

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciprager 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains citalopram hydrobromide equivalent to 40 mg of citalopram.

Excipient with known effect: Each tablet contains 106.56 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 debossed "CM" scoreline "40" on one side and "G" on the other. 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

Posology

Major depressive episodes

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. In general, improvement in patients starts after 2-4 weeks.

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.

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.

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.

Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. A low initial starting dose is recommended to minimise the potential worsening of panic symptoms, which is generally recognised to occur early in the treatment of this disorder. 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 gradually up to a maximum of 40 mg/day (see section 5.1).

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

The maximum efficacy of citalopram in the treatment of panic disorder is achieved after approximately 3 months. Depending on the patient's individual response, it may be necessary to continue treatment for several months or more. There is insufficient data on efficacy from clinical studies lasting more than 6 months.

Elderly (> 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 starting dose is 10 mg daily. The recommended maximum dose is 20 mg daily.

Paediatric population

The safety and efficacy of citalopram has not been established in the treatment of children and adolescents under the age of 18 years. Thus, citalopram should not be used in this population (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. These patients should be clinically monitored (see section 5.2).

Reduced renal function:

Dosage adjustment is not necessary for patients with mild to moderate renal dysfunction. No information is available for cases of severe impairment of renal function (creatinine clearance < 30mL/minute). Particular caution is therefore advised with patients with severe renal impairment (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).

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 symptoms (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

Ciprager should be administered as a single 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.
- *Monoamine Oxidase Inhibitors (MAOIs)* (see sections 4.4 and 4.5):
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with monoamine oxidase inhibitors (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI. Some cases presented with features resembling serotonin syndrome.

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), e.g. moclobemide, 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).

- *5-HT agonists:*
Sumatriptan's serotonergic effects are suspected to be enhanced by SSRIs. Until further evidence is available it is advised not to use citalopram simultaneously with 5-HT agonists e.g. Sumatriptan.
- Citalopram is contraindicated in combination with linezolid unless there are facilities for close observation and monitoring of blood pressure (see section 4.5).
- Citalopram should not be used concomitantly with pimozide (see also 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 reduced kidney and liver function, see section 4.2.

Paediatric population under 18 years of age

Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.2). 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.

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.

Diabetes

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

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 (electroconvulsive therapy)

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

Mania

Citalopram should be used with caution in patients with a history of mania/hypomania. In patients with manic-depressive illness a change towards the manic phase may occur. Citalopram should be discontinued in any patient entering a manic phase.

Psychosis

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

Haemorrhage

There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymosis, purpura, gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings with SSRIs (see section 4.8). Caution is advised in patients taking citalopram, particularly in concomitant use with oral anticoagulants, active substances known to affect platelet function or other active substances that may increase the risk of haemorrhage (e.g. atypical antipsychotics, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), ticlopidine and dipyridamole) 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 and 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 (see section 4.5). Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicinal products

Concomitant use of citalopram with medicinal products with serotonergic effects such as opioids (e.g. buprenorphine and tramadol), tryptophan, oxitriptan, sumatriptan or other triptans is contraindicated (see section 4.5).

Reversible, selective MAO-A inhibitors

The combination of citalopram with MAO-A inhibitors is 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).

Hyponatraemia

Hyponatraemia, probably due to inappropriate anti-diuretic 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.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see sections 4.2 and 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 following discontinuation of SSRIs/SNRIs. 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").

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.

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.

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).

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

Ciprager tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total 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

Monoamine Oxidase Inhibitors (MAOIs)

The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including serotonin syndrome (see section 4.3).

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline, 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: extreme agitation, rigidity, tremor, myoclonus, hyperthermia, vegetative instability with rapid fluctuations of the vital signs, changes in mental state, confusion, irritability and even 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-malarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., 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 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 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 normal.

Co-administration with serotonergic medicinal products (e.g. opioids (buprenorphine and tramadol), tryptophan, oxitriptan, sumatriptan and other triptans) may lead to enhancement of 5-HT associated effects.

In combination with triptans, there is a potential risk of coronary vasoconstriction and hypertension too. Until further information is available, the simultaneous use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, is contraindicated (see sections 4.3 and 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, dipyridamole, 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 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 such as antidepressants (tricyclic antidepressants, SSRIs), neuroleptics (phenothiazine, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol (see section 4.4).

Neuroleptics

Experience with the use of citalopram has shown no clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be ruled out.

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.

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).

Cimetidine

Cimetidine (potent CYP2D6, 3A4 and 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 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) or cimetidine. A reduction in the dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.

Effects of citalopram on other medicinal products

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.

Metoprolol and other CYP2D6 substrates

Caution is recommended when citalopram is co-administered with medicinal products that are mainly metabolised by CYP2D6, 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.

A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram and metoprolol (a CYP2D6 substrate) showed a two-fold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and cardiac rhythm in healthy volunteers.

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 foeto/ 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 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 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 and 4.8).

Breast-feeding

Citalopram is excreted into breast milk in small quantities. 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. Patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration due to the illness itself and psychoactive 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 effects 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, QT prolongation.

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 ($< 1/10,000$), and not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders						Thrombocytopenia
Immune system disorders						Hyper-sensitivity, anaphylactic reaction
Endocrine disorders				Inappropriate ADH secretion		Hyperprolactinaemia
Metabolism and nutrition disorders		Appetite decreased, weight decreased	Increased appetite, weight increased	Hypo-natraemia		Hypokalaemia
Psychiatric disorders	Sleep disorder	Impaired concentration, decreased libido, anxiety, confusional state, abnormal orgasm (female), abnormal dreams, apathy	Aggression, depersonalisation, hallucination, euphoria, mania, increased libido			Panic attack (these symptoms may be due to the underlying disease), bruxism, restlessness, suicidal ideation, suicidal behaviour ¹
Nervous system disorders	Somnolence, insomnia, headache, tremor, nervousness, agitation, giddiness	Paraesthesia, dizziness, disturbance in attention, migraine, taste disturbance,	Syncope, extrapyramidal disorder, seizure	Convulsion grand mal, dyskinesia, Serotonin syndrome, akathisia		Movement disorder

		amnesia				
Eye disorders		Visual disturbance, mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4)				
Ear and labyrinth disorders		Tinnitus				
Cardiac disorders	Palpitations	Tachycardia	Bradycardia			QT-prolongation, ventricular arrhythmia including torsade de pointes
Vascular disorders		Orthostatic hypotension		Haemorrhage		
Respiratory, thoracic and mediastinal disorders		Yawning, rhinitis	Coughing			Epistaxis
Gastrointestinal disorders	Dry mouth, nausea, constipation	Diarrhoea, vomiting, dyspepsia, abdominal pain, flatulence, increased salivation		Gastrointestinal haemorrhage (including rectal haemorrhage)		
Hepatobiliary disorders			Liver function test abnormal	Hepatitis		
Skin and subcutaneous tissue disorders	Increased sweating	Pruritus	Urticaria, alopecia, rash, purpura, photosensitivity reaction	Ecchymosis	Angioedema	
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia				
Renal and urinary disorders		Urinary retention				
Reproductive system and breast disorders		Impotence, ejaculation disorder, ejaculation failure	Female: Menorrhagia			Galactorrhoea Female: Metrorrhagia Postpartum Haemorrhage ² Male: Priapism
General disorders and administration site conditions	Asthenia	Fatigue	Oedema, malaise	Pyrexia		

Number of patients: citalopram / placebo = 1346 / 545

¹ Cases of suicidal ideation and suicidal behaviours 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 and 4.6).

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).

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment:

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, dizziness, 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 HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 OverdoseToxicity

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, giddiness, dystonia, cyanosis, hyperventilation, hyperpyrexia, atrial and ventricular arrhythmia and rhabdomyolysis. Fatal cases have been reported.

Treatment

There is no known specific antidote to citalopram. Treatment should be symptomatic and supportive. If consciousness is impaired, the patient should be intubated. ECG and vital signs should be monitored.

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 (see sections 4.2, 4.4 and 4.5).

Activated charcoal, osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors, ATC code: N06AB04.

Mechanism of action

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of serotonin (5-HT) - uptake. Long-term treatment with citalopram does not induce tolerance to the inhibition of 5-HT-uptake.

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

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT₂, dopamine D₁ and D₂ receptors, α_1 -, α_2 - and β -adrenoceptors, histamine H₁, muscarine, cholinergic, benzodiazepine, and opioid receptors. This is in contrast to many tricyclic antidepressants and some of the other SSRI's. Lack of receptor affinity has been confirmed using a series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

Pharmacodynamic effects

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

Clinical efficacy and Safety

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 7.5 (90%CI 5.9-9.1) msec at the 20 mg/day dose and 16.7 (90%CI 15.0-18.4) msec at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Absorption

Absorption is almost complete and independent of food intake (T_{max} average/mean 3.8 hours). Oral bioavailability is about 80%.

Distribution

The apparent volume of distribution ($(V_d)_B$) is 12-17 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

Biotransformation

Citalopram is metabolised to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma. The concentration of desmethylcitalopram and didesmethylcitalopram is usually 30 – 50% or 5 – 10% of the citalopram concentration. The biotransformation of citalopram into desmethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%).

Elimination

The elimination half-life ($T_{1/2\beta}$) is about 1.5 days and the systemic citalopram plasma clearance (Cl_s) is 0.3-0.4 L/min, and oral plasma clearance (Cl_{oral}) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% to 23% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.3 L/min and renal clearance approximately 0.05-0.08 L/min.

Linearity

The kinetics is linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 300 nmol/L (165-405 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Elderly patients (≥ 65 years)

In elderly patients, longer half-lives (1.5 – 3.75 days) and lower clearance values (0.08 – 0.3 L/min) have been determined as a result of the reduced metabolism. With the same posology, the steady-state plasma values of citalopram in elderly patients are approximately twice as high as in young patients.

Hepatic impairment

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

Renal impairment

Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance < 30 mL/min).

Polymorphism

In vivo examinations of people with reduced activity of the CYP2D6 enzyme have shown no relevant change in the plasma concentration of citalopram. In people with reduced activity of the CYP2C19 enzyme, the plasma concentrations of citalopram observed were twice as high. In known slow CYP2C19 metabolisers, an initial posology of 10 mg should therefore be considered as a precautionary measure (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 in several organs was observed in repeated dose toxicity studies in rats. This reversible effect is known for several lipophilic amines and was not connected with morphological and functional effects. The clinical relevance 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 could be an indirect effect due to 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**Tablet Core

Lactose monohydrate
Maize starch
Cellulose, microcrystalline
Povidone
Crospovidone
Magnesium stearate

Tablet Coating

Titanium dioxide (E171)
Lactose monohydrate
Macrogol 4000
Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC blisters sealed with aluminium foil (also includes unit dose packs). Pack sizes of 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets.

PVC/PVdC blisters sealed with aluminium foil. Calendar pack size of 28 tablets.

High Density Polyethylene (HDPE) containers with polypropylene (PP) caps. Pack size of 100 tablets.

Polypropylene tablet containers with polyethylene caps. Pack size of 100 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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatrix Limited
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Dublin 15
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8 MARKETING AUTHORISATION NUMBER

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