

## CELAPRAM®

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### 1. Product Name

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CELAPRAM 20 mg film coated tablets.

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### 2. Qualitative and Quantitative Composition

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Each tablet contains 24.98 mg of citalopram hydrobromide equivalent to 20 mg of citalopram.

Excipient with known effect: Lactose.

For the full list of excipients, see section 6.1.

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### 3. Pharmaceutical Form

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CELAPRAM 20 mg tablets are oval, white, film-coated tablets, 8 mm x 5.6 mm, marked "CM" breakline "20" on one side and "G" on the other.

The tablet can be divided into equal doses.

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.

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### 4. Clinical Particulars

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#### 4.1 *Therapeutic indications*

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

#### 4.2 *Dose and method of administration*

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.

#### **Dose**

##### **Adults**

CELAPRAM 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 of citalopram should not exceed 40 mg/day as doses above 40 mg/day are associated with an increased risk of QT prolongation.

## **Special populations**

### **Elderly**

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

### **Hepatic impairment**

The maximum recommended dose is 20 mg/day.

### **Renal impairment**

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.).

### **Paediatric**

Safety and efficacy have not been established in this population. Consequently, citalopram should not be used in patients under 18 years of age (see section 4.4).

### **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 section 5.2). For patients taking CYP2C19 inhibitors, e.g. cimetidine and omeprazole, the citalopram dose should not exceed the maximum dose of 20 mg/day.

### **Method of administration**

The dose may be taken in the morning or evening without regard for food.

### **Duration of treatment**

The antidepressive effect usually sets in after 2 to 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 section 4.4). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

## **4.3 Contraindications**

- Hypersensitivity to citalopram and any excipients in CELAPRAM (see section 6.1).
- Concurrent administration of citalopram and Monoamine Oxidase Inhibitors
  - CELAPRAM 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 section 4.4).
- Citalopram is contraindicated in combination with linezolid unless there are facilities for close observation and monitoring of blood pressure (see section 4.5)

- Concomitant use in patients taking pimozide is contraindicated due to the risk of QT prolongation (see section 4.5).

## **4.4 Special warnings and precautions for use**

### **QT-prolongation and Torsade de Pointes**

Clinical studies have shown citalopram can cause a dose-dependent increase in the QTc interval and should not be dosed above 40 mg/day. QT prolongation and Torsade de Pointes has been reported post-marketing.

Citalopram is contraindicated for use in combination with pimozide. Citalopram is not recommended for use in patients at high risk of developing prolongation of the QTc interval. This includes patients with congenital long QT syndrome, structural heart disease or left ventricular dysfunction, concomitant use of other QTc prolonging medicines, bradyarrhythmias, hypokalaemia or severe hypomagnesaemia (or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicine use). However, if citalopram use is considered essential in these patients then citalopram should be used at the lowest possible dose and ECG monitoring should be undertaken prior to starting treatment, at steady state, after dose increases or after starting any potentially interacting medicine. Hypokalaemia and hypomagnesaemia should be corrected prior to initiation of treatment and periodically monitored.

Patients should be informed of symptoms of arrhythmia (e.g. dizziness, palpitations, syncope or new onset seizures) and should be advised to seek medical assistance if they occur. An ECG should be performed in all patients experiencing symptoms that could be indicative of an arrhythmia.

Citalopram should be used with caution in patients with other risk factors for QTc prolongation including age >65 years, female sex, high doses of citalopram and use of medicines that inhibit the metabolism of citalopram. ECG monitoring should be performed in any patient considered at significant risk for QTc prolongation.

Citalopram should be stopped and specialist advice should be sought in patients who have persistent QTc prolongation >500 ms or in whom the QTc interval has increased >60 ms during treatment.

The maximum dose of citalopram is 20 mg/day in elderly patients (>65 years), patients with hepatic dysfunction, CYP2C19 poor metabolisers or patients taking concomitant cimetidine or another CYP2C19 inhibitor (such as omeprazole). Otherwise the maximum dose should be 40 mg/day.

### **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.

### **Sexual dysfunction**

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

### **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.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

### **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.

### **St. John's wort**

Undesirable effects may be more common during concomitant use of citalopram and herbal preparations containing St John's wort (*hypericum perforatum*). Therefore, citalopram should not be taken with St John's wort preparations.

### **Alcohol**

As with other psychotropic drugs, patients should be advised to avoid alcohol use while taking 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.

### **Serotonin Syndrome**

Development of serotonin syndrome may occur in association with treatment with SSRIs particularly when given in combination with MAOIs (see section 4.3) or other serotonergic agents such as opioids for example tramadol, pethidine, dextromethorphan.

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).

If serotonin syndrome is suspected, a dose reduction or discontinuation of at least one of the serotonergic medicines being taken should be considered depending on the severity of the symptoms and supportive symptomatic treatment initiated.

### **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 section 4.2).

### **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 section 5.3). 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 section 4.4).

### **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). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8) Citalopram 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.

### **Reversible cerebral vasoconstriction syndrome**

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as SSRIs or triptans.

## Excipients

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

## Paradoxial anxiety

Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

## 4.5 Interaction with other medicines and other forms of interaction

### Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsade de Pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval.

More frequent ECG monitoring is recommended in patients on concomitant medicines that prolong the QT interval (see section 4.4).

### Monoamine oxidase inhibitors (MAOIs)

Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see section 4.3).

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline, the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued SSRI and have been started on a MAOI.

### 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 section 4.3).

### Serotonergic drugs

Co-administration with serotonergic drugs (e.g. opioids such as pethidine, dextromethorphan tramadol, sumatriptan) may lead to an enhancement of serotonergic effects (see section 4.4). 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 CYP-1A2, -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 metabolisers and extensive -2D6 metabolisers 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 20 mg/day is the maximum recommended dose for patients taking concomitant CYP2C19 inhibitors (e.g. omeprazole) because of the risk of QT prolongation (see section 4.2).

### **Protein binding**

Protein binding is relatively low (< 80%). These properties give citalopram 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 citalopram, combined administration of citalopram 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 a NSAID, aspirin or warfarin potentiates this risk. Thus, patients should be cautioned about using such medicines concurrently with citalopram.

### **Carbamazepine**

Combined administration of citalopram (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 20 mg/day is the maximum recommended dose for patients taking concomitant cimetidine because of the risk of QT prolongation (see section 4.2).

### **Omeprazole**

Co-administration of citalopram (single dose) with omeprazole (a CYP2C19 inhibitor) increased the plasma levels of citalopram. Therefore, citalopram 20 mg/day is the maximum recommended dose for patients taking concomitant omeprazole because of the risk of QT prolongation (see section 4.2). Caution should also be exercised when citalopram is used concomitantly with other CYP2C19 inhibitors (e.g. esomeprazole, lansoprazole).

### **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 sections 4.3). However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

#### **Category C**

Animal studies have shown reproductive toxicity (see section 5.3).

CELAPRAM 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.

Newborn 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, or SNRIs, 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 data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Epidemiological studies have shown that the use of SSRIs (including citalopram), particularly 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 a 4 to 5 times higher than the rate of 1 to 2 per 1000 pregnancies observed in the general population.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see section 4.4 and 4.8)

### **Breast-feeding**

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.

### **Fertility**

Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess of human exposure.

Animal data have shown that citalopram may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

See also section 5.3.

## **4.7 Effects on ability to drive and use machines**

Citalopram does not impair intellectual function and psychomotor performance. However, patients who are prescribed psychotropic medication may be expected to have some impairment of general

attention and concentration and should be cautioned about their ability to drive a car and operate machinery.

#### 4.8 Undesirable effects

Adverse effects observed with citalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually attenuate subsequently.

The 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		CITALOPRAM versus	PLACEBO
	Reaction (WHO preferred term)	(N = 1083)	(N = 486)
		(CT: F = 660; M = 423) (PL: F = 286; M = 200)	
		CITALOPRAM %	PLACEBO %
<b>(100)</b>	<b>SKIN AND APPENDAGES DISORDERS</b>		
	Pruritus	1.0	0.8
	Rash	1.0	1.2
	Sweating increased	11.3*	7.4
<b>(200)</b>	<b>MUSCULO-SKELETAL SYSTEM DISORDERS</b>		
	Myalgia	1.9	1.2
	Arthralgia	1.8	0.8
<b>(410)</b>	<b>CENTRAL &amp; PERIPHERAL NERVOUS SYSTEM DISORDERS</b>		
	Dizziness	10.3	10.1
	Extrapyramidal disorder <sup>1)</sup>	1.5	0.6
	Headache	26.9	26.7
	Paraesthesia	1.4	1.2
	Tremor	8.8*	5.8

<b>(431)</b>	<b>VISION DISORDERS</b>		
	Vision abnormal	4.7	5.1
<b>(432)</b>	<b>HEARING AND VESTIBULAR DISORDERS</b>		
	Tinnitus	1.0	0.6
<b>(500)</b>	<b>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)</b>	<b>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)</b>	<b>METABOLIC AND NUTRITIONAL DISORDERS</b>		
	Weight decrease	1.5	0.6
<b>(1030)</b>	<b>HEART RATE AND RHYTHM DISORDERS</b>		
	Palpitation	7.1	7.4
<b>(1100)</b>	<b>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)</b>	<b>URINARY SYSTEM DISORDERS</b>		
	Micturition disorders	2.3	1.9

<b>(1410)</b>	<b>REPRODUCTIVE DISORDERS, MALE</b>		
	Ejaculation disorders	5.9*	-
	Impotence	2.8	0.5
<b>(1420)</b>	<b>REPRODUCTIVE DISORDERS, FEMALE</b>		
	Menstrual disorders (CT ≤ 50 years: N = 447; PL ≤ 50 years: N = 180)	4.0	2.2
<b>(1810)</b>	<b>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

<sup>1)</sup> including: dyskinesia, dystonia, hyperkinesia, hypertonia, hypokinesia.

### **Dose dependency of adverse events**

The potential relationship between the dose of citalopram administered and the incidence of adverse events was examined in a fixed dose study in depressed patients receiving placebo or citalopram 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 citalopram (N=423) was 5.9%, and 2.8%, respectively. In female depressed patients receiving citalopram (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**

Citalopram 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 citalopram treatment. In addition, a comparison of supine and standing vital sign measures for citalopram and placebo treatments indicated that citalopram treatment is not associated with orthostatic changes.

## Weight changes

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

## Laboratory changes

Citalopram 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 citalopram treatment.

## ECG changes

Electrocardiograms from citalopram (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 > 60 msec 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 citalopram of 1.7 bpm compared to no change in heart rate for placebo.

In a thorough QT study (see table below), citalopram was found to be associated with a dose dependant increase in the QTc interval (see section 4.4).

Citalopram dose	QTc interval increase	95% confidence interval (ms)
20 mg/day	8.5	(6.2, 10.8)
60 mg/day	18.5	(16.0, 21.0)
40 mg/day	12.6*	(10.9, 14.3)*

\*Estimate based on relationship between citalopram blood concentration and QT interval

## Other events observed during the premarketing evaluation of citalopram

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to section 4.8, reported by patients treated with citalopram 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 section 4.8, 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 citalopram, 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 1/1000 patients; rare events are those occurring in fewer than 1/1000 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, torsades 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 citalopram**

Although no causal relationship to citalopram treatment has been found, the following adverse events have been reported to be temporally associated with citalopram 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, inappropriate ADH secretion, 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).

Hyponatraemia has been reported 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 effects**

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. Postpartum haemorrhage has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6). Hyperprolactinaemia has been reported for the therapeutic class of SSRIs/SNRIs (see section 5.1)

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 Overdose**

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

Citalopram is given to depressed patients who are at potential risk of suicide and some reports of attempted suicide with citalopram-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 National Poisons Information Centre (0800 POISON or 0800 764 766).

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## **5. Pharmacological Properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: selective serotonin reuptake inhibitors, ATC code: N06AB04

#### **Mechanism of action**

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 SSRI's, 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,  $\alpha_1$ -,  $\alpha_2$ -,  $\beta$ -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.

### **Clinical efficacy and safety**

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.

## **5.2 Pharmacokinetic properties**

### **Absorption**

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

### **Distribution**

The apparent volume of distribution ( $V_d$ ) <sub>$\beta$</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.

## **Linearity**

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

## **Special populations**

### ***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  $\mu\text{mol/L}$  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 section 4.2).

## **5.3 Preclinical safety data**

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>Page 18 of 19 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/impairment on fertility**

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.

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## **6. Pharmaceutical Particulars**

### **6.1 List of excipients**

CELAPRAM film coated tablets also contains

- lactose
- maize starch
- microcrystalline cellulose
- povidone
- crospovidone
- magnesium stearate
- hypromellose
- macrogol
- titanium dioxide

Contains sulfites and sugars as lactose.

## 6.2 *Incompatibilities*

Not applicable.

## 6.3 *Shelf life*

3 years.

## 6.4 *Special precautions for storage*

Store at or below 25°C.

## 6.5 *Nature and contents of container*

Al/PVC/PVdC blister pack of 28, 84 or 100 tablets.

Not all pack sizes may be marketed.

## 6.6 *Special precautions for disposal*

Not applicable.

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## 7. Medicines Schedule

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Prescription Medicine

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## 8. Sponsor Details

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Viatris Ltd  
PO Box 11-183  
Ellerslie  
AUCKLAND  
[www.viatris.co.nz](http://www.viatris.co.nz)  
Telephone 0800 168 169

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## 9. Date of First Approval

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13 February 2003

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## 10. Date of Revision of the Text

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10 August 2023

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### Summary table of changes

Section	Summary of new information
Heading	Addition of trade mark symbol
2	Updated "excipients with known effect" section
4.3, 4.4	Minor formatting updates
4.4, 4.6, 4.9, 5.3	Minor editorial changes
4.4	Addition for serotonin syndrome information

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4.5	Relocation of serotonin syndrome information to section 4.4 Hepatic enzymes section updated
4.8	Addition of information on hyperprolactinemia.
-	Addition of trade attribution statement

CELAPRAM® is a Viatris company trade mark.