Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cipramil 20 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg citalopram (as 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 the UK:
White, oval tablets deeply scored on one face, with the letters ‘C’ and ‘N’ on either side of 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

Adults

Treating Depression
Citalopram should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response this may be increased to a maximum of 60 mg daily. The dose may be given in the morning or evening.

A treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse.

Treating Panic Disorder
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. A single dose of 10 mg daily is recommended for the first week before increasing the dose to 20 mg daily. The dose may be further increased, up to a maximum of 60 mg daily dependent on individual patient response; however an optimum dose of 20-30 mg daily was indicated in a clinical study.

Maximum effectiveness of citalopram in treating panic disorder is reached after about 3 months and the response is maintained during continued treatment. Dependent on individual patient response it may be necessary to continue treatment for several months.

Elderly patients
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children & Adolescents (under 18 years)
Not recommended, as safety and efficacy have not been established in this population.

Reduced hepatic function
Dosage should be restricted to the lower end of the dose range.

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

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.

4.3 Contraindications

Hypersensitivity to citalopram. Sumatriptan's serotonergic effects are suspected to be enhanced by SSRIs. Until further evidence is available it is advised not to use citalopram simultaneously with 5-HT agonists e.g. sumatriptan.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age

Cipramil 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 (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Suicide/ suicidal thoughts:
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 Prozac 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, 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 patient’s less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drugs 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 thought and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

As with other SSRIs, citalopram should not be given to patients receiving Monoamine Oxidase Inhibitors (MAOIs), or for 14 days after their discontinuation. MAOIs should not be introduced for seven days after discontinuation of citalopram. Rarely, the occurrence of 'serotonin syndrome' has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, tremor, myoclonus and hyperthermia, may indicate the development of this condition.

SSRIs should be administered with caution in patients treated concomitantly with anticoagulants, drugs which have an effect on platelet function (e.g. NSAIDs acetylsalicylic acid, aspirin and ticlopidine) or other drugs that may increase the risk of bleeding.
Caution should be exercised in patients with a history of bleeding abnormalities.
Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

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

Undesirable effects may be more common during concomitant use of serotonin re-uptake inhibitors and herbal preparations containing St Johns Wort (Hypericum perforatum).

As with most antidepressants, citalopram should be discontinued if the patient enters a manic phase. There is little clinical experience of concurrent use of citalopram and ECT.

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

As improvement of the depressive state may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. It is general clinical experience with all antidepressants that the risk of suicide may increase in the early stages of recovery.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Potentially suicidal patients should not have access to large quantities of drugs.

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

Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see 4.4 *Special warnings and precautions for use).*

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80%). These properties give citalopram a low potential for clinically significant drug interactions.

There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Routine monitoring of lithium levels need not be adjusted.

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. In animal studies cimetidine had little or no

influence on citalopram kinetics.

SSRIs may increase the risk of bleeding if they are administered concomitantly with anticoagulants or drugs which have an effect on platelet function *(see 4.4 Special Warnings and Precautions for Use).*

No pharmacodynamic interactions have been noted in clinical studies in which citalopram has been given concomitantly with benzodiazepines, neuroleptics, analgesics, lithium, alcohol, antihistamines, antihypertensive drugs, beta-blockers and other cardiovascular drugs.

4.6 Pregnancy and lactation

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.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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

Caution is recommended.

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 prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, sweating increased and tremor. The incidence of each in excess over placebo is low (<10%).

In comparative clinical trials with tricyclic antidepressants the incidence of adverse events occurring with citalopram was found to be lower in all cases.

Treatment emergent adverse events reported in clinical trials (N=2985):

Frequent (≥ 5 - 20%)
Skin and appendages disorders: Sweating Increased (13%).
Central and Peripheral nervous system disorders: Headache (19%), tremor (12%), dizziness (8%).
Vision disorders: Accommodation Abnormal (5%).
Psychiatric disorders: Somnolence (17%), insomnia (12%), agitation (6%), nervousness (6%).
Gastro-intestinal system disorders: Nausea (20%), mouth dry (18%), constipation (10%), diarrhoea (7%).
Heart rate and rhythm disorders: Palpitation (6%).
Body as a whole: Asthenia (11%).

Less frequent (1 - ≤ 5%)
Skin and appendages disorders: Rash, pruritus.
Central and Peripheral nervous system disorders: Paraesthesia, migraine.
Vision disorders: Vision abnormal.
Special senses other, disorder: Taste perversion.
Psychiatric disorders: sleep disorder, libido decreased, concentration impaired, dreaming abnormal, amnesia, anxiety, appetite increased, anorexia, apathy, impotence, confusion, yawning.
Gastro-intestinal system disorders: Dyspepsia, vomiting, abdominal pain, flatulence, saliva increased.
Metabolic and nutritional disorders: Weight decrease, weight increase.
Cardiovascular disorders, general: Hypotension postural.
Heart rate and rhythm disorders: Tachycardia.
Respiratory system disorders: Rhinitis.
Urinary system disorders: Micturition disorder, polyuria.
Reproductive disorders, male: Ejaculation failure.
Reproductive disorders, female: Anorgasmia female.
Body as a whole: Fatigue.

Rare (<1%)
Musculo-skeletal system disorder: Myalgia.
*Central and Peripheral nervous system disorders:*Extrapyramidal disorder, convulsions.
Hearing and vestibular disorders: Tinnitus.
Psychiatric disorders: Euphoria, libido increased, suicide attempt.
Respiratory system disorders: Coughing.
Body as a whole: Malaise.

Hyponatraemia, sometimes associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of SSRIs and other antidepressants.

Treatment with SSRIs has occasionally been associated with symptoms suggestive of postural hypotension, hypotension, hypertension and tachycardia. There have also been rare reports of supraventricular and ventricular arrhythmias. To date causality has not been established.

Rarely there have been reports of bleeding abnormalities such as ecchymosis, purpura, gastrointestinal, gynaecological, mucosal and cutaneous bleeding with SSRIs *(see Section 4.4 Special Warnings and Precautions for Use).*

Side effect in Discontinuation: Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs), including Cipramil. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Cipramil should be avoided. The majority of symptoms experienced on withdrawal of SSRIs are non-serious and self-limiting.

Cases of suicidal ideation and suicidal behaviour have been reported during Citalopram therapy or early after treatment discontinuation *(see section 4.4).*

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 this risk is unknown.

4.9 Overdose

Citalopram is given to patients at potential risk of suicide and some reports of attempted suicide have been received. Detail is often lacking regarding precise dose or combination with other drugs and/or alcohol.

Symptoms
Experience from 8 cases considered due to citalopram alone has recorded the following symptoms/signs: somnolence, coma, stiffened expression, episode of grand mal convulsion, sinus tachycardia, occasional nodal rhythm, sweating, nausea, vomiting, cyanosis, hyperventilation. No case was fatal. The clinical picture was inconsistent, no observation being made in more than two individuals.

Six fatalities have been reported. In one overdose was suspected; high post mortem plasma levels were seen although it is not technically possible to interpret these with confidence.

In the remaining five a combination with other drugs had been taken. The clinical syndrome observed prior to death in three of these cases where citalopram was taken with moclobemide was interpreted as that of serotonin syndrome. No clinical details are available on the other two.

Treatment
There is no specific antidote. Treatment is symptomatic and supportive. Gastric lavage should be carried out as soon as possible after oral ingestion. Medical surveillance is advisable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: N 06 AB 04

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 the most Selective Serotonin Reuptake Inhibitor (SSRI) yet described, with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-$HT_{1A,}$ 5-HT_2, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side-effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Like tricyclic antidepressants, other 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. There was potentiation of d-amphetamine-induced hyperactivity following administration of citalopram.

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

In humans citalopram does not impair cognitive (intellectual function) and psychomotor performance and has no or minimal sedative properties, either alone or in combination with alcohol.

Citalopram did not reduce saliva flow in a single dose study in human volunteers and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters. Citalopram has no effect on the serum levels of prolactin and growth hormone.

5.2 Pharmacokinetic properties

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

Distribution
The apparent volume of distribution $(V_d)_\beta$is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

Biotransformation
Citalopram is metabolised to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma.

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

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

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg.

There is no clear relationship between citalopram plasma levels and therapeutic response or side-effects.

Elderly patients (≥ 65 years)
Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

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

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

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Microcrystalline cellulose
Copovidone
Glycerol
Croscarmellose sodium
Magnesium stearate
Hypromellose
Macrogol 400
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 container and outer package of the product on the market in the country of origin.

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 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

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/021/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 25 August 2006

10 DATE OF REVISION OF THE TEXT

September 2010