Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cipramil 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg citalopram (as 24.98 mg citalopram hydrobromide).

Excipient with known effect: Lactose monohydrate 23.1 mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oval, scored, film-coated tablets marked 'C' and 'N' symmetrically around the score. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

Cipramil 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 20 mg daily. Depending on individual patient response, the dose may be increased to a maximum of 40 mg daily.

Duration of treatment:
The antidepressant effect usually sets in after 2 to 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time, usually up to 6 months after recovery in order to prevent relapse. In patients with recurrent depression (unipolar) maintenance therapy may need to be continued for a number of years to prevent new episodes.

Panic Disorder
Adults:
A single oral dose of 10 mg is recommended for the first week before increasing the dose to 20 mg daily. Depending on individual patient response, the dose may be increased to a maximum of 40 mg daily.

Duration of treatment:
Maximum effectiveness of citalopram in treating panic disorder is reached after about 3 months and the response is maintained during continued treatment.

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.

Children & Adolescents (<18 years)
Citalopram should not be used in the treatment of children and adolescents under the ageof 18 years (see section 4.4).

Reduced renal function
Dosage adjustment is not required if the patient has mild to moderate renal impairment. Caution is advised in patients with severe renal impairment (creatinine clearance less than 30 ml/min, see section 5.2).

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).

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 SSRI.
Abrupt discontinuation should be avoided. When stopping treatment with citalopram the dose should be gradually reduced over a period of at least one or two weeks in order to reduce the risk of withdrawal reactions (see section 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 tablets are administered as a single daily dose.
Citalopram tablets and can be taken any time of the day without regard to food intake.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

MAOIs (monoamine oxidase inhibitors)

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).

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).

4.4 Special warnings and precautions for use

Treatment of elderly patients and patients with reduced kidney and liver function, see section 4.2.

Use in children and adolescents under 18 years of age
Antidepressants 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.

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 especially seem to be at particularly high risk.

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/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

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

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

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

Serotonin syndrome
In rare cases, serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus, and hyperthermia may indicate the development of this condition. Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

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

Haemorrhage
There have been reports of cutaneous bleeding time and/or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings with SSRIs (see section 4.8). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking SSRIs, particularly with 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).

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

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).

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

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see 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.

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

QT interval prolongation

Citalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including Torsade de Pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1).

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

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

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

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

Angle-Closure Glaucoma
SSRIs including citalopram may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Citalopram should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

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

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

4.5 Interaction with other medicinal products and other forms of interactions

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

Contraindicated combinations

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, the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.
Some cases presented with features resembling serotonin syndrome. Symptoms of an active substance interaction with a MAOI include:
Hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma (see section 4.3).

QT interval prolongation
Pharmacokinetic and pharmacodynamic studies between citalopram and other medicinal products that prolong the QT interval have not been performed. An additive effect of citalopram and these medicinal products cannot be excluded. Therefore, co-administration of citalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. fentiazine 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 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 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) that can increase the risk of haemorrhage (see section 4.4).

ECT (electroconvulsive therapy)
There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and citalopram (see section 4.4).

Alcohol
No pharmacodynamic or pharmacokinetic interactions have been demonstrated between citalopram and alcohol. However, the combination of citalopram and alcohol is not advisable.

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

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

Pharmacokinetic interactions
Biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%) isozymes of the cytochrome P450 system. The fact that citalopram is metabolised by more than one CYP enzyme 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).

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 30 mg once daily (a CYP2C19 inhibitor) resulted in a 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 (see section 4.4).

Effects of citalopram on other medicinal products

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. flecanide, 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.

Metoprolol

Co-administration with metoprolol resulted in a twofold increase in the plasma levels of metoprolol, but did not statistically significantly increase the effect of metoprolol on the blood pressure and cardiac rhythm.

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6 as compared to other SSRIs established as significant inhibitors.

Levomeprozamine, digoxin, carbamazepine

Thus, no change or only very small changes of no clinical importance were observed when citalopram was given with CYP1A2 substrates (clozapine and theophylline), CYP2C9 (warfarin), CYP2C19 (imipramine and mephenytoin), CYP2D6 (sparteine, imipramine, amitriptyline, risperidone) and CYP3A4 (warfarin, carbamazepine (and its metabolite carbamazepine epoxide and triazolam).

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin (indicating that citalopram neither induce nor inhibit 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

A large amount of data on pregnant women (more than 2500 exposed outcomes) indicate no malformative feto/neonatal toxicity. Citalopram can be used in 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, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breast-feeding
Citalopram is excreted into breast milk. It is estimated that the suckling infant will receive about 5% of the weight related maternal daily dose (in mg/kg). No or only minor events have been observed in the infants. However, the existing information is insufficient for assessment of the risk to the child.
Caution is recommended.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse 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.

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 (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable effect
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, depersonalization, hallucination, mania
	Not Known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[1]
Nervous system disorders	Very common	Somnolence, insomnia, headache
	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	Mydriasis
	Not Known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Not Known	Electrocardiogram QT prolonged, ventricular arrhythmia including Torsade de Pointes
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 disorders	Very common	Sweating increased
	Common	Pruritus
	Uncommon	Urticaria, alopecia, rash, purpura, photosensitivity
	Not Known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue 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	Galactorrhoea Female: Metorrhagia, postpartum haemorrhage[2)] Male: Priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

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 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).

Bone Fractures
Epidemiological studies, mainly 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 section 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 Overdose

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

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

Treatment
There is no known specific antidote to citalopram. Treatment should be symptomatic and supportive. Activated charcoal, osmotically working laxative (such as sodium sulphate) and gastric lavage should be considered. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

ATC-code: N 06 AB 04

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

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.

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.

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.

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.

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. Citalopram like other SSRIs may increase plasma prolactin, an effect secondary to the prolactin stimulating role of serotonin and of no clinical importance.

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} mean 3 hours). Oral bioavailability is about 80%.

Citalopram oral drops, solution have an approximately 25% higher bioavailability compared to tablets.

Distribution
The apparent volume of distribution (V_d)is about 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 concentrations of demethylcitalopram and didemethylcitalopram are usually 30-50% and 5-10% of the citalopram concentration, respectively. The biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%).

Elimination
The elimination half-life ($T_{½}$) is about 1.5 days and the systemic citalopram plasma clearance (Cl_s)is about 0.3-0.4 L/min, and oral plasma clearance (Cl_{oral}) is about 0.4 L/min.

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

Linearity
The kinetics are 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.

Elderly patients (>65 years)
Longer half-lives (1.5-3.75 days) and decreased clearance values (0.08-0.3 L/min) due to a reduced rate of metabolism have been demonstrated in elderly patients. Steady state values were about twice as high in the elderly as in younger patients treated with the same dose.

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 <30 mL/min).

Polymorphism
In vivo investigations have shown that the metabolism of citalopram exhibits no clinically important polymorphism of the sparteine/debrisoquine oxidation (CYP2D6). For CYP2C19, as a precaution, an initial dose of 10 mg should be considered for known poor metabolisers (see section 4.2).

5.3 Preclinical safety data

Acute toxicity
Citalopram has low acute toxicity.

Chronic toxicity
In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram.

Reproduction studies
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 childbearing potential.

Embryotoxicity studies in rats with doses of 56 mg/kg/day, which cause maternal toxicity showed bone anomalies in the region of the vertebral column and ribs. The maternal plasma level was then 2-3 times the therapeutic concentration in man. In rats citalopram did not have any effect on fertility, pregnancy and postnatal development but diminished the birth weight of the pups. Citalopram and its metabolites reach foetal concentrations, which are 10-15 times the maternal plasma level.

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.

Mutagenic and carcinogenic potential
Citalopram has no mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Maize starch,
Lactose Monohydrate,
Cellulose, microcrystalline,
Copovidone,
Glycerol 85%,
Croscarmellose Sodium,
Magnesium stearate,

Coating
Hypromellose 5,
Macrogol 400,
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Press through packs consisting of aluminium foil and UPVC/PVdC foil in cartons containing 28, 56 or 98 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

Lundbeck (Ireland) Limited
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Citywest Business Park
Citywest
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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