Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciprapine 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg citalopram as citalopram hydrobromide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Round, white, biconvex tablets with a diameter of 10 mm.
The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of major depressive episodes.

4.2 Posology and method of administration

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

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. Citalopram should be withdrawn slowly, it is advised that the dose is gradually reduced over 1-2 week periods.

Depression

Adults:
Citalopram should be administered as a single dose of 20 mg daily. Dependent on individual patient response, the dose may be increased to a maximum of 40 mg daily.

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 and adolescents under the age of 18
Not recommended, as safety and efficacy have not been established in this population.

Reduced renal function
Dosage adjustment is not required if the patient has mild to moderate renal impairment. No information is available on treatment of patients with severe renal impairment (creatinine clearance less than 20 ml/min) (see Section 4.4 Special warnings and special precautions for use).

Reduced hepatic function
An initial dose of 10 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient
response, the dose may be increased to a maximum of 20 mg daily. Caution and extra careful dose titration is advised

in patients with severely reduced hepatic function (see section 5.2).These patients should be clinically monitored (see Section 4.4 Special warnings and special precautions for use).

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).

4.3 Contraindications

- Hypersensitivity to citalopram or to any of the excipients.

- 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.

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible 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. 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.

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

Citalopram should be prescribed in the smallest quantity of tablets in order to reduce the risk of overdose.
Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan and tryptophan.

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

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.

There is little clinical experience of concurrent administration of citalopram and
electro-convulsive therapy, therefore caution is advisable.

Citalopram should be used with caution in patients with a history of mania/hypomania. Citalopram should be discontinued in any patient entering a manic phase.
There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymosis, gynaecological haemorrhages, gastrointestinal bleedings and other
cutaneous or mucous bleedings with SSRIs (see Section 4.8 Undesirable effects).
Caution is advised in patients taking SSRIs, particularly in concomitant use with active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage as well as in patients with a history of bleeding disorders (see Section 4.5 Interactions).

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

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

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.

Patients with a history of suicide-related events, 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.

<u>QT interval prolongation</u>
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.

<u>Use in children and adolescents under 18 years of age</u>

Ciprapine 40mg film-coated tablets 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.

The use of citalopram in patients with severe renal impairment (creatinine clearance less than 20 ml/min.) is not

recommended as no information is available on use in these
patients (see Section 4.2 Posology and method of administration).

In cases of impaired hepatic function dose reduction is recommended (see Section 4.2 Posology and method of administration) and liver function has to be closely monitored.
Hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has been reported rarely, predominantly in the elderly, and generally reverses on discontinuation of therapy.

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 Interactions).

At the beginning of the treatment, insomnia and agitation can occur. A dose titration may be helpful.

Increased levels of a minor metabolite of citalopram (didemethylcitalopram) could theoretically prolong the QTc interval in susceptible individuals. ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac
conditions did not reveal clinically significant changes. However, ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

4.5 Interaction with other medicinal products and other forms of interaction

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 that prolong the QT interval, such as Class 1A 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.

Pharmacodynamic interactions
The simultaneous use of citalopram and MAO-inhibitors can result in severe side effects, in-cluding the serotonin syndrome (see Section 4.3 Contraindications).

The serotonergic effect of sumatriptan may be potentiated by selective serotonin re-uptake inhibitors (SSRIs). 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 Special warnings and special precautions for use).

Caution is warranted for patients who are being treated simultaneously with
anticoagulants, medicinal products that affect the function of thrombocytes, such as NSAIDs, acetylsalicylic acid, dipyridamol, and ticlopidine or other medicines (e.g. atypical antipsy-chotics, phenothiazines, tricyclic depressants) that can increase the risk of haemorrhage (see Section 4.4 Special warnings and special precautions for use).

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

Undesirable effects may be more common during concomitant use of citalopram and herbal preparations containing St John's wort (Hypericum perforatum) (see Section 4.4 Special warnings and special precautions for use).

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

Influence of other medicinal products on the pharmacokinetics of citalopram

Pharmacokinetic interactions
Pharmacokinetic interactions based on plasma-protein binding should not be expected. Cita-lopram is a weak inhibitor of CYP2D6. Although clinically relevant medicinal interactions with citalopram are unusual, an interaction cannot be excluded if citalopram is administered simultaneously with another medicinal product that is metabolised by CYP2D6. Co-administration of citalopram and metoprolol (CYP2D6 sub-strate) resulted in a two-fold increase in the plasma levels of metoprolol. No clinically significant effects on blood pressure or heart rate were observed.

Cimetidine (potent CYP2D6, 3A4 and IA2 inhibitor) caused a moderate increase in the aver-age steady state levels of citalopram. Caution is advised when administering citalopram in combination with cimetidine. Dose adjustment may be warranted.

There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic effects when SSRIs were administered in combination with lithium or tryptophan. Caution is advised during simultaneous use of citalopram with these active substances. Routine monitoring of lithium levels should be continued as usual.

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.

No pharmacokinetic interaction was observed between citalopram and levomepromazine, digoxin or carbamazepine and its metabolite carbamazepine-epoxide.

The absorption and other pharmacokinetic properties of citalopram have not been reported to be affected by food.

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:

There are limited data from the use of Citalopram in pregnant women. 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.

Studies in rats have shown teratogenic effects at high doses which caused maternal toxicity (see Section 5.3 Preclinical safety data). The potential risk for humans is unknown. Citalopram should only be used in pregnancy if considered clearly necessary.

Withdrawal symptoms may occur in the neonate after maternal citalopram use near term.Cases of withdrawal symptoms in the newborn child have been described after the use of SSRI at the end of pregnancy.

Lactation:

Citalopram is excreted in milk in small quantities. The advantages of breastfeeding should outweigh the potential adverse effects for the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions observed with citalopram are in general mild and transient. They are most prominent during the first weeks of treatment and usually attenuate as the
depressive state improves.

Treatment emergent adverse events reported in clinical trials:

	very common (> 10 %)	**common (> 1 %, <10%)**	**uncommon (>0,1%, < 1 %)**	**very rare (<0,01%, including isolated reports)**	**Frequency unknown**
Psychiatric disorders	somnolence, insomnia, agitation, nervousness	sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, suicide attempt, confusion	euphoria, increased libido	hallucinations, mania, depersonalisation panic attack (these symptoms may be due to the underlying disease)	
Nervous system disorders	headache, tremor, dizziness	migraine, paraesthesia	extrapyramidal disorder, convulsions		
Cardiac disorders	palpitations	tachycardia	bradycardia	supraventricular and ventricular arrhythmia	Ventricular arrhythmia including torsade de pointes
Vascular disorders		postural hypotension**,** hypotension, hypertension			
Gastrointestinal disorders	nausea, dry mouth, constipation, diarrhoea	dyspepsia, vomiting, abdominal pain, flatulence, increased salivation			
Renal and urinary		micturition disorder,			

disorders		polyuria			
Metabolism and nutrition disorders		weight decrease, weight increase			
Hepato-biliary disorders			increased liver enzyme values		
Respiratory disorders		rhinitis, sinusitis	coughing		
Reproductive system disorders		ejaculation failure, female anorgasmia, dysmenorrhoea, impotence		galactorrhoea	
Skin disorders	increased sweating	rash, pruritus	photosensitivity	angiodema	
Eye disorders	abnormal accommodation	abnormalities of vision			
Special senses disorders		taste abnormalities			
Ear and labyrinth disorders			tinnitus		
Musculoskeletal disorders			myalgia	arthralgia	
General disorders	asthenia	fatigue, yawning	allergic reactions, syncope, malaise	anaphylactoid reactions	

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

Rare (>0.01%**,** < 0.1 %)
Haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucous
membranes) can occur on rare occasions.

In rare cases a serotonin syndrome has been reported in patients using SSRIs.
Hyponatriaemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has been reported rarely, predominantly in the elderly (see Section 4.4
"Special warnings and special precautions for use").

Frequency Not Known:
Cases of suicidal ideation and suicidal behaviors have been reported during Citalopram therapy or early after treatment disciontinuation (see section 4.4)

Withdrawal reactions
Withdrawal reactions may occur when treatment is stopped, although the preclinical and clinical data do not suggest that citalopram causes dependency. Withdrawal reactions include: dizziness, paraesthesia, headache, nausea and anxiety. Most of the withdrawal reactions are mild and self-limiting in nature. If treatment is being stopped, it is advised that the dose is gradually reduced over 1-2 week periods.

Class effects
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 the risk is unknown.

4.9 Overdose

Symptoms of overdose

Eight cases are known of acute citalopram overdose, at doses of up to 2000 mg. The following symptoms were observed: somnolence, coma, stupor, seizure, sinus tachycardia, transpiration, nausea, retching, cyanosis, hyperventilation and rarely ECG changes. All patients recovered.
Six fatal cases are known, mainly after combination with other medicinal products.

Treatment of an overdose
There is no known specific antidote to citalopram. Treatment should be symptomatic and sup-portive.
If possible, the patient should be made to vomit, after which activated carbon and an osmotically working laxative (such as sodium sulfate) should be given. Stomach evacuation should be con-sidered. If consciousness is impaired the patient should be intubated. Monitoring of cardiac and vital signs is recommended together with general symptomatic supportive measures.

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:
Antidepressant, Selective serotonin reuptake inhibitors
ATC code: N06AB04

Mechanism of action and pharmacodynamic effects
Tolerance to the inhibitory effect of citalopram on 5-HT uptake does not occur during long-term treatment.
The antidepressant effect is probably connected with the specific inhibition of serotonin uptake in the brain neurons.
Citalopram has almost no effect on the neuronal uptake of noradrenaline, dopamine and gamma-aminobutyric acid. Citalopram shows no affinity, or only very little, for cholinergic, histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.
Citalopram is a bi-cyclic isobenzophurane-derivative that is chemically not related to tricyclic and tetracyclic antidepressants or other available antidepressants. The main metabolites of citalopram are also selective serotonin uptake inhibitors, though to a lesser degree. The metabolites are not reported to contribute to the overall antidepressant effect.
In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 7.5 (90%CI 5.9-9.1) msec at the 20 mg/day dose and 16.7 (90%CI 15.0-18.4) msec at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

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

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

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

In vivo research has demonstrated that the plasma levels of citalopram and its metabolites depend on the sparteine/debrisoquine phenotype and the mephenytoin phenotype. However, it is not necessary to dose individually according to these phenotypes.

Elimination:
The plasma half-life is approximately 1½ days. After systemic administration, the plasma clearance is approximately 0.3-0.4 l/min and after oral administration the plasma clearance is approximately 0.4 l/min.
Citalopram is mainly eliminated via the liver (85%), but also partly (15%) via the kidneys. Of the quantity of citalopram administered, 12- 23 % is eliminated unaltered via the urine. Hepatic clearance is approximately 0.3 l/min and renal clearance is 0.05-0.08 l/min.
Steady-state concentrations are reached after 1-2 weeks. A linear relationship has been demonstrated between the steady-state plasma level and the dose administered. At a dose of 40 mg per day, an average plasma concentration of approximately 300 nmol/l is reached. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Characteristics relating to patients
Longer plasma half-life values and a smaller clearance have been found in older patients due to a reduced metabolism. The elimination of citalopram progresses more slowly in patients with reduced liver function. The plasma half-life of citalopram is approximately twice as long and the steady-state plasma concentration approximately twice as high in comparison with patients with a normal liver function.
The elimination of citalopram progresses more slowly in patients with a mild to moderate renal function disorder, without any major impact on the pharmacokinetics of citalopram. No information is available on treatment of patients with severe renal impairment (creatinine clearance less than 20 ml/min) (see Section 4.4 Special warnings and special precautions for use).

5.3 Preclinical safety data

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.

In laboratory animals no evidence for a special hazard for humans was found. This is based on conventional studies of safety pharmacology, repeated dose toxicity, 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. Embryotoxicity studies in rats have shown skeletal anomalies at high maternal toxic doses. The effects could possibly be related to the pharmacological activity or could be an indirect effect related to maternal toxicity. The potential risk for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Mannitol
Microcrystalline cellulose
Colloidal silica, anhydrous
Magnesium stearate

Coating:
Hypromellose
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ciprapine 40 mg film-coated tablets; packed in PVC/PVDC/Al blisters are available in pack sizes of 10, 14, 20, 28, 30, 50, 56, 98 and 100 tablets per box, 100x1 unit dose blister.

HDPE tablet container with a LDPE tamper evident cap containing 250, 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 281/117/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 18 February 2009

10 DATE OF REVISION OF THE TEXT

September 2012