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## Name of Medicine

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### Cipramil®

#### Citalopram hydrobromide Film-coated Tablets 20 mg

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## Presentation

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Cipramil tablets contain citalopram hydrobromide, 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 tablets are oval, white, film-coated tablets, 8 mm × 5.5 mm, marked "C" and "N" symmetrically around the score-line.

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## Uses

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### Actions

Biochemical and behavioural 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 one of 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<sub>1A</sub>, 5-HT<sub>2</sub>, DA D<sub>1</sub> and DA D<sub>2</sub> receptors, α<sub>1</sub>-, α<sub>2</sub>- β-adrenoceptors, histamine H<sub>1</sub>, 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 of tricyclic antidepressants 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.

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 (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 although dry mouth occurred significantly more frequently than with placebo in clinical trials. 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. The dose response curve is flat.

### Pharmacokinetics

#### Absorption

Absorption is almost complete and independent of food intake (T<sub>max</sub> mean 3 hours). Oral bioavailability is about 80%.

## Distribution

The apparent volume of distribution ( $V_d$ )<sub>β</sub> is about 12-17 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

## Biotransformation

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

## Elimination

The elimination half-life ( $T_{1/2\beta}$ ) is about 1½ days and the systemic citalopram plasma clearance ( $Cl_s$ ) is about 0.3-0.4 L/min, and oral plasma clearance ( $Cl_{oral}$ ) is about 0.4 L/min. Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys; 12-23% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.3 L/min and renal clearance about 0.05-0.08 L/min.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 300 nmol/L (165-405 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

## 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. Patients with a mean serum creatinine value of 278 μmol/L had a mean  $T_{1/2\beta}$  of 49.5 hours versus 36.8 hours in healthy volunteers. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

## Elderly patients (> 65 years)

Longer half-lives (1.5-3.75 days) and decreased clearance values (0.08-0.3 L/min) due to a reduced rate of metabolism have been demonstrated in elderly patients. Steady state levels were about twice as high in the elderly than in younger patients treated with the same dose.

## Polymorphism

There was no 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).

## Indications

Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

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## Dosage and Administration

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The dose may be taken in the morning or evening without regard for food. As the treatment result in general can be evaluated only after 2-3 weeks' treatment, a possible dose increase in increments of 10 mg should take place with intervals of 2-3 weeks.

### Adults

Cipramil should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response and severity of depression the dose may be increased to a maximum of 40 mg daily. The maximum daily dose should not be exceeded as doses above 40mg/day are associated with an increased risk of QT prolongation.

### **Elderly patients**

The starting dose is 10mg/day. The dose can be increased by 10mg to a maximum of 20mg/day.

### **Use in children and adolescents (under 18 years of age)**

Safety and efficacy have not been established in this population. Consequently, citalopram should not be used in children and adolescents under 18 years of age (see Warnings and Precautions).

### **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**

The antidepressive effect usually sets in after 2-4 weeks. 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 SSRIs**

Abrupt discontinuation should be avoided. When stopping treatment with citalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see Warnings and 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.

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## **Contraindications**

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

Citalopram is contraindicated in patients with congenital long QT syndrome.

**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 Warnings and Precautions).

**Pimozide** - Concomitant use in patients taking pimozide is contraindicated due to the risk of QT prolongation (see Interactions).

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## **Warnings and Precautions**

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### **Warnings**

#### ***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 and should not be used concomitantly with pimozide. 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.

**Children and adolescents (under 18 years of age)** – In clinical trials, adverse events related to suicidality (suicidal thoughts and suicidal behaviours) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in children and adolescents treated with SSRIs (and venlafaxine) compared to those treated with placebo.

**Clinical worsening and suicide risk** – Patients of any age with major depressive disorder may experience worsening of their depression and/or 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 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.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, 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. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania. 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, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. In addition, there is a possibility of an increased risk of suicidal behaviour in young adults.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of such events and to seek medical advice immediately if these symptoms present.

**Mania and bipolar disorder** – A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood 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. 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. It should be noted that citalopram is not approved for use in treating bipolar disorder.

## **Precautions**

**Information for patients and families** - Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially during

antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

**Monoamine Oxidase Inhibitors** - Simultaneous administration of citalopram and a Monoamine Oxidase Inhibitor (MAOI) may cause serotonin syndrome, a serious, sometimes fatal, reaction in patients receiving an SSRI in combination with a MAOI and in patients treated with an SSRI and a MAOI in close proximity. Some cases presented with features resembling neuroleptic malignant syndrome. Symptoms and signs of serotonin syndrome include: rapid onset, clonus, myoclonus, tremor, shivering, hyperreflexia, hyperthermia, rigidity, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma.

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.

**Hyponatraemia** - probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs. Risk factors include old age and concomitant therapy with diuretics; most cases occur during the first 3 weeks of therapy.

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

**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.

**Mydriasis** - Mydriasis has been reported in association with SSRIs such as citalopram. Therefore caution should be used when prescribing citalopram in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

**Withdrawal symptoms seen on discontinuation of SSRIs** - 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. Fatal arrhythmias with prolonged QTc interval were observed in preclinical (animal toxicology) studies (see Warnings and Precautions - *Other*). 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.

Due to the risk of QT prolongation, ECG monitoring is advised when using citalopram in patients with risk factors for QT prolongation (see Warnings).

**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.

**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.

## ***Pregnancy and Lactation***

Category C

Citalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit, taking into account the risks of untreated depression.

For citalopram and escitalopram only limited clinical data are available regarding exposed pregnancies.

In an embryo-foetal developmental toxicity study in rats, reduced body weight and minor delays in foetal ossification were noted at maternotoxic doses at which the systemic exposure in terms of AUC was ~ 11-fold greater than would be obtained in humans in a clinical setting. These effects were not seen when the AUC was ~ 6-fold greater, and no teratogenicity was evident when the AUC was ~ 15-fold greater. However, epidemiological studies have suggested that the use of some SSRIs and SNRIs during pregnancy is associated with an increased risk of congenital abnormalities. The relevance for citalopram remains unknown.

There were no peri- or postnatal effects following the dosing of pregnant rats (conception through to weaning) where the systemic exposure levels (based on AUC) were approximately twice that of those expected clinically. However, the number of still births was increased and the size, weight and postnatal survival of offspring were decreased when the systemic exposure level (AUC) was ~5-fold greater than the expected clinical level.

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. Abrupt discontinuation should be avoided during pregnancy.

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. In the majority of cases the complications begin immediately or soon (< 24 hours) after delivery.

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 persistent 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.

Citalopram is excreted into human breast milk. Studies in nursing mothers have shown that the mean combined dose of citalopram and demethylcitalopram transmitted to infants via breast milk (expressed as a percentage of the weight-adjusted maternal dose) is 4.4 - 5.1% (below the notional 10% level of

concern). Plasma concentrations of these drugs in infants were very low or absent and there were no adverse effects. Whilst the citalopram data support the safety of use in breast-feeding women, the decision to breast-feed should always be made as an individual risk/benefit analysis.

### **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 and should be cautioned about their ability to drive a car and operate machinery.

### **Other**

**Preclinical safety** - For comparison the recommended daily therapeutic dose is 0.3-0.9 mg/kg. Fatty infiltration of the liver was seen in male rats but not in females and was greater when citalopram was given by gavage (8 mg/kg/day for 3 months) than in a more sustained manner via the diet (32 mg/kg/day for 12 months). Citalopram (25 mg/kg/day for 28 days) given as infusion over 30 minutes did not induce signs of fatty infiltration. The fatty infiltrations, which are completely reversible, are therefore connected with excessive first-pass metabolic transformation in the male rat. This has no clinical parallel, since first-pass metabolism is modest in man. Induction of completely reversible phospholipidosis was seen in both male and female rodents receiving 60 and 120 mg/kg/day (rats, 52 weeks) and 100 and 240 mg/kg/day (mice, 26 weeks). There was no evidence of phospholipidosis in dogs. Citalopram has not shown any signs of phospholipidosis in humans. The ratio between the doses which caused phospholipidosis in rats and mice and the therapeutic dose is high (ratio rats/human 53 and ratio mice/humans 167). The phenomenon is also seen with many other marketed cationic amphiphilic drugs including most tricyclic antidepressants, several neuroleptics, some cardiovascular agents and no clinical problems related to phospholipidosis have been observed with these drugs.

After life-long treatment (2 years) retinal changes were observed in the top dose group of albino rats given 80 mg/kg/day. No changes were observed after 1 year. Albino rats having no pigmentation are light sensitive and the changes are most likely related to drug-induced mydriasis (pupillary dilatation). No changes have been observed in pigmented mice or in dogs.

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

In dogs convulsions and death occurred when plasma citalopram levels exceeded 6,000 nmol/L (more than 20 times the average patient level). By preventing convulsive episodes with diazepam intravenous infusion could be continued up to 70 mg/kg resulting in plasma concentrations of up to 21,000 nmol/L without indications of serious toxicity.

Repeated dose toxicity studies demonstrated that fatal arrhythmias may occur at combined high levels of the didemethyl metabolite (which affects the heart) and citalopram (central nervous effects). Neither citalopram alone nor the metabolite alone produce dangerous arrhythmias. The didemethyl metabolite, however, prolongs the QT interval - an action which can develop into fatal arrhythmia when coupled with centrally mediated effects induced by convulsive or near convulsive doses of citalopram. Fatal arrhythmias may occur in dogs simultaneously exposed to citalopram levels exceeding about 2,600 nmol/L and didemethyl metabolite levels exceeding about 1,000 nmol/L. However, the kinetics differ greatly between dogs and man and the didemethyl metabolite is much less prominent in man.

<b>Dose 40 mg citalopram per day</b>	<b>No. of patients in steady state</b>	<b>Mean (nmol/L)</b>	<b>SD (nmol/L)</b>
Citalopram	2,087	276	186
Dimethylcitalopram	2,067	116	113
Didemethylcitalopram	2,020	22	20

Pharmacokinetic data indicate that high levels of citalopram following an overdose will not be combined with immediate high levels of the metabolite, which require a two step demethylation, i.e. maximum levels of the didemethyl metabolite are obtained 2-3 days after a single dose. The highest didemethyl level of 140 nmol/L was found 2-3 days after an overdose of 1,200 mg citalopram and the citalopram level at that time was 1,950 nmol/L. The metabolite related cardiovascular findings in dogs are therefore of no concern for the clinical use of citalopram.

**Carcinogenicity/mutagenicity** - 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.

## 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  $\geq 5\%$  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 %
<b>(100) SKIN AND APPENDAGES DISORDERS</b> Pruritus Rash Sweating increased	1.0 1.0 11.3*	0.8 1.2 7.4
<b>(200) MUSCULO-SKELETAL SYSTEM DISORDERS</b> Myalgia Arthralgia	1.9 1.8	1.2 0.8
<b>(410) CENTRAL &amp; PERIPHERAL NERVOUS SYSTEM DISORDERS</b> Dizziness Extrapyramidal disorder <sup>1)</sup> Headache Paraesthesia Tremor	10.3 1.5 26.9 1.4 8.8*	10.1 0.6 26.7 1.2 5.8
<b>(431) VISION DISORDERS</b> Vision abnormal	4.7	5.1
<b>(432) HEARING AND VESTIBULAR DISORDERS</b> Tinnitus	1.0	0.6

<b>(500) PSYCHIATRIC DISORDERS</b>		
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	-
<b>(600) GASTRO-INTESTINAL SYSTEM DISORDERS</b>		
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
<b>(800) METABOLIC AND NUTRITIONAL DISORDERS</b>		
Weight decrease	1.5	0.6
<b>(1030) HEART RATE AND RHYTHM DISORDERS</b>		
Palpitation	7.1	7.4
<b>(1100) RESPIRATORY SYSTEM DISORDERS</b>		
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
<b>(1300) URINARY SYSTEM DISORDERS</b>		
Micturition disorders	2.3	1.9
<b>(1410) REPRODUCTIVE DISORDERS, MALE</b>		
Ejaculation disorders	5.9*	-
Impotence	2.8	0.5
<b>(1420) REPRODUCTIVE DISORDERS, FEMALE</b>		
Menstrual disorders (CT ≤ 50 years: N=447; PL ≤ 50 years: N=180)	4.0	2.2
<b>(1810) BODY AS A WHOLE</b>		
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

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

#### ***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 60 mg. 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 0.5 kg 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 Cipramil (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables.

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.

The only statistically significant drug-placebo difference observed was a decrease in heart rate for Cipramil of 1.7 bpm compared to no change in heart rate for placebo.

In a thorough QT study, citalopram was found to be associated with a dose-dependent increase in the QTc interval (see **WARNINGS – 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 80 mg/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 the 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. *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 and 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:* thrombocytopenia.

### **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: angioedema, choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), hepatitis, cholestatic hepatitis, hyponatraemia, neuroleptic malignant syndrome, mania, 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.

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## **Interactions**

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### ***Drugs that prolong the QT interval***

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

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

*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 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and  $C_{max}$  of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated (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.

**Hepatic enzymes** - The metabolism of citalopram is only partly dependent on the hepatic 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.

*In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40mg) and ketoconazole (200mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple dose administration of citalopram, suggesting that co-administration of citalopram with a medicine that inhibits CYP2D6 is unlikely to have clinically significant effects on citalopram metabolism.

Citalopram 20mg/day is the maximum recommended dose for patients taking concomitant CYP2C19 inhibitors (e.g. omeprazole) because of the risk of QT prolongation (see DOSAGE AND ADMINISTRATION).

**Protein binding** - Protein binding is relatively low (< 80%). These properties give Cipramil a low potential for clinically significant drug interactions.

**Lithium and tryptophan** - There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic effects when other SSRIs have been given with lithium and tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Increased monitoring of lithium levels is not required.

**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 40 mg/day Cipramil, combined administration of Cipramil and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

**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.

**Carbamazepine** - Combined administration of Cipramil (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/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, a documented enzyme inhibitor, caused a moderate increase in the average steady state levels of citalopram. Therefore, citalopram 20mg/day is the maximum recommended dose for patients taking concomitant cimetidine because of the risk of QT prolongation (see DOSAGE AND ADMINISTRATION).

**Alcohol** - Neither pharmacodynamic nor pharmacokinetic interaction with alcohol has been shown. However, 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, antihistamines, antihypertensive drugs, beta-blockers and other cardiovascular drugs.

Although citalopram does not bind to opioid receptors it potentiates the antinociceptive effect of commonly used opioid analgesics.

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

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## Overdosage

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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.

An adult patient has survived intoxication with 5,200 mg citalopram.

### 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 600 mg 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 Uses.

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).

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## Pharmaceutical Precautions

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### ***Instructions for Use/Handling***

Nil

### ***Incompatibilities***

Nil

### ***Shelf Life***

5 years

### ***Special Precautions for Storage***

Store below 25°C.

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## Medicine Classification

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Prescription only medicine

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## Package Quantities

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- Film-coated tablets containing 24.98 mg citalopram hydrobromide, corresponding to 20 mg citalopram base.
  - Blister packs of 28 tablets.
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## Further Information

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### ***Excipients:***

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

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## Name and Address

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## Date of Preparation

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6 January 2012