. ECG monitoring is advisable in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT-interval, or in patients with altered metabolism (such as with liver impairment).

The following should be considered: Administering oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50 %.

Osmotically working laxative (such as sodium sulphate) and stomach evacuation. If consciousness is impaired the patient should be intubated.

Convulsions should be controlled with intravenous diazepam if they are frequent or prolonged.

5. PHARMACOLOGICAL PROPERTIES

A 1.2 Psychoanaleptics (antidepressants)

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Mechanism of action

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT) uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.

Citalopram is a very Selective Serotonin Reuptake Inhibitor (SSRI), with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT $_{1A}$, 5-HT$_2$, DA D$_1$ and D$_2$ receptors, α_1-, α_2-, β-adrenoceptors, histamine H$_1$, muscarine cholinergic, benzodiazepine, and opioid receptors. Tests have confirmed the lack of receptor affinity.

This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.

5.1 Pharmacodynamic properties

Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Like tricyclic antidepressants, other SSRIs and MAO inhibitors, citalopram suppresses REM-sleep and increases deep slow-wave sleep.

Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics. Potentiation of d-amphetamine-induced hyperactivity following administration of citalopram occurs.

In humans citalopram does not impair cognitive (intellectual function) and psychomotor

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performance and has no or minimal sedative properties, either alone or in combination with alcohol.

In a study citalopram did not reduce saliva flow in humans and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters.

Citalopram has no effect on the serum levels of prolactin and growth hormone.

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) msec at the 20 mg/day dose and 16,7 (90 % CI 15,0-18,4) msec at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Absorption

Absorption is almost complete and independent of food intake (T_{max} average/mean 3,8 hours). Oral bioavailability is about 80 %.

Distribution

The apparent volume of distribution (V_d)β is about 12,3 L/kg. The plasma protein binding is below 80 % for citalopram and its main metabolites.

Biotransformation

Citalopram is metabolized to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma.

Elimination

The elimination half-life ($T_{½β}$) is about 1,5 days and the systemic citalopram plasma

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clearance (Cl_S) is about 0,33 L/min, and oral plasma clearance (Cl_{oral}) is about 0,41 L/min. Citalopram is excreted mainly via the liver (85 %) and the remainder (15 %) via the kidneys. About 12 % of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0,35 L/min and renal clearance about 0,068 L/min.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Elderly patients (≥ 65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

Citalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of citalopram is about twice as long and steady state citalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

Reduced renal function

Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

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Cellulose microcrystalline, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate and maize starch,

Coating

Opadry white which contains hypromellose, macrogol 400 and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

28’s: Printed unit cartons containing 2 blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 14 tablets each.

30’s: Printed unit cartons containing 3 blister packs (composed of transparent PVC and silver coloured aluminium foil backing) of 10 tablets each.

6.6 Special precautions for disposal <and other handling>

No special requirements

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7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets,

Cape Town,

South Africa, 8001

8 REGISTRATION NUMBER(S)

A39/1.2/0548

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 March 1994

10 DATE OF REVISION OF THE TEXT

31 March 2021

Signature: