SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 10mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10mg citalopram (as citalopram hydrobromide).

Excipient with known effect: Each film-coated tablet contains 11.5 mg lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

White round film-coated tablet without a score line

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

Posology

Adults:

Treatment of major depressive episodes

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

As with all antidepressant medicinal products, dosage should be reviewed and adjusted, if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased up to a maximum of 40 mg a day (see section 5.1).

Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.

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 gradually in 10 mg steps 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 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

Children and adolescents under the age of 18:

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

Reduced hepatic function:

An initial dose of 10 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function (see section 5.2). These patients should be clinically monitored.

Reduced renal function:

Dosage 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 dosage 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.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concommitant treatment with pimozide (see also section 4.5).
- Citalopram is contraindicated in the 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).

- MAOIs (monoamine oxidase inhibitors)
- Some cases presented with features resembling serotonin syndrome.
- Citalopram should not be given to patients receiving Monoamine Oxidase Inhibitors (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).

4.4 Special warnings and precautions for use

Elderly

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 ofpatients with reduced kidney and liver function and poor CYP2C19 metabolisers (see section 4.2).

Paediatric Population

Use in children and adolescents under 18 years of age

Citalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

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 usually subsides within the first two weeks of starting treatment. . It is recommended to start treatment with a low dose to reduce the risk of paradoxical anxiety (see section 4.2).

Hyponatraemia

Hyponatraemia, possibly caused by syndrome of inappropriate secretion of antidiuretic hormone (SIADH), has been reported as a rare adverse reaction with the use of SSRIs; this reaction usually reverses upon treatment withdrawal. The risk seems to be higher in older women.

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.

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIshas 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% 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 electrical 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 "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 dosage may need to be adjusted.

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.

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.

ECT (electro-convulsive therapy)

There is little clinical experience of concurrent administration of SSRIs and electro-convulsive therapy, 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).

Serotonin syndrome

In rare cases a 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.

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

Serotonergic medicines

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 the psychotic symptoms.

Reversible, selective MAO-A inhibitors

The combination of citalopram with MAO-A inhibitors is generally not recommended due to the risk of onset of a serotonin syndrome (see section 4.5).

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

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.

ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

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

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

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products 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

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 selective MAOI selegiline and the reversible MAOIs linezolide (non-selective) and moclobemide (selective for type A) and in patients who have recently discontinued an SSRI and have been started on a MAOI.

In some cases symptoms corresponding to serotonin syndrome have been observed. Symptoms of an interaction between the active substance and a MAOI include: hyperthermia, rigidity, tremor, myoclonus, autonomic instability with possible rapid changes in vital signs and altered mental status including confusion, irritability and serious agitation which may develop into delirium and coma (see section 4.3).

Pimozide

Concomitant use of citalopram and pimozide is contra-indicated (see section 4.3). Concomitant administration of a single dose of 2 mg pimozide to healthy volunteers, who were treated with racemic citalopram 40 mg/day for 11 days, caused only an increase in the AUC and Cmax 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 contra-indicated.

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) etc., 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 not recommended

Serotonergic medicinal products

Lithium and tryptophan

No pharmacokinetic 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

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

Haemorrhage

Caution is warranted for patients who are being treated simultaneously with anticoagulants, medicinal products that affect the platelet function of thrombocytes, such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, dipyridamol, and ticlopidine or other medicines (e.g. atypical antipsychotics, phenothiazines, tricyclic antidepressants) 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 drugs 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 [phenothiazines, thioxanthenes and butyrophenones], mefloquin, bupropion and tramadol).

Neuroleptics

Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

Pharmacokinetic interactions

Biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%) isoenzymes 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.

Effect 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 “Lithium and tryptophan”).

Cimetidine

Cimetidine (potent CYP2D6, 3A4, 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram. Caution is advised when administering citalopram in combination with cimetidine. Dose adjustment may be 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, fluvoxamine, lansoprazole, ticlopidine). A reduction in the dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.

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 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 cardiac rhythm in healthy volunteers.

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2 and CYP2C19 and CYP 2D6’ 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. 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 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, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1,000 pregnancies. In the general population 1 to 2 cases of PPHN per 1,000 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. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

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 prominent during the first 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 ≥ 1% of patients in double-blind placebo-controlled trials or in the post-marketing period. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to< 1/10); uncommon (≥ 1/1,000-to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (<1/10,000), not known (cannot be estimated from available data).

System organ class	Frequency	Undesirable effect
Blood and lymphatic disorders	Not known	Thrombocytopenia
Immune system disorders	Uncommon	Hypersensitivity
	Very rare	Anaphylactic reaction
Endocrine disorders	Rare	Vasopressin hypersecretion (Schwartz-Bartter syndrome/SIADH)
	Not known	Inappropriate ADH secretion, Hyperprolactinaemia*
Metabolism and nutrition disorders	Common	Decreased appetite, weight decreased,
	Uncommon	Weight increased, increased appetite
	Rare	Hyponatraemia
	Not known	Hypokalaemia
Psychiatric disorders	Very common	Sleep disorder
	Common	Agitation, decreased libido, abnormal orgasm (female), anxiety, nervousness, confusional state, apathy, abnormal dreams
	Uncommon	Aggression, depersonalisation, hallucinations, mania, euphoria, increased libido
	Not known	Panic attacks, bruxism, restlessness, suicidal ideation andsuicidal behaviour[1]
Nervous system disorders	Very common	Somnolence, lethargy (urge to sleep), insomniaheadache,
	Common	Tremor, paraesthesia, dizziness, migraine, disturbance in attention, amnesia
	Uncommon	Fainting, cramps, extrapyramidal disorders
	Rare	Convulsion grand mal , dyskinesia, taste disturbance, psychomotor restlessness/akathisia (see section 4.4)
	Not known	Convulsions, serotonin syndrome, movement disorders
Eye disorders	Very common	Abnormal accommodations
	Common	Visual disturbances
	Uncommon	Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Very common	Palpitations
	Common	Tachycardia

	Uncommon	Bradycardia
	Not known	Ventricular arrhythmia including torsade de pointes, QT-prolongation on ECG[2]
Vascular disorders	Common	Hypotension, hypertension, orthostatic hypotension
	Rare	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Common	Yawning, rhinitis, sinusitis
	Uncommon	Coughing
	Not known	Epistaxis (nose bleeding)
Gastrointestinal disorders	Very common	Dry mouth, nausea, constipation
	Common	Diarrhoea, vomiting. dyspepsia, abdominal pain, flatulence, increased salivation
	Not known	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis
	Not known	Liver function test abnormal
Skin and subcutaneous tissue disorders	Very common	Increased sweating
	Common	Pruritus, rash
	Uncommon	Urticaria, alopecia, purpura, photosensitivity
	Very rare	Angioedemas
	Not known	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
	Very rare	Galactorrhoea
	Not known	Female: Metrorrhagia Male: Priapism postpartum haemorrhage**;
General disorders and administration site conditions	Very common	Asthenia
	Common	Fatigue, pyrexia
	Uncommon	Oedemas, malaise

* This event has been reported for the therapeutic class of SSRIs/SNRIs (section 5.1)

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

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

[2] Cases of QT-prolongation and ventricular arrhythmia including torsades 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, 5.1).

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 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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.

Fatal dose is not known. 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, QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, 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.

Rarely, features of the "serotonin syndrome" may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment

There is no known specific antidote to citalopram.

Treatment should be symptomatic and supportive and include 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, e.g. liver impairment.

Consider 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 should be considered.

If consciousness is impaired the patient should be intubated.

Control convulsions with intravenous diazepam if they are frequent or prolonged.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant, 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, benzodiazepine and opioid histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.

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.

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.

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.

Pharmacodynamic effects

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. There was potentiation of d-amphetamine-induced hyperactivity following administration of citalopram.

In humans citalopram does not impair cognitive (intellectual function) and psychomotor performance and has no or minimal sedative properties, either alone or in combination with alcohol.

Citalopram did not reduce saliva flow in a single dose study in human volunteers 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 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

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 (100-500 nmol/L) is reached. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Characteristics relating to patients

Elderly (≥ 65 years)

Longer plasma half-life values and a smaller clearance have been found in older patients due to a reduced metabolism.

Reduced hepatic function

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.

Reduced renal function

The elimination of citalopram progresses more slowly in patients with a mild to moderate renal function disorder, 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 drugs. 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:

microcrystalline cellulose

Glycerol 85 %

Magnesium stearate

Maize starch

Lactose monohydrate

Copovidone

Sodium starch glycollate (type A)

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

Or
Sepifilm 752 blanc (SEPPIC)-Ready to use coating material:
Hypromellose
Microcrystalline cellulose
Macrogol 40 Stearate Type I
Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

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 and inserted into a carton.

10, 14, 20, 28, 30, 50, 56, 60, 98, 100 film-coated tablets in blister intended for dose-dispensing and hospitals.

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

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Campbell Road

Tadley

RG26 5EG

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 51718/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

09/04/2026