

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CITROL 20 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of citalopram (as hydrobromide).

Excipient with known effect

Each film-coated tablet contains 21.85 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong, biconvex film-coated tablet, scored on one side and embossed C20. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of major depressive episodes
Treatment of panic disorder with or without agoraphobia

4.2 Posology and method of administration

Citalopram should be administered as a single oral dose, either in the morning or in the evening. The tablets can be taken with or without food, but with fluid.

Adults:

- Treatment of major depressive episodes

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. Following treatment initiation, an antidepressant effect should not be expected for at least two weeks. Treatment should continue until the patient has been free of symptoms for 4-6 months to give adequate protection against the possibility of a relapse.

- Treatment of panic disorder

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. **This is to avoid paradox reactions (i.e. panic, anxiety) (see section 4.4).**

The first therapeutic effects usually appear after 2 – 4 weeks. Full therapeutic response may take up to 3 months to develop. It may be necessary to continue treatment for several months. Documentation from clinical efficacy studies exceeding 6 months is insufficient.

Elderly:

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 patients is 20 mg daily.

Paediatric population:

Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

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). These patients should be clinically monitored.

Renal impairment:

Dose adjustment is not necessary for patients with mild to moderate renal dysfunction. The use of citalopram in patients with severe renal impairment (creatinine clearance less than 20 ml/min.) is not recommended as no information is available on use in these patients.

Poor metabolisers regarding 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).

For the different dose regimens suitable strengths should be prescribed.

Withdrawal symptoms seen on discontinuation of citalopram

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 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 physician may continue decreasing the dose, but at a more gradual rate.

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**

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

Renal and hepatic impairment

Caution should be used in the treatment of patients with reduced kidney and liver function and poor CYP2C19 metabolisers (see section 4.2).

Use in children and adolescents under 18 years of age

Citalopram should not be used in the treatment of children and adolescents under 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.

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.

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.

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.

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 medicinal products 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 pharmacotherapy 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.

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. Should the patient enter a manic phase citalopram should be discontinued.

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), 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 "Withdrawal symptoms seen on discontinuation of citalopram", section 4.2).

Diabetes

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

Seizures

Seizures are a potential risk with antidepressant medicinal products. 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.

ECT (electro-convulsive therapy)

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

Haemorrhage

There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymosis, gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings with SSRIs (see Section 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with 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).

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

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. Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicinal products

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

Psychosis

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

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).

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 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 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.

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.

Citrol 20 mg film-coated tablets contain lactose and sodium

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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

MAO-inhibitors

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, tremor, myoclony, vegetative/autonomic instability with possible rapid fluctuations of vital signs, change in mental status including confusion, irritability and extreme agitation that switch to delirium and coma (see section 4.3).

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. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), is contraindicated.

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 QT_c 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 MAO-B inhibitor)

A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered citalopram (20 mg daily) and selegiline (10 mg daily) (a selective MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10 mg daily) is contraindicated (see section 4.3).

Serotonergic medicinal products

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.

Co-administration with serotonergic medicinal products (e.g. tramadol, 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).

St. John's Wort

Dynamic interactions between SSRIs and the 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

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 medicinal products (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 [SSRIs], neuroleptics [butyrophenones, thioxanthenes], mefloquin, 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).

Cimetidine

Cimetidine (potent CYP2D6, 3A4, 1A2 inhibitor) caused a moderate increase in the average steadystate levels of citalopram. Caution is advised when administering citalopram in combination with cimetidine. Dose adjustment may be warranted.

Omeprazole and other CYP2C19 inhibitors

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). A reduction in the dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.

Metoprolol

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. Dose adjustment may be warranted. Co-administration with metoprolol resulted in a twofold increase in the plasma levels of metoprolol, but did not statistically significant increase the effect of metoprolol on the blood pressure and cardiac rhythm.

Effects of citalopram 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 heart rate in healthy volunteers. Caution is advised in case of concomitant use of metoprolol and citalopram. Dose adjustment may be necessary.

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 fetoneonatal 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 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.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly 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. 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.

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 ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10000$ to $\leq 1/1000$); very rare ($\leq 1/10000$), not known (cannot be estimated from available data).

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic disorders	Not known	Thrombocytopenia
Immune system disorders	Not known	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Rare	Vasopressin hypersecretion (Schwartz-Bartter syndrome/SIADH)
Metabolism and nutrition disorders	Common	Appetite decreased, weight decreased
	Uncommon	Weight increased, increased appetite,
	Rare	Hyponatraemia
	Not known	Hypokalaemia
Psychiatric disorders	Common	Agitation, nervousness, libido decreased, abnormal orgasm (female), anxiety, confusional state, apathy, impaired concentration, abnormal dreams, memory loss
	Uncommon	Aggression, depersonalisation, hallucination, mania/euphoria, increased libido
	Not known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour ¹
Nervous system disorders	Very common	Lethargy (urge to sleep), insomnia, headache, somnolence
	Common	Paraesthesia, tremor, sleeping disorders, migraine, disturbance in attention, dizziness
	Uncommon	Fainting, syncope
	Rare	Convulsion grand mal, dyskinesia, psychomotor taste disturbance
	Not known	Serotonin syndrome, akathisia, movement disorders, convulsions, extrapyramidal disorders, cramps
Eye disorders	Uncommon	Mydriasis
	Not known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus

Cardiac disorders	Uncommon	Palpitations, bradycardia, tachycardia
	Not known	Ventricular arrhythmia including torsade de pointes, Electrocardiogram QT prolonged
Vascular disorders	Rare	Haemorrhage
	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Yawning, rhinitis, sinusitis
	Uncommon	Dyspnoe
	Rare	Coughing
	Not known	Epistaxis
Gastrointestinal disorders	Very common	Dry mouth, nausea,
	Common	Diarrhoea, vomiting, dyspepsia, abdominal pain, flatulence, increased salivation, constipation
	Not known	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis
	Not known	Liver function test abnormal, pancreatitis
Skin and subcutaneous tissue disorders	Very common	Increased sweating
	Common	Pruritus
	Uncommon	Urticaria, alopecia, purpura, photosensitivity reaction, rash
	Not known	Angioedema, ecchymosis
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Common	Polyuria, micturition disorder
	Uncommon	Urinary retention
Reproductive system and breast disorders	Common	Impotence, ejaculation disorder, ejaculation failure, dysmenorrhoea
	Uncommon	Female: Menorrhagia
	Not known	Female: Metrorrhagia Male: Priapism, galactorrhoea Hyperprolactinaemia Postpartum haemorrhage ²
General disorders and administration site conditions	Very common	Asthenia
	Common	Fatigue, pyrexia
	Uncommon	Oedema, malaise

¹ Cases of suicidal ideation and suicidal behaviour have been reported during citalopram 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).

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

Withdrawal symptoms seen on discontinuation of SSRI treatment

Discontinuation of citalopram (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. 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 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRC Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Toxicity

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

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, atrial, ventricular arrhythmia and rhabdomyolysis. Fatal cases have been reported.

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.

ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medicinal products that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors, ATC code: N06A B04

Citalopram is an antidepressant with a strong and selective inhibitory action on the uptake of 5-hydroxytryptamine (5-HT, serotonin).

Mechanism of action and pharmacodynamic effects

Tolerance to the inhibitory effect of citalopram on 5-HT uptake does not occur during long-term treatment.

The antidepressant effect is probably connected with the specific inhibition of serotonin uptake in the brain neurons.

Citalopram has almost no effect on the neuronal uptake of noradrenaline, dopamine and gamma-aminobutyric acid.

Citalopram shows no affinity, or only very little, for cholinergic, histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.

Citalopram is a bi-cyclic isobenzophurane-derivative that is chemically not related to tricyclic and tetracyclic antidepressants or other available antidepressants. The main metabolites of citalopram are also selective serotonin uptake inhibitors, though to a lesser degree. The metabolites are not reported to contribute to the overall antidepressant effect.

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

General characteristics of the active substance

Absorption

Citalopram is rapidly absorbed following oral administration: the maximum plasma concentration is reached on average after 4 (1-7) hours. Absorption is independent of food intake. Oral bioavailability is approximately 80%.

Distribution:

The apparent distribution volume is 12-17 l/kg. The plasma-protein binding of citalopram and its metabolites is below 80%.

Biotransformation:

Citalopram is metabolised into demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and the deaminated propionic acid-derivative. The propionic acid-derivative is pharmacologically inactive. Demethylcitalopram, didemethylcitalopram and citalopram-N-oxide are selective serotonin uptake inhibitors, although weaker than the parent compound.

The main metabolizing enzyme is CYP2C19. Some contribution from CYP3A4 and CYP2D6 is possible.

Elimination:

The plasma half-life is approximately 1½ days. After systemic administration, the plasma clearance is approximately 0.3-0.4 l/min and after oral administration the plasma clearance is approximately 0.4 l/min.

Citalopram is mainly eliminated via the liver (85%), but also partly (15%) via the kidneys. Of the quantity of citalopram administered, 12-23 % is eliminated unaltered via the urine. Hepatic clearance is approximately 0.3 l/min and renal clearance is 0.05-0.08 l/min.

Steady-state concentrations are reached after 1-2 weeks. A linear relationship has been demonstrated between the steady-state plasma level and the dose administered. At a dose of 40 mg per day, an average plasma concentration of approximately 300 nmol/l is reached. There is no clear relationship between citalopram plasma levels and therapeutic response or adverse reactions.

Characteristics relating to patients

Longer plasma half-life values and a smaller clearance have been found in older patients due to a reduced metabolism. The elimination of citalopram progresses more slowly in patients with reduced liver function. The plasma half-life of citalopram is approximately twice as long and the steady-state plasma concentration approximately twice as high in comparison with patients with a normal liver function.

The elimination of citalopram progresses more slowly in patients with a mild to moderate renal function disorder. A longer half-life and a small increase in the exposure of citalopram have been observed without any major impact on the pharmacokinetics of citalopram. No information is available on treatment of patients with severe renal impairment (creatinine clearance less than 20 ml/min).

Polymorphism

Poor metabolisers regarding CYP2C19 have been observed having twice as high plasma concentrations of escitalopram compared to extensive metabolisers. No relevant changes in the exposure were observed in poor metabolisers regarding CYP2D6 (see section 4.2).

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 has been observed in several organs following multiple administration in rats. The effect was reversible at discontinuation. Accumulation of phospholipids has been observed in long term animal studies with many cation-amphophilic medicinal products. The clinical relevance of these results is not clear.

Reproduction toxicity studies in rats have demonstrated skeletal anomalies in the offspring, but no increased frequency of malformations. The effects may be related to the pharmacological activity or may be a consequence of maternal toxicity. Peri- and postnatal studies have revealed reduced survival in offspring during the lactation 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****Core:**

Cellulose, microcrystalline

Glycerol 85 %

Magnesium stearate

Maize starch

Lactose monohydrate

Copovidone
Sodium starch glycolate (type A)

Coating:

Macrogol 6000
Hypromellose
Talc
Titanium dioxide (colouring agent E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Shelf life after first opening:
Bottles: 12 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The film-coated tablets are packed in PVDC/PVC/aluminium blisters or are packed in a HDPE bottle and inserted in a carton.

Pack sizes:

Blister: 7, 10, 12, 14, 20, 28, 30, 40, 49, 49x1, 50, 50x1, 56, 98, 100, 100x1, 250 film-coated tablets
Bottle: 100, 105, 250* film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd.,
Bantry,
Co. Cork,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/064/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th November 2004
Date of last renewal: 8th November 2008

10 DATE OF REVISION OF THE TEXT

