

1. NAME OF THE MEDICINAL PRODUCT

Citalopram Viatrix 20 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 24.98 mg citalopram hydrobromide equivalent to 20 mg citalopram.

Excipient with known effect:

Each tablet contains 52.52 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

A white, oval, normal convex film-coated tablet marked with “CM” scoreline “20” on one side and “G” on the other. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depressive episodes.

Panic disorder with or without agoraphobia.

Prophylaxis of recurrence of episodes of depression.

4.2 Posology and method of administration

Posology

Depression

Adults:

Citalopram should be administered as a single oral dose of 20 mg daily.

Dependent on individual patient response, the dose may be increased to a maximum of 40 mg daily.

Panic disorder

Adults:

A single oral dose of 10 mg is recommended for the first week before increasing the dose to 20 mg daily. Dependent on individual patient response, the dose may be increased to a maximum of 40 mg daily. Maximum effect is achieved after about 3 months and the response is maintained during continued treatment, usually up to 6 months.

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.

Paediatric population (<18 years of age)

Citalopram should not be used in the treatment of children and adolescents under 18 years of age (see 4.4 Special warnings and precautions for use).

Renal impairment

Reduction of dose is not necessary in mild or moderate renal insufficiency. Caution is recommended in patients with severe renal impairment (creatinine clearance less than 20ml/min) (see section 5.2).

Hepatic impairment

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 (see section 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, (see section 5.2).

Duration of treatment

The antidepressant effect can generally first be assessed after 2-3 weeks of treatment. The treatment should continue for at least three months, usually six months, after improvement. Maximum effect will usually be achieved in about three months. For prophylaxis, the duration of treatment is also long term.

Withdrawal symptoms seen on discontinuation of SSRI treatment

Abrupt discontinuation should be avoided. When stopping treatment with Citalopram the dose 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 and section 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 physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

Oral use.

Citalopram Viartis is administered once per day. Citalopram Viartis can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Monoamine Oxidase Inhibitors (MAOIs). Some cases presented with features resembling serotonin syndrome.
Citalopram should not be given to patients receiving MAOIs including selegiline in daily doses exceeding 10 mg/day.
- Citalopram should not be given for fourteen days after discontinuation of an irreversible MAOI or for the time specified after discontinuation of a reversible MAOI (RIMA) as stated in the prescribing text of the RIMA. MAOIs should not be introduced for seven days after discontinuation of citalopram (see section 4.5).
- Citalopram is contraindicated in combination with linezolid unless there are facilities for close observation and monitoring of blood pressure (see section 4.5).
- Citalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.
- Citalopram is contraindicated together with medicinal products that are known to prolong the QT-interval (see section 4.5).

4.4 Special warnings and precautions for use

Elderly patients and patients with renal or hepatic impairment

Treatment of elderly patients and patients with impaired renal or hepatic function, see section 4.2.

Paediatric population under 18 years of age

Citalopram Viartis should not be used in the treatment of children and adolescents under age of 18 years. Suicide-related behaviours (suicide attempts 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. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Mania

In patients with manic-depressive illness a change towards the manic phase may occur. Should the patient enter a manic phase citalopram should be discontinued.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which citalopram 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 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 drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need 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.

Serotonin syndrome

In rare cases, 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 (see section 4.5). Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, buprenorphine, tramadol, oxitriptan, and tryptophan. Serotonin syndrome may occur when SSRIs are used concomitantly with these substances (see section 4.5).

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 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 a rare adverse reaction with the use of SSRIs and generally reverses on discontinuation of therapy. Elderly female patients seem to be at particularly high risk.

Psychosis

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

Haemorrhage

There have been reports of prolonged 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 who are receiving concomitant use of active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage, e.g. anticoagulants, salicylic acid derivatives, non-steroidal anti-inflammatory/ antirheumatic drugs (NSAIDs), as well as in patients with a history of bleeding disorders (see section 4.5).

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

ECT (electroconvulsive therapy)

There is limited clinical experience of concurrent administration of SSRIs and ECT; therefore caution is advisable.

Seizures

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

Diabetes

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

St. John's wort

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

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.

QT interval prolongation

Citalopram has been found to cause a dose-dependent prolongation of the QT-interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia, 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 and should be corrected before treatment with citalopram is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

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

Withdrawal symptoms seen on discontinuation of SSRI treatment:

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a recurrence prevention clinical trial with citalopram, adverse events after discontinuation of active treatment were seen in 40% of patients versus 20% in patients continuing citalopram.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), 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. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2 "Withdrawal symptoms seen on discontinuation of SSRI treatment").

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.

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.

Excipients

Citalopram Viartis contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic interactions

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

Contraindicated combinations

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between citalopram and other medicinal products that prolong the QT interval have not been performed. An additive effect of citalopram and these medicinal products cannot be excluded. Therefore, co-administration of citalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. fentiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.

Monoamine Oxidase Inhibitors (MAOIs)

The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including the 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 monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline and the reversible MAOIs linezolid and 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. Symptoms of an active substance interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, change in mental status including confusion, irritability and extreme agitation leading to delirium and coma (see section 4.3).

Pimozide

Co administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Combinations requiring precaution for use

Selegiline (selective irreversible MAO-B inhibitor)

A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered citalopram (20 mg daily) and selegiline (10 mg daily) (a selective irreversible MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10 mg daily) is contraindicated (see section 4.4) due to the risk of developing serotonergic syndrome.

Serotonergic medicinal products

Co-administration with serotonergic medicinal products e.g. buprenorphine, tramadol and sumatriptan may lead to enhancement of 5-HT associated effects. Until further information is available, the simultaneous use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

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 citalopram with these medicinal products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

St. John's Wort

Dynamic interactions between SSRIs and herbal remedy St. John's Wort (*Hypericum perforatum*) can occur, resulting in an increase in incidence of undesirable effects (see section 4.4). Pharmacokinetic interactions have not been investigated.

Haemorrhage

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

ECT (electroconvulsive therapy)

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and citalopram (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.

Medicinal products inducing hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias (see section 4.4).

Medicinal products lowering the seizure threshold

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

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. 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 citalopram with other medicinal products in clinical practice has very low likelihood of producing 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 citalopram

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).

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. Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. Dose adjustment of citalopram may be warranted.

Cimetidine

Cimetidine, a known potent CYP2D6, 3A4 and 1A2 enzyme inhibitor, caused a moderate increase in the average steady state levels of citalopram. Caution is advised when administering citalopram in combination with cimetidine.

Effects of citalopram on other medicinal products

Metoprolol

Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when citalopram is co-administered with medicinal products 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 warranted. Co-administration with metoprolol resulted in a two-fold increase in the plasma levels of metoprolol but did not statistically significant increase the effect of metoprolol on the blood pressure and cardiac rhythm.

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 no 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. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Published data on pregnant women (more than 2500 exposed outcomes) indicate no malformative feto/ neonatal toxicity. However, citalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

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

The following symptoms may occur in the neonate 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 withdrawal 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 in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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).

Breast-feeding

Citalopram is excreted into breast milk in small amounts. 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. Caution is recommended

The advantages of breast-feeding should be weighed against the possible risks for the child.

Male fertility

Animal data have shown that citalopram may affect sperm quality (see section 5.3). Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

Citalopram has minor or moderate influence on the ability to drive and use machines. Psychoactive medicinal products can reduce the ability to make judgements and to react to emergencies. Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 Undesirable effects

Adverse reactions observed with citalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually attenuate subsequently. The adverse reactions are presented at the MedDRA Preferred Term Level.

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

The table shows the percentage of adverse drug reactions associated with SSRIs and/or citalopram seen in either $\geq 1\%$ of patients in double-blind placebo-controlled trials or in the post-marketing period.

Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$), not known (cannot be estimated from the available data).

	Very common	Common:	Uncommon	Rare	Not Known
Blood and lymphatic system disorders		Palpitations			Thrombocytopenia
Immune system disorders					Hypersensitivity, anaphylactic reaction

	Very common	Common:	Uncommon	Rare	Not Known
Endocrine disorders					Inappropriate ADH secretion, Hyperprolactinaemia
Metabolism and nutrition disorders		Appetite decreased, weight decreased	Increased appetite, weight increased	Hyponatremia	Hypokalaemia
Psychiatric disorders		Nervousness, anxiety, impaired concentration, agitation, abnormal dreams, libido decreased, apathy, confusional state, abnormal orgasm (female),	Euphoria, aggression, depersonalization, hallucination, mania		suicidal ideation, suicidal behaviours ¹ , panic attack, bruxism, restlessness
Nervous system disorders	Somnolence, insomnia, headaches	Tremor, paraesthesia, dizziness, disturbance in attention	Syncope	Convulsion grand mal, dyskinesia, taste disturbance	Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders		Accommodation disorders	Mydriasis		Visual disturbance
Ear and labyrinth disorders		Tinnitus			
Cardiac disorders			Bradycardia, tachycardia		QT-prolongation, ventricular arrhythmia including torsade de pointes ¹
Vascular disorders				Haemorrhage	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Rhinitis, yawning	Cough, dyspnoea		Epistaxis

	Very common	Common:	Uncommon	Rare	Not Known
Gastrointestinal disorders	Dry mouth, nausea	Constipation, diarrhoea, vomiting, abdominal pain, dyspepsia, salivation, flatulence			Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders				Hepatitis	Liver function test abnormal
Skin and subcutaneous tissue disorders	Sweating increased	Pruritus	Photo-sensitivity reaction, urticaria, alopecia, rash, purpura		Ecchymosis, angioedema
Musculoskeletal and connective tissue		Myalgia, arthralgia			
Renal and urinary disorders			Urinary retention		
Reproductive system and breast disorders		Micturitional disorders, ejaculation disorders, irregular menstruation, ejaculation failure, impotence	Female: Menorrhagia, anorgasmia		Male: Priapism, galactorrhoea Female: Metrorrhagia Postpartum Haemorrhage ²
General disorders and administration site conditions		Anorexia, asthenia, general feeling of illness, fatigue	Oedema	Pyrexia	

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

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

Class effects

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.

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 hypokalemia, or with pre-existing QT prolongation or other cardiac disease (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

Withdrawal symptoms seen on discontinuation of SSRIs

Discontinuation of Citalopram (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), 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. 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 Citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and section 4.4).

4.9 Overdose

Toxicity

Comprehensive clinical data on citalopram overdose are limited and many cases involve concomitant overdoses of other drugs/alcohol. Fatal cases of citalopram overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medications.

Symptoms

The following symptoms have been seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT interval prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, and atrial and ventricular arrhythmia.

Management

There is no known specific antidote to citalopram. 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. In the event of seizures, diazepam may be useful. Cardio-toxic effects have not been observed.

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, e.g. liver impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, selective serotonin reuptake inhibitors (ATC code: N06AB04)

Citalopram is a racemate in which one of the enantiomers (the S-form) has pharmacological effects. The pharmacodynamic effect is specifically related to a potent and selective inhibition of serotonin (5-HT)-uptake. Long-term treatment with citalopram does not induce tolerance to inhibition of 5-HT-uptake.

Citalopram has no or only minimal effects on noradrenaline (NA), dopamine (DA) or gammaaminobutyric acid (GABA) uptake.

Citalopram has no or very low affinity for the serotonin receptors 5-HT_{1A}, 5-HT₂, the dopamine receptors D₁ and D₂ receptors, alpha₁-, alpha₂-, beta-adrenoceptors, histamine H₁ and cholinergic (muscarine) receptors.

Reduction of REM (rapid eye movement) sleep is considered to be a predictor of antidepressant effect. Citalopram suppresses REM sleep and increases deep slow-wave sleep.

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

Citalopram is a racemate in which the S-enantiomer is considered to be responsible for the pharmacodynamic effect. The pharmacokinetic information is based on the racemate.

Food

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

Absorption

Absorption is almost complete and independent of food intake. Peak plasma levels are reached after approx. 4 hours (range 1-6 hours) after administration. Oral bioavailability is >80%.

Distribution

The volume of distribution (V_d)_{beta} is approx. 14 (12-17) l/kg.

Binding to plasma proteins is approx. 80% for citalopram and its main metabolites.

Biotransformation

Citalopram is metabolised to demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and to a deaminated propionic acid derivative. Unchanged citalopram predominates in plasma. The principal metabolites of citalopram, demethylcitalopram and didemethylcitalopram, are both SSRIs. They are less potent and less selective than citalopram. They are not considered to contribute to in the antidepressant effect.

Elimination

The elimination half-life ($T_{1/2\beta}$) is approx. 36 hours (range 28-42 hours) and the systemic citalopram plasma clearance (Cl_s) is approx. 0.3-0.4 l/min. Citalopram is eliminated mainly via the liver (85%) and the remainder (15%) via the kidneys; 12-(23)% of the daily dose is excreted in urine as unchanged citalopram. Metabolic clearance is approx. 0.3 l/min and renal clearance approx. 0.05-0.08 l/min.

The kinetics are linear. Steady-state levels in plasma are reached within 1-2 weeks and vary four-fold between individuals. There is no clear correlation between plasma levels of citalopram 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 observed.

Impaired hepatic function

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

Impaired renal function

Citalopram is eliminated rather more slowly in patients with mild to moderate impairment of renal function, but otherwise no major effect on the pharmacokinetics of the substance has been seen. At

present no information on treatment of patients with severely impaired renal function (creatinine clearance <20 ml/min) is available.

It is not known whether the kinetics for the active enantiomer are different in patients who are slow metabolisers of sparteine/debrisoquine (CYP2D6) or mephenytoin (CYP2C19).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety, pharmacology, genotoxicity and carcinogenic potential. Phospholipidosis in several organs has been observed with repeated administration to rats. The effect is reversible on discontinuation. In animal studies accumulation of phospholipids has been seen in long-term studies with many cation-amphiphilic drugs. The clinical relevance of this finding is not clear.

Reproduction toxicological studies in rats have shown skeletal abnormalities in the offspring, but no increased frequency of malformation. The effects may be related to the pharmacological activity or may be a consequence of maternal toxicity. Peri- and post-natal studies have shown reduced survival in offspring during the suckling period. The potential risk for humans is unknown.

Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess of human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Maize starch
Lactose monohydrate
Cellulose, microcrystalline
Povidone
Crospovidone
Magnesium stearate

Tablet Coating

Hypromellose
Lactose monohydrate
Macrogol
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister packs PVC/PVdC/Al foil, 12, 14, 20, 28, 30, 50, 56, 98, 100, 250, 500 tablets.

Blister packs PVC/PVdC/Al foil, calendar pack, 28 tablets.

Blister packs PVC/PVdC/Al foil, single dose, 14, 28, 50, 56, 100, 250, 500 tablets.

HDPE bottle with screw cap, 100, 250, 500 tablets.

Polypropylene bottle with tamper-evident snap-on closure of polyethylene, 100, 250, 500 tablets.

Bottle for dose-dispensing of polypropylene with polyethylene closure: 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2025-01-08