PRODUCT INFORMATION

CIPRAMIL® FILM-COATED TABLETS

NAME OF THE MEDICINE

Citalopram hydrobromide

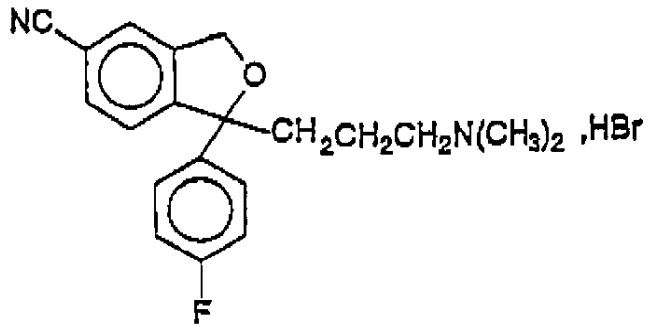
Chemical name:
1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide. The active is present as a racemate.

CAS number:
[59729-32-7]

Molecular formula:
$C_{20}H_{21}FN_2O$, HBr

Molecular weight:
405.32

Structural formula:



DESCRIPTION

Citalopram hydrobromide is a fine white to off-white, crystalline material.

Citalopram hydrobromide is sparingly soluble in water, soluble in ethanol (96%), freely soluble in chloroform and very slightly soluble in diethylether. No polymorphic forms have been detected.

Cipramil 20mg tablets are oval, white, scored, film-coated tablets marked "C" and "N".

The tablets contain the following excipients: starch - maize, lactose, cellulose - microcrystalline, PVP/VA copolymer, glycerol, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide.

PHARMACOLOGY

Pharmacological actions

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.

On the basis of in vitro studies, citalopram is one of the most selective Serotonin Reuptake Inhibitor (SSRI) yet developed, with no, or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. In comparison with other SSRIs the decreasing order of selectivity is escitalopram, citalopram, sertraline, paroxetine, fluvoxamine and fluoxetine. The clinical relevance of this in vitro finding has not been established.

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 DA D_2 receptors, α_1 receptors, α_2 receptors, 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.

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 (based upon a five week single blind study in 16 depressed patients given doses up to 40mg daily).

Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics in rats. The clinical significance of this finding has not been established.

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram but 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 function or psychomotor performance to the same extent as amitriptyline and it has slight sedative properties. There were results suggestive of impairment in some tests (critical flicker fusion, coding skills, body sway, immediate memory recall).

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. Like other SSRIs, citalopram increases plasma prolactin, an effect secondary to the prolactin stimulating role of serotonin.

Pharmacokinetics

Absorption

Oral bioavailability is about 80% and independent of food intake (T_{max} mean 3.8 hours). The bioavailability of each enantiomer has not been studied separately, but the pharmacokinetics of each enantiomer is different.

Distribution

The apparent volume of distribution $(V_d)_\beta$ is about 12-17 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites. After six weeks on 40-60mg/day in 10 patients, the mean serum concentration of S-(+)-citalopram was about 50% of the R-(-)-citalopram concentration and the mean serum concentration of R-(-)-DCIT was 1.5 times that of S-(+)-DCIT.

Metabolism

Citalopram is metabolised to the active demethylcitalopram (DCIT), 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 1½ days and the systemic citalopram plasma clearance (Cl_s) is about 0.3-0.4 L/min, and total (oral) plasma clearance (Cl_{oral}) is about 0.4 L/min.

About 12-23% of the daily dose is excreted unchanged in the urine. Hepatic (residual) clearance is about 0.3 L/min and renal clearance about 0.05-0.08 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 40mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects in a study of 650 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 major impact on the pharmacokinetics of citalopram.

Elderly patients (> 65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Polymorphism
There was no clinically relevant difference in the AUC between poor and extensive metabolisers with respect to CYP2D6 following administration of citalopram. The AUC for poor metabolisers with respect to CYP2C19 was less than 2-fold higher than the AUC observed in the extensive metabolisers (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

Citalopram in the dose range 20-80mg/day is more effective than placebo in the treatment of depression in the majority of trials, including relapse prevention trials. In the double-blind, placebo-controlled trials a total of 1083 patients received citalopram and 486 received placebo. There were three fixed dose trials of 6 weeks duration. In one trial a total of 650 patients with major depression were randomly allocated in approximately equal groups (~ 130 per group) to receive placebo or 10mg, 20mg, 40mg or 60mg citalopram. In the other two fixed dose studies, placebo was compared with 20mg or 40mg citalopram. Between 88 and 97 patients were treated in each group in one trial and approximately 48 in each group in the other. The remaining 5 trials of 4 or 6 weeks duration used flexible doses in the range of 20-80mg/day.

In two relapse prevention or maintenance studies of 24 weeks duration, 257 patients were treated with citalopram and 116 with placebo. In one study, 147 citalopram-treated patients who were responders (MADRS $\leq$ 12) in two 6 weeks fixed dose studies were rerandomised to receive placebo (N=42) or continue their previous treatment with 20mg (N=48) or 40mg citalopram (N=57). In the other study MADRS-responders (score $\leq$ 12) continued from an open 8-week trial and were randomised to receive placebo (N=74) or continue with their optimal dose of citalopram (range 20-60mg daily, N=152). In both studies citalopram independent of dose reduced relapse rates and prolonged time to relapse compared to placebo.

The majority of the patients in the placebo-controlled trials received 40mg/day. The minimal effective dose was 20mg/day. Analyses of subgroups of patients showed that patients experiencing their first episode of depression or with less severe depression responded well to the minimal effective dose of 20mg while patients suffering from severe or recurrent depression achieved better results with 40 or 60mg/day.

Citalopram demonstrates an equivalent therapeutic efficacy to tricyclic and tetracyclic antidepressants and other SSRIs in the treatment of major depression. The active comparator studies were chiefly randomised double-blind studies. In the trials versus tri- and tetracyclic antidepressants (TTCA), a total of 682 patients received citalopram and 389 TTCAs. In the comparative trials versus other SSRIs, there were 439 citalopram treated patients and 451 treated with other SSRIs. In the 6-week comparison to imipramine, 20-30mg (N=187) and 40-60mg (N=193) citalopram were equally effective as imipramine 100-150mg (N=92). In an 8-week comparison carried out in hospital settings with fixed doses, 40mg citalopram (N=158) was equally effective to 20mg fluoxetine (N=158). Likewise in a general practice study, 20mg citalopram (N=173) was equally effective to 20mg fluoxetine (N=184). A 6-week comparison to fluvoxamine in flexible doses (citalopram 20-40mg (N=108)/fluvoxamine 100-200mg (N=109) also demonstrated equal efficacy.

INDICATIONS

Treatment of major depression.

CONTRAINDICATIONS

Hypersensitivity to citalopram and any excipients in Cipramil (see DESCRIPTION).

Congenital long QT syndrome (see PRECAUTIONS).

Monoamine Oxidase Inhibitors - Cipramil should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI, and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. Similarly, at least 14 days should be allowed after stopping citalopram before starting a MAOI or RIMA. Cases of serious reactions, such as potentially life-threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see PRECAUTIONS, Interactions with other medicines).

Pimozide - Concomitant administration of citalopram and pimozide is contraindicated due to the risk of QT interval prolongation (see Interactions with other medicines).

PRECAUTIONS

Use with caution in the following circumstances:

QT Prolongation and Torsade de Pointes
Citalopram can cause a dose-dependent increase in the QT interval and should not be dosed above 40mg/day. Torsade de Pointes has been reported postmarketing. Citalopram should not be used in patients with congenital long QT syndrome. Patients at higher risk of developing prolongation of the QT interval include those with congestive heart failure, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or drugs. Hypokalaemia and hypomagnesaemia should be corrected prior to initiation of treatment and periodically monitored. Consider more frequent ECG monitoring in these patients and those with other risk factors for QT prolongation. Dose escalations over 20mg/day in elderly patients (>65 years), patients with hepatic dysfunction, CYP2C19 poor metabolisers or patients taking concomitant cimetidine or another CYP2C19 inhibitor are not recommended.

The influence of citalopram on QT interval at doses of 20mg and 60mg per day was evaluated in a randomised, placebo and active (moxifloxacin 400mg) controlled cross-over, escalating multiple-dose study in 119 healthy subjects. The change from baseline in QT_C (Fridericia correction) was 7.5 msec at the 20mg/day dose and 16.7 msec at the 60mg/day dose.

Citalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Clinical worsening and suicide risk associated with psychiatric disorders - The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvements may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

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.

Pooled analyses of 24 short-term (4 to 16 week), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive-compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analyses of short-term studies of antidepressant medications have also shown an increased risk of suicidal thinking and behaviour, known as suicidality, in young adults aged 18 to 24 years during initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years, there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Cipramil should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Haemorrhage - Bleeding abnormalities of the skin and mucous membranes have been reported with the use of SSRIs (including purpura, ecchymosis, haematoma, epistaxis, vaginal bleeding and gastrointestinal bleeding). Cipramil should therefore be used with caution in patients concomitantly treated with 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 past history of abnormal bleeding or those with predisposing conditions. Pharmacological gastroprotection should be considered for high risk patients.

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

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 and it may be necessary to review the use of SSRIs/SNRIs.

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.

Mania - A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

ECT (electroconvulsive therapy) - There is little clinical experience of concurrent use of citalopram and ECT, therefore caution is advised.

Effects on ability to drive and use machines - Patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration and should be cautioned about their ability to drive a car and operate machinery.

Discontinuation/withdrawal - Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt.

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 DOSAGE AND ADMINISTRATION).

Use in patients with cardiac disease - Citalopram has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Like other SSRIs, citalopram causes a small decrease in heart rate. Consequently, caution should be observed when citalopram is initiated in patients with pre-existing slow heart rate.

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.

Preclinical Safety - High doses of citalopram, which resulted in high plasma concentrations of citalopram and metabolites, has been associated with convulsions and ECG abnormalities in experimental animals.

Effects on fertility
In rats, female fertility was unaffected by oral treatment with citalopram doses which achieved plasma drug concentrations slightly in excess of those expected in humans, but effects on male rat fertility have not been tested with adequate oral doses.

Use in pregnancy
Category C

Limited clinical data are available regarding exposure to citalopram during pregnancy.

Reproduction studies performed in rats and rabbits at oral doses of up to 112 and 32mg/kg, respectively, have revealed no evidence of teratogenic effects. Studies in rats have shown increased post-implantation loss, reduced foetal weight and foetal developmental changes. A no effect oral dose of 56mg/kg/day was established for foetal development. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Newborns should be observed if maternal use of citalopram had continued into the later stages of pregnancy, particularly into the third trimester. If citalopram is used until or shortly before birth, discontinuation effects in the newborn are possible.

Newborns exposed to citalopram, other SSRIs (Selective Serotonin Reuptake Inhibitors), or SNRIs (Serotonin Norepinephrine Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

Epidemiological studies have shown that the use of SSRI's (including citalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistant pulmonary hypertension of the newborn (PPHN). The risk of PPHN among

infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher than the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Use in lactation
Citalopram appears in human breast milk in very low concentrations. In nursing mothers, caution is recommended as it is not known whether citalopram excreted in milk may affect the infant.

Paediatric use (< 18 years)
The efficacy and safety of citalopram for the treatment of major depressive disorder has not been established in children and adolescents less than 18 years of age. Consequently, citalopram should not be used in children and adolescents less than 18 years of age.

Carcinogenicity
Citalopram did not show any carcinogenic activity in long term oral studies using mice and rats at doses up to 240 and 80 mg/kg/day, respectively.

Genotoxicity
In assays of genotoxic activity, citalopram showed no evidence of mutagenic or clastogenic activity.

Interactions with other medicines

Drugs that prolong the QT interval – More frequent ECG monitoring is recommended in patients on concomitant medications that prolong the QT interval (see PRECAUTIONS – QT Prolongation and Torsade de Pointes).

MAOIs - Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see CONTRAINDICATIONS).

Treatment with citalopram may be instituted 14 days after discontinuation of irreversible MAOIs and a minimum of one drug free day after discontinuation of moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of citalopram.

Serotonin syndrome
Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with citalopram should be discontinued if such events occur and supportive symptomatic treatment initiated.

Pimozide - Co-administration of a single dose of pimozide 2mg to subjects treated with racemic citalopram 40mg/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 (see CONTRAINDICATIONS)

Serotonergic drugs - Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to an enhancement of serotonergic effects. Similarly, *Hypericum perforatum* (St John's Wort) should be avoided as adverse interactions have been reported with a range of drugs including antidepressants.

Lithium and tryptophan - There have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore concomitant use of SSRIs with these drugs should be undertaken with caution.

Imipramine and other tricyclic antidepressants (TCAs) - 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. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the co-administration of citalopram and tricyclic antidepressants.

Medicines affecting the central nervous system - Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Medicines lowering the seizure threshold - SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes, butyrophenones), mefloquine, bupropion and tramadol).

Digoxin - In subjects who had received 21 days of 40mg/day Cipramil, combined administration of Cipramil and digoxin (single dose of 1mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Carbamazepine - Combined administration of Cipramil (40mg/day for 14 days) and carbamazepine (titrated to 400mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are co-administered.

Metoprolol - A pharmacokinetic interaction between citalopram and metoprolol was observed, resulting in a twofold increase in metoprolol concentrations. The change in metabolism of metoprolol suggests an interaction between metoprolol and demethylcitalopram related to the CYP2D6 isoenzyme. There was no statistically significant increase in the effect of metoprolol on blood pressure and heart rate in healthy volunteers by adding citalopram.

Cimetidine - Cimetidine caused a moderate increase in the average steady state levels of citalopram. Citalopram 20mg/day is the maximum recommended dose for patients taking concomitant cimetidine because of the risk of QT prolongation.

Hepatic enzymes - 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, tricyclic antidepressants and some SSRIs).

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, but did suggest that it is a weak inhibitor of CYP1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these isoenzymes. However, *in vivo* data to address this question are very limited.

Citalopram steady state levels were not significantly different in poor metabolisers and extensive -2D6 metabolisers after multiple dose administration of Cipramil, suggesting that co-administration, with Cipramil, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism.

Since CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of -3A4 (e.g., ketoconazole, itraconazole, and macrolide antibiotics) and potent inhibitors of CYP2C19 (e.g., omeprazole, cimetidine) might decrease the clearance of citalopram. Citalopram 20mg/day is the maximum recommended dose for patients taking concomitant cimetidine or another CYP2C19 inhibitor because of the risk of QT prolongation (see Dosage and Administration).

Medicines that interfere with haemostasis (NSAIDs, aspirin, warfarin, etc) – Serotonin release by platelets plays an important role in haemostasis. There is an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of abnormal bleeding. Concurrent use of an NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with Cipramil.

Alcohol - The combination of SSRIs and alcohol is not advisable.

Others - 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.

Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics with the exception of pimozide (see CONTRAINDICATIONS and Interactions with other medicines - *Pimozide*). However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

ADVERSE 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 most commonly observed adverse events associated with the use of citalopram in double-blind, placebo-controlled trials and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, increased sweating, tremor, diarrhoea and ejaculation disorder. The incidence of each in excess over placebo is low.

In comparative double-blind clinical trials with tri- and tetracyclic antidepressants (TTCAs), the incidence of 10 adverse events was statistically significantly higher on TTCAs (dry mouth, increased sweating, constipation, tremor, dizziness, somnolence, abnormal accommodation, postural hypotension, palpitation, perverted taste) compared to citalopram. For two events (nausea, ejaculation disorder) the incidence was statistically higher on citalopram compared to TTCAs.

In the comparative trials versus other SSRIs no statistical significant differences between the groups were found.

Adverse events reported in clinical trials with citalopram treated patients include:

Treatment emergent adverse events in > 1% in any group of the patients in placebo-controlled trials

For adverse events with a frequency ≥ 5% a * indicates statistically significant difference between the groups (P<0.05).

SYSTEM ORGAN CLASS **Reaction (WHO Preferred Term)**		**CITALOPRAM versus PLACEBO** (N = 1083) (N = 486) (CT: F = 660; M = 423) (PL: F = 286; M = 200)	
		CITALOPRAM **%**	**PLACEBO** **%**
(100)	**SKIN AND APPENDAGES DISORDERS**		
	Pruritus	1.0	0.8
	Rash	1.0	1.2
	Sweating increased	*11.3****	7.4
(200)	**MUSCULO-SKELETAL SYSTEM DISORDERS**		
	Myalgia	1.9	1.2
	Arthralgia	1.8	0.8
(410)	**CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS**		
	Dizziness	10.3	10.1
	Extrapyramidal disorder[1)]	1.5	0.6
	Headache	26.9	26.7
	Paraesthesia	1.4	1.2
	Tremor	*8.8**	5.8
(431)	**VISION DISORDERS**		
	Vision abnormal	4.7	5.1
(432)	**HEARING AND VESTIBULAR DISORDERS**		
	Tinnitus	1.0	0.6
(500)	**PSYCHIATRIC DISORDERS**		
	Agitation	2.5	1.2
	Anorexia	4.2	1.2
	Anxiety	3.5	2.7
	Concentration impaired	1.7	1.0
	Confusion	1.4	0.6
	Dreaming abnormal	0.8	1.6
	Insomnia	18.8	18.9
	Libido decreased	2.5	0.4
	Nervousness	4.0	3.7
	Somnolence	*17.9**	10.3
	Suicide attempt	1.3	1.2
	Yawning	2.0	-

1) including: dyskinesia, dystonia, hyperkinesia, hypertonia, hypokinesia.

SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM %	PLACEBO %
(600) GASTRO-INTESTINAL SYSTEM DISORDERS		
Abdominal pain	3.2	1.9
Constipation	8.4	8.2
Diarrhoea	*7.9******	4.7
Dyspepsia	4.5	3.7
Flatulence	1.7	1.2
Mouth dry	*20.0******	12.6
Nausea	*21.4******	13.2
Vomiting	3.8	2.5
(800) METABOLIC AND NUTRITIONAL DISORDERS		
Weight decrease	1.5	0.6
(1030) HEART RATE AND RHYTHM DISORDERS		
Palpitation	7.1	7.4
(1100) RESPIRATORY SYSTEM DISORDERS		
Coughing	1.7	0.8
Pharyngitis	3.2	2.5
Rhinitis	4.6	2.9
Sinusitis	2.4	2.9
Upper respiratory tract infection	4.9	4.1
(1300) URINARY SYSTEM DISORDERS		
Micturition disorders	2.3	1.9
(1410) REPRODUCTIVE DISORDERS, MALE		
Ejaculation disorders	5.9*****	-
Impotence	2.8	0.5
(1420) REPRODUCTIVE DISORDERS, FEMALE		
Menstrual disorders (CT ≤ 50 years: N = 447; PL ≤ 50 years: N = 180)	4.0	2.2
(1810) BODY AS A WHOLE		
Asthenia	11.5	11.7
Back pain	2.0	2.3
Chest pain	1.2	0.6
Fatigue	4.9	3.3
Fever	2.3	0.4
Influenza-like symptoms	1.0	1.0
Pain	1.3	1.3

Dose Dependency of Adverse Events

The potential relationship between the dose of Cipramil administered and the incidence of adverse events was examined in a fixed dose study in depressed patients receiving placebo or Cipramil 10, 20, 40, and 60mg. Jonckheere's trend test revealed a positive dose response ($p<0.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

Male and Female Sexual Dysfunction with SSRIs

While sexual dysfunction is often part of depression and other psychiatric disorders, there is increasing evidence that treatment with selective serotonin reuptake inhibitors (SSRIs) may induce sexual side effects. This is a difficult area to study because patients may not spontaneously report symptoms of this nature, and therefore, it is thought that sexual side effects with the SSRIs may be underestimated. In placebo-controlled clinical trials (table),

the reported incidence of decreased libido for the whole population was 2.5%; ejaculation disorder (primarily ejaculatory delay), and impotence in male depressed patients receiving Cipramil (N=423) was 5.9%, and 2.8%, respectively. In female depressed patients receiving Cipramil (N=660), the reported incidence of anorgasmia was 0.5%. The reported incidence of decreased libido was 0.4% among depressed patients receiving placebo, whilst sex specific adverse events were not reported among male and female depressed patients receiving placebo.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Cipramil and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Cipramil treatment. In addition, a comparison of supine and standing vital sign measures for Cipramil and placebo treatments indicated that Cipramil treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with Cipramil in controlled trials experienced a weight loss of about 0.5kg compared to no change for placebo patients.

Laboratory Changes

Cipramil and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, haematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Cipramil treatment.

ECG Changes

Electrocardiograms from citalopram (n=802) and placebo (n=241) groups were compared with respect to outliers defined as subjects with QTc changes over 60msec from baseline or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (tachycardic or bradycardic outliers respectively). In the citalopram group 1.9% of the patients had a change from baseline in QTcF>60msec compared to 1.2% of the patients in the placebo group. None of the patients in the placebo group had a post-dose QTcF>500 msec compared to 0.5% of the patients in the citalopram group. The incidence of tachycardic outliers was 0.5% in the citalopram group and 0.4% in the placebo group. The incidence of bradycardic outliers was 0.9% in the citalopram group and 0.4% in the placebo group.

In a thorough QT study, citalopram was found to be associated with a dose dependent increase in the QTc interval (see PRECAUTIONS – QT Prolongation and Torsade de Pointes).

Other Events Observed During the Premarketing Evaluation of Cipramil

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the Adverse Effects section, reported by patients treated with Cipramil at multiple doses in a range of 10 to 80mg/day during any phase of a trial within the premarketing database of 4,422 patients. All reported events are included except those already listed in the table or elsewhere in the Adverse Effects section, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with Cipramil, they were not necessarily caused by it.

Events are further categorised by body system and listed in order of decreasing frequency according to the following definitions: very common adverse events are those occurring on one or more occasions in at least 1/10 patients; common adverse events are those occurring in less than 1/10 but at least 1/100; uncommon adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients; unknown cannot be estimated from available data.

Skin and Appendages Disorders

Uncommon: photosensitivity reaction, urticaria, acne, eczema, skin discoloration, alopecia, dermatitis, skin dry, psoriasis, rash. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, pruritus ani. *Unknown:* ecchymosis, angioedema.

Musculoskeletal System Disorders

Uncommon: arthritis, muscle weakness, skeletal pain. *Rare:* bursitis, osteoporosis.

Central and Peripheral Nervous System Disorders

Common: migraine. *Uncommon:* vertigo, leg cramps, involuntary muscle contractions, speech disorder, abnormal gait, hypoaesthesia, neuralgia, ataxia, convulsions. *Rare:* abnormal coordination, hyperesthesia, ptosis, stupor.

Vision Disorders

Common: abnormal accommodation. *Uncommon:* conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, abnormal lacrimation, cataract, diplopia. *Unknown:* visual disturbance.

Special Senses Other, Disorders

Common: taste perversion. *Rare:* taste loss.

Psychiatric Disorders

Common: amnesia, apathy, depression, increased appetite, aggravated depression. *Uncommon:* aggressive reaction, increased libido, paroniria, drug dependence, depersonalisation, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis, mania. *Rare:* catatonic reaction, melancholia, suicide-related events. *Unknown*: bruxism, restlessness.

Gastrointestinal System Disorders

Common: saliva increased. *Uncommon:* gastritis, gastroenteritis, eructation, haemorrhoids, dysphagia, gingivitis, stomatitis, teeth grinding, oesophagitis. *Rare:* colitis, gastric ulcer, duodenal ulcer, gastroesophageal reflux, diverticulitis, glossitis, hiccups, rectal haemorrhage. *Unknown:* gastrointestinal haemorrhage.

Immune System Disorders

Unknown: anaphylactic reaction, hypersensitivity NOS.

Liver and Biliary System Disorders

Uncommon: ALT increased, gamma-GT increased, AST increased. *Rare:* cholecystitis, cholelithiasis, bilirubinaemia, jaundice, hepatitis. *Unknown:* liver function test abnormal.

Metabolic and Nutritional Disorders

Common: increased weight, decreased weight. *Uncommon:* thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare:* hypokalaemia, obesity, hypoglycaemia, dehydration.

Endocrine Disorders

Rare: hypothyroidism, goitre, gynaecomastia.

Cardiovascular Disorders, General

Common: postural hypotension, hypotension. *Uncommon*: hypertension, oedema (extremities), cardiac failure, bradycardia, tachycardia. *Unknown:* orthostatic hypotension.

Myo-, Endo- and Pericardial & Valve Disorders

Uncommon: angina pectoris, myocardial infarction, myocardial ischaemia.

Heart Rate and Rhythm Disorders

Common: tachycardia. *Uncommon:* bradycardia, extrasystoles, atrial fibrillation. *Rare:* bundle branch block, cardiac arrest, QT prolongation, Torsade de Pointes.

Vascular (Extracardiac) Disorders

Uncommon: cerebrovascular accident, flushing, transient ischemic attack. *Rare:* phlebitis.

Respiratory System Disorders

Uncommon: bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.

Red Blood Cell Disorders

Uncommon: anaemia. *Rare:* hypochromic anaemia.

White Cell and Reticuloendothelial System Disorders

Uncommon: leucopenia, leukocytosis, lymphadenopathy. *Rare:* granulocytopenia, lymphocytosis, lymphopenia.

Platelet, Bleeding & Clotting Disorders

Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes,

including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding. *Rare:* pulmonary embolism, coagulation disorder, gingival bleeding. *Unknown:* thrombocytopaenia.

Urinary System Disorders

Common: polyuria. *Uncommon:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial oedema, haematuria, oliguria, pyelonephritis, renal calculus, renal pain.

Reproductive Disorders/Female

Common: amenorrhoea. *Uncommon:* lactation nonpuerperal, breast pain, breast enlargement, vaginal haemorrhage, menorrhagia. *Unknown:* metrorrhagia.

Reproductive System and Breast Disorders/Male

Unknown: priapism, galactorrhoea.

Body as a Whole

Uncommon: hot flushes, rigors, alcohol intolerance, syncope. *Rare:* hayfever.

Other Events Observed During the Postmarketing Evaluation of Cipramil

Although no causal relationship to Cipramil treatment has been found, the following adverse events have been reported to be temporally associated with Cipramil treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the Adverse Effects section: choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), cholestatic hepatitis, hyponatraemia, neuroleptic malignant syndrome, pancreatitis, serotonin syndrome, spontaneous abortion, thrombocytopenia, ventricular arrhythmia, priapism, and withdrawal syndrome.

Akathisia has been reported very rarely (< 1/10,000).

Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease.

Class effect

Epidemiological studies, mainly conducted 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.

DOSAGE AND ADMINISTRATION

Cipramil should be administered as a single daily dose. The dose may be taken in the morning or evening without regard for food.

Adults

The starting dose is 20mg/day. The dose can be increased in increments of 10mg until satisfactory clinical response is achieved. The maximum dose is 40mg/day. As the

treatment result in general can be evaluated only after 2-3 weeks' treatment, a possible dose increase should take place with intervals of 2-3 weeks.

Elderly patients
The starting dose is 10mg/day. The dose can be increased by 10mg to a maximum of 20mg/day. As the treatment result in general can be evaluated only after 2-3 weeks' treatment, a possible dose increase should take place after an interval of 2-3 weeks.

Children and adolescents (< 18 years of age)
The safety and efficacy of citalopram for the treatment of major depressive disorder have not been established in this population. Citalopram should not be used in children and adolescents under the age of 18 years.

Reduced hepatic function
The maximum recommended dose is 20mg/day.

Reduced renal function
Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Poor metabolisers of CYP2C19 and patients taking CYP2C19 inhibitors
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 Pharmacokinetics). Patients taking cimetidine or other CYP2C19 inhibitors should not exceed the maximum dose of 20mg/day.

Duration of treatment
In treating depression a treatment period of at least six months is usually necessary to provide adequate maintenance against the potential for relapse.

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 a least one to two weeks in order to reduce the risk of withdrawal reactions (see PRECAUTIONS). 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.

OVERDOSAGE

In general, the main therapy for all overdoses is supportive and symptomatic care.

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

Symptoms

The following symptoms have been seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, nodal rhythm, ventricular arrhythmia, and very rare cases of Torsade de Pointes.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. The use of activated charcoal should be considered. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Medical surveillance is advisable. ECG monitoring is recommended when more than 600mg have been ingested. Convulsions may be treated with diazepam.

Elimination half-life ($T_{1/2\beta}$) and T_{max} are independent of the dose taken. Information on these pharmacokinetic parameters can be found under PHARMACOLOGY.

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

PRESENTATION AND STORAGE CONDITIONS

Blister packs of 28 film-coated tablets containing 20mg citalopram (as hydrobromide).

Storage conditions

Store below 25°C.

Shelf-life

5 years

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 - Prescription only medicine

DATE OF APPROVAL

Date of TGA approval: 3 December 2007

Date of most recent safety amendment: 25 November 2011.

“Cipramil” is the registered trademark of H. Lundbeck A/S.