Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 40mg/ml Oral Drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of Citalopram Oral Drops contains 40mg of citalopram (as hydrochloride). Each 1ml of Citalopram Oral Drops, solution contains 20 drops.

Each drop contains 2mg citalopram (as hydrochloride).

Excipients with known effect:

76mg/ml ethanol, 1mg/ml methyl hydroxybenzoate (E218) and 0.1mg/ml propyl hydroxybenzoate (E216).

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Oral Drops, Solution.

A colourless to yellowish clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

Citalopram 40mg/ml Oral Drops is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 Posology and method of administration

Posology

Depression

Adults:

Citalopram should be administered as a single oral dose of 16mg (8 drops) daily. Dependent on individual patient response, the dose may be increased to a maximum of 32mg (16 drops) 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. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Panic disorder

Adults:

A single oral dose of 8mg (4 drops) is recommended for the first week before increasing the dose to 16mg (8 drops) daily. Dependent on individual patient response, the dose may be increased to a maximum of 32mg (16 drops) daily.

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

Elderly patients (> 65 years of age)

For elderly patients the dose should be decreased to half of the recommended dose, e.g. 8mg (4 drops) to 16mg (8 drops) daily. The recommended maximum dose for the elderly is 16mg (8 drops) daily.

Children (< 18 years of age)

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

Reduced hepatic function

An initial dose of 8mg (4 drops) 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 16mg (8 drops) daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function (see section 5.2).

Reduced renal function

Dosage adjustment is not necessary in cases of mild or moderate renal impairment. No information is available in cases of severe renal impairment (creatinine clearance <20ml/min).

Poor metabolisers of CYP2C19

An initial dose of 8mg (4 drops) 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 16mg (8 drops) daily depending on individual patient response, (see section 5.2).

Method of administration

Citalopram 40mg/ml Oral drops should only be mixed with water, orange or apple juice. The resulting solution must be drunk immediately by the patient.

Citalopram oral drops can be taken as a single daily dose, at any time of day, without regard to food intake.

Citalopram oral drops have approximately 25% increased bioavailability compared to tablets. Consequently doses of tablets correspond to doses of drops as follows:

Tablets	**Solution**	
10mg	8mg	(4 drops)
20mg	16mg	(8 drops)
30mg	24mg	(12 drops)
40mg	32mg	(16 drops)
60mg	48mg	(24 drops)

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

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 10mg/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 should not be used concomitantly with pimozide (see also section 4.5).

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

Citalopram is contraindicated together with medicinal products that are known to prolong QT-interval (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age:

Citalopram 40mg/ml Oral Drops 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.

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.

Elderly patients:

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

Reduced kidney and liver function:

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

Paradoxical anxiety:

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 a particularly high risk.

Akathisia/psychomotor restlessness:

The use of citalopram 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.

Diabetes:

In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and or oral hypoglycaemic dosage may need to be adjusted.

Glaucoma:

As with other SSRIs, Citalopram can cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

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 medicines:

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

Seizures:

Seizures are a potential risk with antidepressant drugs. The drug 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:

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

Reversible, selective MAO-A inhibitors:

The combination of citalopram with MAO-A inhibitors is generally not recommended due to the risk of the 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).

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.

Haemorrhage:

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

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.

Consideration should be given to factors which may affect the disposition of a minor metabolite of citalopram (didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in susceptible individuals. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see Posology) reduces the likelihood of this effect.

QT interval prolongation

Elevated levels of a side metabolite (didemethylcitalopram) can theoretically prolong the QT interval in patients predisposed, patients with congenitally prolonged QT syndrome or in patients with hypokalaemia/hypomagnesaemia. ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

Citalopram has been found to cause a dose-dependent prolongation of the QT-interval. Cases of QT interval

prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1).

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with Citalopram is started.

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

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

Excipients with recognised action or effect:

Citalopram 40mg/ml Oral Drops contain methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). The drops also contain small amounts of ethanol less than 100mg per maximum allowed dose (48mg equivalent to 24 drops daily).

Withdrawal symptoms seen on discontinuation of citalopram treatment:

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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 electric shock sensations), sleep disturbances (including intense dreams), agitation or anxiety, nausea, 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 Posology and method of administration).

Psychosis:

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

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 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: agitation, tremor, myoclonus, and hyperthermia.

Pimozide

Co-administration of a single dose of pimozide 2mg to subjects treated with racemic citalopram 40mg/day for 11 days caused an increase in AUC and Cmax of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram, resulted in a mean increase of the QTc interval of approximately 10msec. 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 (20mg daily) and selegiline (10mg daily) (a selective MAO B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10mg daily) is not recommended.

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, 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 QT prolongation or hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of other QT interval prolonging medicines or hypokalaemia/hypomagnesaemia-inducing drugs as they, like citalopram, potentially prolong the QT interval.

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]), mefloquine, bupropion and tramadol).

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.

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%) 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, a known enzyme-inhibitor, caused a slight rise in the average steady-state citalopram levels. Caution is therefore recommended when administering high doses of citalopram in combination with high doses of cimetidine. Co-administration of escitalopram (the active enantiomer of citalopram) with omeprazole 30mg 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) or cimetidine. 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 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.

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

Thus no change or 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).

Contraindicated combinations

QT interval prolongation

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

Influences of other medicinal products on the pharmacokinetics of citalopram

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.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy:

A large amount of data on pregnant women (more than 2500 exposed outcomes) indicate no malformative foeto/neonatal toxicity. Citalopram can be used druing pregnancy if clinically needed, taking into account the aspects mentioned below.

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.

Lactation:

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.

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 prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves. 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, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, < 1/1000); very rare (<1/10000), not known (cannot be estimated from available data).

MedDRA SOC	**Frequency**	**Preferred term**
Blood and lymphatic disorders	Not Known	Thrombocytopenia
Immune system disorders	Not Known	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Not Known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Appetite decreased, weight decreased
	Uncommon	Increased appetite, weight increased
	Rare	Hyponatraemia
	Not Known	Hypokalaemia
Psychiatric disorders	Common	Agitation, libido decreased, anxiety, nervousness confusional state, abnormal orgasm (female), abnormal dreams
	Uncommon	Aggression, depersonalisation, hallucination, mania
	Not Known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[2]
Nervous system disorders	Very common	Somnolence, insomnia
	Common	Tremor, paraesthesia, dizziness, disturbance in attention
	Uncommon	Syncope
	Rare	Convulsion grand mal, dyskinesia, taste disturbance
	Not Known	Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	Uncommon	Mydriases (which may

		lead to acute narrow angle glaucoma), see section 4.4 Special warnings and precautions for use)
	Not Known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Not Known	QT-prolongation[1]
Vascular disorders	Rare	Haemorrhage
	Not Known	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Common	Yawning
	Not Known	Epistaxis
Gastrointestinal disorders	Very common	Dry mouth, nausea
	Common	Diarrhoea, vomiting, constipation
	Not Known	Gastrointestinal haemorrhage (including rectal haemorrhage
Hepatobiliary disorders	Rare	Hepatitis
	Not Known	Liver function test abnormal
Skin and subcutaneous tissue disorder	Very common	Sweating increased
	Common	Pruritus
	Uncommon	Urticaria, alopecia, rash, purpura, photosensitivity reaction
	Not Known	Ecchymosis, angioedemas
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Uncommon	Urinary retention
Reproductive system and breast disorders	Common	Impotence, ejaculation disorder, ejaculation failure
	Uncommon	Female: Menorrhagia
	Not Known	Female: Metrorrhagia Male: Priapism Galatorrhoea
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema
	Rare	Pyrexia

Number of patients: citalopram / placebo = 1346 / 545

[1] 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).

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

The following additional adverse events have also been reported in clinical trials:

Very common: Headache, asthenia, sleep disorder.

Common: Migraine, palpitation, taste perversion, impaired concentration, amnesia, anorexia, apathy, dyspepsia, abdominal pain, flatulence, increased salivations, rhinitis.

Rare: Increased libido, coughing, malaise.

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 citalopram 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, 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 section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use).

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail:medsafety@hpra.ie.

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 2g 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, mydriases, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, hyperpyrexia, and atrial and ventricular arrhythmia.

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

Prolonged bradycardia with sever 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 specific antidote. An ECG should be taken. Consider activated charcoal in adults and children who have ingested more than 5mg/kg body weight within 1 hour. Activated charcoal given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50%. Control convulsions with intravenous diazepam if they are frequent or prolonged. Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable.

Osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered.

If consciousness is impaired the patient should be intubated.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors

ATC-code: N06A AB04

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

Citalopram is the most selective Selective Serotonin Reuptake Inhibitor (SSRI) yet described, 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 SSRI's, citalopram has no or very low affinity for a series of receptors including 5-$HT_{1A,}$ 5-HT_2, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Like tricyclic antidepressants, other SSRI's 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.

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

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.

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 20mg/day dose and 16.7 (90%CI 15.0-18.4) msec at the 60mg/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} mean 2 hours) after ingestion of drops and T_{max} mean 3 hours after intake of tablets. Oral bioavailability is about 80% after ingestion of tablets. Relative bioavailability of drops is approximately 25% greater than the tablets.

Distribution:

The apparent volume of distribution $(V_d)_\beta$ is about 12.3 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.

Elimination:

The elimination half-life ($T_{½\beta}$) is about 1.5 days and the systemic citalopram plasma clearance (Cl_s) is about 0.33 L/min, and oral plasma clearance (Cl_{oral}) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min.

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

Elderly patients (≥ 65 years):

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

Reduced hepatic function:

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

Reduced renal function:

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

5.3 Preclinical safety data

Citalopram has low acute toxicity. In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. Based on data from reproduction toxicity studies (segment I, II and III) there is no reason to have special concern for the use of citalopram in women of child-bearing potential. Citalopram has no mutagenic or carcinogenic potential.

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

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate.(E216)
Ethanol (96%)
Hydroxyethylcellulose
Purified water

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years unopened.

Once the bottle is open use within 16 weeks.

Once the product is diluted drink immediately.

6.4 Special precautions for storage

There are no specific storage instructions for this product.

6.5 Nature and contents of container

Amber type III glass bottle containing 15ml of product, fitted with a low density polyethylene dropper and either a tamper-evident, polypropylene screw cap or a child resistant, polypropylene or high density polyethylene cap.

6.6 Special precautions for disposal and other handling

Citalopram 40mg/ml Oral Drops should only be mixed with water, orange juice or apple juice. The resulting solution must be drunk immediately by the patient.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Any unused medicinal product, or product passed its shelf life, opened or unopened, or waste material should be disposed of in accordance with local requirements, consult your pharmacist regarding disposal.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd April 2009

10 DATE OF REVISION OF THE TEXT

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