

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cipramil 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg citalopram as citalopram hydrobromide

Excipients: Lactose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from the Netherlands and Italy

White, oval, scored tablet marked “C” and “N” symmetrically around the score.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of 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

Depression

Adults

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

Panic Disorder

Adults

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

OCD

Adults

An initial dose of 20mg daily is recommended. Dependent on individual patient response, the dose may be increased to a maximum of 40mg 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.

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).

Method of Administration

Citalopram tablets are administered as a single daily dose and can be taken at any time of the day without regard to food intake.

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.

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

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 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 (see section 6.1).

MAOIs (monoamine oxidase inhibitors)

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with monoamine oxidase inhibitor (MAOI), including the selective MAOB inhibitor selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI. Some cases presented with features resembling serotonin syndrome.

Citalopram must not be used in combination with a MAOI including selegiline in doses above 10 mg daily.

Treatment with citalopram may be instituted 14 days after discontinuation of non-selective MAOIs and minimum one day after discontinuation of moclobemide. Treatment with MAOIs may be introduced 7 days after discontinuation of citalopram (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Concomitant treatment with pimozone.

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 Posology and Method of Administration).

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs. Elderly female patients especially seem to be a risk group.

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 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

Although animal experiments have shown that citalopram has no epileptogenic potential it should, like other antidepressants, be used with caution in patients with a history of seizures.

Diabetes

As described for other psychotropics citalopram may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance.

Serotonin syndrome

If citalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan, caution is advisable.

Rarely, the occurrence of “serotonin syndrome” has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia, may indicate the development of this condition (see section 4.5 Interaction with other medicinal products and other forms of interactions).

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is advised in patients taking SSRIs, particularly with concomitant use of oral anticoagulants; medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a history of bleeding disorders (see section 4.5 Interaction with other medicinal products and other forms of interaction)

ECT (electroconvulsive therapy)

There is limited 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 onset of a serotonin syndrome (see section 4.5

Interactions with other medicinal products and other forms of interaction)

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

St John's Wort

Concomitant use of SSRIs and herbal remedies containing St John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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 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.

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 Undesirable Effects). 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

Posology and method of administration)

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

At the pharmacodynamic level there have only been few documented cases of serotonin syndrome with citalopram and moclobemide and buspirone.

Contraindicated combinations

MAOIs (non-selective as well as selective A (moclobemide) - risk of “serotonin syndrome” (see section 4.3 Contraindications)

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-malarian 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. Patients tolerated the selegiline-citalopram combination well.

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.

Co administration with serotonergic medicinal products (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.

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 Special Warnings and Precautions for Use)

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Caution is

advised in patients taking SSRIs, particularly with concomitant use of oral anticoagulants; medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyramole) as well as in patients with a history of bleeding disorders (see section 4.4 Special Warnings and Precautions for Use)

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 Special Warnings and Precautions for Use)

Alcohol

The combination of SSRIs and alcohol is not advisable. However, clinical studies have revealed no adverse pharmacodynamic interactions between citalopram and alcohol.

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 and co-administration of citalopram with other medicinal products in clinical practice has very low likelihood of producing pharmacokinetic medicinal product interactions.

Influence 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.

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.

Thus no change in pharmacokinetics 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 triazolam).

In a pharmacokinetic interaction study citalopram did not cause any changes in the pharmacokinetics of digoxin meaning that citalopram neither induces nor inhibits P-glycoprotein.

4.6 Fertility, pregnancy and lactation

Pregnancy

Clinical experience of use in pregnant women is limited but no reports, which may cause concern have been received.

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.

Neonates should be observed if maternal use of Cipramil continues into the later stages of pregnancy, particular 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.

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.

4.7 Effects on ability to drive and use machines

Citalopram does not impair intellectual function and psychomotor performance. However, patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration either due to the illness itself, the medication or both and should be cautioned about their ability to drive a car and operate machinery.

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, <1/10); uncommon (≥ 1/1000, <1/100); rare (≥ 1/10000, <1/1000); very rare (<1/10000), not known (can not be estimated from available data).

MedDRA SOC	Frequency	Preferred term
Blood and lymphatic disorders	Not Known	Thrombocytopenia
Immune system disorders	Not Known	Hypersensitivity NOS Anaphylactic reaction
Endocrine disorders	Not Known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Appetite decreased NOS ¹
	Uncommon	increased appetite
	Rare	Hyponatremia,
Psychiatric disorders	Common	Agitation, libido decreased, anxiety, nervousness, confusional state, abnormal orgasm (female)
	Uncommon	Aggression, depersonalization, hallucination, mania
	Rare	Suicide-related events (see section 4.4)
	Not Known	Panic attack, bruxism, restlessness
	Very common	Somnolence, insomnia NEC ²
	Common	Tremor, paraesthesia NEC
	Uncommon	Syncope

Nervous system disorders	Rare	Convulsion grand mal, dyskinesia
	Not Known	Convulsions NOS, serotonin syndrome, extrapyramidal disorder NEC, akathisia, movement disorder
Eye disorders	Uncommon	Mydriasis
	Not Known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Frequency unknown	Ventricular arrhythmia including torsade de pointes
Vascular disorders	Not Known	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Common	Yawning
	Not Known	Epistaxis
Gastrointestinal disorders	Very common	Dry mouth, Nausea
	Common	Diarrhoea NOS ¹ , vomiting
	Not Known	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Very common	Sweating increased
	Common	Pruritus
	Uncommon	Urticaria, alopecia, rash, purpura NOS
	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 NOS ¹ , ejaculation failure
	Uncommon	Female: Menorrhagia
	Not Known	Female: Metrorrhagia Male: Priapism, galactorrhoea
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema
Investigations	Common	Weight decreased
	Uncommon	Weight increased
	Not Known	Liver function test abnormal

Number of patients: Citalopram / placebo = 1346 / 545

¹ NOS = Not otherwise specified

² NEC = Not elsewhere classified

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).

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 section 4.4).

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, and mydriasis.

Treatment

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal might be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT₂, DA D₁ and D₂ receptors, α_1 - α_2 , β -adrenoceptors, histamine H₁, 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.

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.

5.2 Pharmacokinetic propertiesAbsorption

Absorption is almost complete and independent of food intake ($T_{\max}$ mean 3 hours). Oral bioavailability is about 80%.

Distribution

The apparent volume of distribution (V_d) _{β} 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 ($T_{1/2\beta}$) 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 <20 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).

Pharmacokinetic / pharmacodynamic relationship

There is no clear relationship between citalopram plasma levels and therapeutic response or side effects. The metabolites do not contribute to the overall antidepressant effect.

5.3 Preclinical safety dataAcute toxicity

Citalopram has a low acute toxicity.

Chronic toxicity

In chronic 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.

Citalopram appears in milk in low concentrations.

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. Clinical experience of use in pregnant women and during lactation is limited.

Mutagenic and carcinogenic potential

Citalopram has no mutagenic or carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Maize starch
Lactose
Microcrystalline cellulose
Copovidone
Glycerol
Croscarmellose sodium
Magnesium stearate
Hypromellose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Keep in the original container in order to protect from light.

6.5 Nature and contents of container

An over-labelled cardboard carton containing two blisters. Each blister contains 14 tablets.

Or

An over-labelled cardboard carton containing one blister which contains 28 tablets.

Pack size: 28 tablets.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/51/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th February 2010

10 DATE OF REVISION OF THE TEXT

March 2012