Summary of Product Characteristics

1. TRADE NAME OF MEDICINAL PRODUCT
   Cipramil® Tablets 20 mg
   Cipramil® Tablets 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   24.98 mg citalopram hydrobromide corresponding to 20 mg citalopram base.
   49.96 mg citalopram hydrobromide corresponding to 40 mg citalopram base.
   The tablet can be divided into equal halves.

3. PHARMACEUTICAL FORM
   Tablet

4. CLINICAL PARTICULARS
   4.1. Therapeutic indications
   For the treatment of states of Depression and Panic disorder
   4.2. Posology and method of administration
   4.2.1. Posology
   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 taken in the morning or evening without regard for food.
   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 oral 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

Cipramil **is not recommended to be used** in the treatment of children and adolescents under the age of 18 years, see section 4.4.

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).

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.
The onset of action in treating OCD is 2-4 weeks with further improvement over time.
When stopping therapy the drug should be gradually withdrawn during a couple of weeks.

4.2.2. Method of administration

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

4.3. Contra-indications

Hypersensitivity to citalopram or to any of the excipients.

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 MAO-B 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).

Concomitant treatment with pimozide (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 **is not recommended** in the treatment of children and adolescents under age of 18 years. Suicide related behaviors (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.

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. Especially elderly female patients seem to be a risk group.

Suicide
The possibility of suicide attempt is inherent in depression and may persist until significant improvement occurs, either spontaneously or following treatment.
Patients being treated with antidepressants should be monitored carefully especially at the beginning of treatment for clinical worsening and/or the emergence of suicidality (suicidal ideation and behaviour).
This precaution should also be observed when treating other psychiatric disorders because of the possibility of co-morbidity with major depressive disorder.

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 24 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.

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. The drug should be discontinued in any patient who develops seizures. Citalopram should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

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.

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; drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs), ticlopidine and dipyridamole) as well as in patients with a history of bleeding disorders (see section 4.5).

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

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

Withdrawal symptoms
After prolonged administration abrupt cessation of SSRIs may produce withdrawal symptoms such as dizziness, paraesthesia, tremor, anxiety, nausea and palpitation in some patients. It is recommended that withdrawal of treatment should proceed by tapering off the dosage over one to two weeks to avoid occurrence of discontinuation symptoms. These symptoms are not indicative of addiction.

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

4.5. Interactions with other medicaments and other forms of interaction.
Citalopram is neither the source nor the cause of clinically important drug-drug interactions.

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).

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 Cmax 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 drugs
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 drugs should be undertaken with caution.

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

Dynamic interactions between SSRIs and herbal remedy St John's wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects.

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; drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs), ticlopidine and dipyramole) as well as in patients with a history of bleeding disorders (see section 4.4).

ECT (electroconvusive therapy)
There is little clinical experience establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and citalopram, therefore caution is advisable.

Alcohol

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

Pharmacoknetic 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 drugs in clinical practice has very low likelihood of producing pharmacokinetic drug interactions.

Influence of other medicinal products on the pharmacokinetics of citalopram
Co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of citalopram.

A pharmacokinetic interaction study of lithium and citalopram did not reveal any pharmacokinetic interactions.

Cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram. No general dose reduction for citalopram is recommended during co-administration with cimetidine.

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 induce nor inhibit P-glycoprotein.

4.6. 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.

Using SSRIs in the third trimester may result in effects, including neurobehavioral disturbances, in the newborn infant.

The following effects were reported in neonates with SSRIs administered to pregnant women until date of birth: irritability, tremor, hypertonia, increased muscle tone, constant crying, difficulty in suckling or in sleeping. They may either indicate serotonergic effects or withdrawal syndrome. If used during pregnancy SSRIs should never be stopped abruptly.

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. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

4.7. Effects on ability to drive and use machines

Citalopram 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, mouth dry, 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, suicide attempt, confusion, yawning.
Gastrointestinal 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: Exrapyramidal disorder, convulsions.
Hearing and vestibular disorders: Tinnitus.
Psychiatric disorders: Euphoria, libido increased.
Respiratory system disorder: Coughing.
Body as a whole: Malaise.

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRI 's, citalopram has not 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 tricylic antidepressants, other SSRI's and MAO inhibitors, citalopram suppresses REM-sleep and increases deep slow-wave sleep.
Although citalopram does not bind to opioid receptors it potentiates the anti- nociceptive effect of commonly used opioid analgesics.
There was potentiation of damphetamine-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 metabolized 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 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 is 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 or 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.~~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

Tablets: Maize starch, Lactose monohydrate, Microcrystalline-cellulose, Copolyvidone, Glycerol 85%, Croscarmellose Sodium Type A, Magnesium stearate, Hypromellose 5, Macrogol 400, Titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Each pack has an expiry date.

Citalopram tablets are valid for 5 years.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Press through blisters of 14, 28, 56, 98 and 100 tablets.

6.6. Instructions for use/handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

H. Lundbeck A/S
Ottiliavej 9
DK-2500 Copenhagen- Valby
Denmark

8. Drug license number

Cipramil 20mg - 102 51 28198 00
Cipramil 40mg — 142.50.32025 32025 00

9. Date of (partial) revision of the text

1/2010

10. Name and address of importer

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