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1. PRODUCT NAME

Citalopram, tablets, film-coated, 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance

Each film-coated tablet contains 24.99 mg citalopram hydrobromide Ph. Eur corresponding to 20 mg of citalopram base.

Citalopram hydrobromide is a fine white to off-white, crystalline material. Sparingly soluble in water, soluble in ethanol (96%), freely soluble in chloroform and very slightly soluble in diethyl ether. No polymorphic forms have been detected.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

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 (also refer Section 4.4 Special warnings and precautions).

3. PHARMACEUTICAL FORM

Oral, film-coated tablets

Presentation

White to off-white, oval, biconvex, film-coated tablets with break-line on one side & '20' embossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

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

4.2 Dose and method of administration

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 10mg should take place with intervals of 2-3 weeks.

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Adults

Should be administered as a single oral dose of 20mg daily. Dependent on individual patient response and severity of depression the dose may be increased to a maximum of 40mg daily.

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

A maximum dose of 20mg/day is recommended for patients known to be CYP2C19 poor metabolisers or in patients taking cimetidine or other CYP2C19 inhibitors.

A dose of 20mg/day is recommended for patients with hepatic impairment and patients aged >60 years. A dose of 40mg/day should be only used for non-responding patients.

Poor metabolisers of CYP2C19

An initial dose of 10mg daily during the first two weeks of treatment is recommended for patients who are known to be poor metabolisers with respect to CYP2C19.

A maximum dose of 20mg/day is recommended for patients known to be CYP2C19 poor metabolisers depending on individual patient response. For patients taking CYP2C19 inhibitors eg. cimetidine and omeprazole, the citalopram dose should not exceed the maximum dose of 20mg/day.

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 (*refer Section 4.4 Special warnings and precautions for use*).

Reduced hepatic function

A dose of 20mg/day is recommended for patients with hepatic impairment and patients aged >60 years. A dose of 40mg/day should only be used for non-responding patients.

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.).

Duration of treatment

The anti-depressive 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

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potential for relapse.

There have been post-marketing reports of withdrawal reactions with citalopram, as with the other SSRIs. If discontinuation is contemplated, the dose should be tapered gradually over several weeks, according to the patient's need.

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.

4.3 Contraindications

- Hypersensitivity to citalopram and any excipients in Citalopram film-coated tablets (*refer Section 6.1 list of excipients*).
- Concurrent administration of citalopram and Monoamine Oxidase Inhibitors
 - Citalopram 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 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 MAOI or the RIMA, moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (*refer Section 4.4 Special warnings and precautions for use*).
- Concomitant use in patients taking pimozide is contraindicated due to the risk of QT prolongation (*refer Section 4.5 Interaction with other medicines and other forms of interaction*).

4.4 Special warnings and precautions for use

Warnings

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. Consequently, citalopram should not be used in children and adolescents less than 18 years of age.

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 patients 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 depression disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating

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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 or 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. It should be noted that escitalopram is not approved for use in treating bipolar disorder.

QT- Prolongation and Torsades de Pointes

Clinical studies have shown that citalopram use is associated with dose-dependent QT prolongation. In addition, there have been post-marketing reports of QT prolongation and Torsades de Pointes in association with citalopram use.

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 in caution in patients with other risk factors for QTc prolongation including age >65 years, female sex, high doses of citalopram and use of

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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 for patients known to be CYP2C19 poor metabolisers; and in patients taking cimetidine or other CYP2C19 inhibitors (such as omeprazole). Otherwise the maximum dose should be 40mg/day.

Paradoxical anxiety

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

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.

Bone fractures

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.

Thunderclap Headaches

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

Alcohol

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

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.

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,

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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.

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.

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

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

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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.

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. However, the electrocardiograms of 1,116 patients who received citalopram in clinical trials were evaluated and the data indicate that citalopram is not associated with the development of clinically significant ECG abnormalities. Fatal arrhythmias with prolonged QTc interval were observed in preclinical (animal toxicology) studies (*refer Section 5.3 Preclinical safety data*).

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 other risk factors of QT prolongation including structural heart disease/LV dysfunction, bradycardia, hypokalaemia or severe hypomagnesaemia, or who are taking other medicines that prolong QT interval. Caution is advised in treating patients with diseases, or who are taking medicines, that cause hypokalaemia or hypomagnesaemia (*refer Section 4.4 Special warnings and precautions for use*).

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

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gastrointestinal bleeding). 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.

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.

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.

Excipients

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

4.5 Interaction with other medicines and other forms of interaction

MAOIs

Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (*refer Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use*).

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.

Serotonergic medicines

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SSRIs may theoretically interact with 5-HT agonists. Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects. Until further evidence is available it is advised not to use Citalopram simultaneously with 5-HT agonists. 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.

CYP3A4 and 2C19 inhibitors

In vitro studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, co-administration of citalopram (40mg) and ketoconazole (200mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram suggesting that the co-administration with citalopram or a medicine that inhibits CYP2D6 is unlikely to have clinically significant effects on citalopram metabolism. Co-administration of citalopram (single dose) with omeprazole (a CYP2C19 inhibitor) increased the plasma levels of citalopram. Citalopram 20mg/day is the maximum recommended dose for patients taking concomitant CYP2C19 inhibitors (e.g. omeprazole) because of the risk of QT-prolongation (*refer Section 4.2 Dose and method of administration*).

CYP2D6 inhibitors

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, with citalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism.

Protein binding

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

Pimozide

Co-administration of a single dose of pimozide 2mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AU 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.

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Due to the interaction noted at a low dose of pimozole, concomitant administration of citalopram and pimozole is contraindicated (*refer Section 4.3 Contraindications*).

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 re-uptake 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 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

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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

As a documented enzyme inhibitor, cimetidine 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 (*refer Section 4.2 Dose and method of administration*).

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 (*refer Section 4.2 Dose and method of administration*). 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.

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 with concomitant use of medicines that can cause QT-prolongation and/or TdP (*refer Section 4.4 Special warnings and precautions for use, QT-prolongation and Torsade de Pointes*).

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.

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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 (*refer Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interaction - Pimozide*). However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

Category C

Animal studies have shown reproductive toxicity (*refer Section 4.4 'Special warnings and precautions for use' for Carcinogenicity and Mutagenicity and refer to Fertility below*).

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 that 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 an increased risk of congenital abnormalities associated with the use of SSRIs and SNRIs in pregnancy. 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.

Animal data have shown that citalopram may affect sperm quality (see Further Information – Preclinical Safety). 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.

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New-born 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 new-born are possible. Abrupt discontinuation should be avoided during pregnancy.

New-borns 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 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. The use of SSRIs in pregnancy, particularly use in late pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The absolute risk among those who used SSRIs late in pregnancy was estimated to be 4 to 5 times higher than the rate of 1 to 2 per 1,000 pregnancies observed in the general population.

Neonates 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 and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRS or, possibly, a drug discontinuation syndrome. In the majority of cases the complications begin immediately or soon (<24 hours) after delivery.

Neonates 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 the birth, discontinuation effects in the newborn are possible. Abrupt discontinuation should be avoided during pregnancy.

Use in Lactation

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)

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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 supports 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 the 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.

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 are listed in the following tables:

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

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

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

* Statistically significant adverse events between groups, with a frequency of greater than 5% ($P < 0.05$).

Including: dyskinesia, dystonia, hyperkinesias, hypetonia, hypokinesia.

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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.

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ECG changes

In a thorough QT study (see table below), citalopram was found to be associated with a dose-dependent increase in the QTc interval (*refer Section 4.4 Special warnings and precautions for use - QT-prolongation and Torsade de Pointes*).

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)*

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 patients has a change from baseline 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 citalopram of 1.7 bpm compared to no change in heart rate for placebo.

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 the **Undesirable effects**, 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 4422 patients.

All reported events are included except those already listed in the table or elsewhere in the **Undesirable effects**, 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 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients; unknown cannot be estimated from the available data.

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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.

Rare: catatonic reaction, melancholia, suicide-related events.

Unknown: bruxism, restlessness.

Gastro-intestinal 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 Disorder

Unknown: anaphylactic reaction, hypersensitivity NOS.

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Liver and Biliary System Disorders

Uncommon: ALT increased, gamma-GT increased, ALP increased, AST.

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-, Pericardial & Valve Disorders

Uncommon: angina pectoris, myocardial infarction, myocardial ischaemia.

Heart Rate and Rhythm Disorders

Common: tachycardia. *Uncommon:* bradycardia, extrasystoles. atrial fibrillation.

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, dyspnoea, 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.

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Platelet, Bleeding & Clotting Disorders Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes, including purpura, epistaxis, haematomas, vaginal bleeding and gastrointestinal bleeding.

Rare: pulmonary embolism, coagulation disorder, gingival bleeding.

Unknown: 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 post marketing 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 UNDESIRABLE EFFECTS: 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, inappropriate ADH secretion 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 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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{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 patients at 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: drowsiness, convulsions, tachycardia, somnolence, coma, nausea, vomiting, tremor, cyanosis, sweating and rare ECG changes, including QTc prolongation, nodal rhythm, ventricular arrhythmia and very rare cases of Torsades de Pointes. Fatalities have been reported.

Treatment

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

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

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 0800 764 766 for New Zealand). An adult patient has survived intoxication with 5,200 mg citalopram.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions

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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_{1A}, 5-HT₂, DA D₁ and DA D₂ receptors, α ₁-, α ₂- β -adrenoceptors, histamine H₁, 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 prolactin and 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%.

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Distribution

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

Biotransformation

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

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 is 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 (0.08-0.3L/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

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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 (*refer Section 4.2 Dose and method of administration*).

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/humans 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.

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Repeated dose toxicity studies demonstrated that fatal arrhythmias may occur at combined high levels of the didemthyl 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.

Dose 40 mg citalopram per day	No. of patients in steady state	Mean (nmol/L)	SD (nmol/L)
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citalopram Tablets, Film-coated 20mg contains the following excipients: lactose monohydrate, maize starch, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, purified talc, macrogol 400 and purified water.

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 (*Refer to Section 4.4 Special Warning and precautions*).

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

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6.3 Shelf life

36 months from date of manufacture when stored below 25°C.

6.4 Special precautions for storage

Store below 25°C. Store in the original package. Protect from heat and light.

6.5 Nature and contents of container

Blisters packs of 28, 56 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

PSM Healthcare Limited, t/a API Consumer Brands
14-16 Norman Spencer Drive,
PO Box 76 401
Manukau City, AUCKLAND 2241
Freephone 0508 776746

9. DATE OF FIRST APPROVAL

19/02/2009

10. DATE OF REVISION OF THE TEXT

October 2019

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
All	Update to the SPC-style format as per new datasheet template effective 1/03/2017 and updated template, and other minor changes.
4.4	Special warnings and precautions for use updated to include sexual dysfunction.