

NEW ZEALAND DATA SHEET

CITALOPRAM

Citalopram (as citalopram hydrobromide) 20mg Film-coated Tablets

PRESENTATION

CITALOPRAM 20mg Film-coated Tablets are white to off-white, oval, biconvex, film-coated tablets with 'BL' embossed on one side & '20' on the other.

The tablets contain Lactose.

INDICATIONS

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

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

Adults

CITALOPRAM 20 mg Film-coated Tablets 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 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.

Elderly patients

The recommended daily dose is 20 mg starting with 10 mg daily. Dependent on individual patient response and severity of depression the dose may be increased to a maximum of 40 mg daily.

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

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

Reduced hepatic function

Patients with reduced hepatic function should receive dosages of no more than 30 mg/day.

Reduced renal function

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

Poor metabolisers of CYP2C19

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 20 mg daily depending on individual patient's response (see *Pharmacokinetics*).

Duration of treatment

The antidepressive effect usually sets in after 2-4 weeks. A treatment period of at least six months is usually necessary to provide adequate maintenance against the potential for relapse.

Withdrawal symptoms seen on discontinuation of SSRIs

Abrupt discontinuation should be avoided. When stopping treatment with citalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see WARNINGS AND PRECAUTIONS). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

CONTRAINDICATIONS

Hypersensitivity to citalopram and any excipients in CITALOPRAM 20mg Film-coated Tablets (see FURTHER INFORMATION).

Concurrent administration of CITALOPRAM 20mg Film-coated Tablets and Monoamine Oxidase Inhibitors (see Warnings and Precautions).

Citalopram is contraindicated in patients with congenital long QT syndrome. Concomitant use of pimozide is contraindicated due to the risk of QT prolongation.

WARNINGS AND PRECAUTIONS

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.

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 therapeutics 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 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 esitalopram 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 should not be used in patients with congenital long QT syndrome; and should not be used concomitantly with pimozide. Citalopram should be used cautiously and ECG monitoring should be undertaken for patients with other risk factors for QT prolongation including structural heart disease/LV dysfunction, bradycardia, hypokalaemia or severe hypomagnesaemia, and concomitant use of other medicines that can prolong the QT interval. Modifiable risk factors (such as electrolyte abnormalities) should be corrected prior to starting citalopram.

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 does should be 40mg/day.

Precautions

Information for patients and families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Monoamine Oxidase Inhibitors

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

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

Hyponatraemia

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.

Withdrawal symptoms seen on discontinuation of SSRIs

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt.

On-set of these symptoms usually occurs within a week of discontinuation or dose reduction, and symptoms may last from a few days to three weeks. Other causes of symptoms should be excluded, e.g. re-emergence of depression.

Limited withdrawal reactions have been observed with citalopram: dizziness, headache and nausea. The withdrawal effects are mild and self-limiting.

It is recommended that discontinuation of treatment should be proceeded by tapering off the dosage over one to two weeks to avoid occurrence of withdrawal symptoms. These symptoms are not indicative of dependence.

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 (see FURTHER INFORMATION). 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.

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). 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.

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.

Use in Pregnancy

Citalopram should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under close supervision of a physician.

Animal studies have not shown any evidence of teratogenic potential and citalopram does not affect reproduction. However, epidemiological studies have suggested an increased risk of congenital abnormalities associated with the use of SSRIs and serotonin noradrenaline re-

uptake inhibitors (SNRIs) in pregnancy. 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 after the first 20 weeks of 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 reported to be about 6 to 12 per 1,000 women, compared to 1 to 2 per 1,000 women in the general population of the USA.

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.

Neonates should be observed if maternal use of citalopram had continued into the later stages of pregnancy, particularly into the third trimester. Abrupt discontinuation should be avoided during pregnancy.

Use in Lactation

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

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.

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.

ADVERSE EFFECTS

Adverse effects observed with citalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually attenuate subsequently. The most commonly observed adverse events associated with the use of citalopram in double-blind, placebo-controlled trials and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, increased sweating, tremor, diarrhoea and ejaculation disorder. The incidence of each in excess over placebo is low.

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

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

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

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

Note: For adverse events with a frequency $\geq 5\%$ a * indicates statistically significant difference between the groups ($P < 0.05$).

SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM versus PLACEBO (N = 1083) (N = 486) (CT: F = 660; M = 423) (PL: F = 286; M = 200)	
	CITALOPRAM %	PLACEBO %
(100) SKIN AND APPENDAGES DISORDERS		
Pruritis	1.0	0.8
Rash	1.0	1.2
Sweating increased	11.3*	7.4
(200) MUSCULO-SKELETAL SYSTEM DISORDERS		
Myalgia	1.9	1.2
Arthralgia	1.8	0.8
(410) CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dizziness	10.3	10.1
Extrapyramidal disorder [#]	1.5	0.6
Headache	26.9	26.7
Paraesthesia	1.4	1.2
Tremor	8.8*	5.8
(431) VISION DISORDERS		
Vision abnormal	4.7	5.1
(432) HEARING AND VESTIBULAR DISORDERS		
Tinnitus	1.0	0.6
(500) PSYCHIATRIC DISORDERS		
Agitation	2.5	1.2
Anorexia	4.2	1.2
Anxiety	3.5	2.7
Concentration impaired	1.7	1.0
Confusion	1.4	0.6
Dreaming abnormal	0.8	1.6
Insomnia	18.8	18.9
Libido decreased	2.5	0.4
Nervousness	4.0	3.7
Somnolence	17.9*	10.3
Suicide attempt	1.3	1.2
Yawning	2.0	-
(600) GASTRO-INTESTINAL SYSTEM DISORDERS		
Abdominal pain	3.2	1.9
Abdominal pain	8.4	8.2
Constipation	7.9*	4.7
Diarrhoea	4.5	3.7
Dyspepsia	1.7	1.2
Flatulence	20.0*	12.6
Mouth dry	21.4*	13.2
Nausea	3.8	2.5
Vomiting		

(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 Pharyngitis Rhinitis Sinusitis Upper respiratory tract infection	1.7 3.2 4.6 2.4 4.9	0.8 2.5 2.9 2.9 4.1
(1300) URINARY SYSTEM DISORDERS Micturition disorders	2.3	1.9
(1410) REPRODUCTIVE DISORDERS, MALE Ejaculation disorders Impotence	5.9* 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 Back pain Chest pain Fatigue Fever Influenza-like symptoms Pain	11.5 2.0 1.2 4.9 2.3 1.0 1.3	11.7 2.3 0.6 3.3 0.4 1.0 1.3

Including: dyskinesia, dystonia, hyperkinesias, hypetonia, 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

In a thorough QT study, citalopram was found to be associated with a dose-dependent increase in the QTc interval (See Warnings – QT prolongation and Torsades de Pointes). 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 ADVERSE EFFECTS section, 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 ADVERSE EFFECTS section, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasise that, although the events reported occurred during treatment with 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.

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.

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 Disorder

Unknown: anaphylactic reaction, hypersensitivity NOS.

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.

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 & 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 edema, 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 ADVERSE EFFECTS section: angioedema, choreoathetosis, epidermal necrolysis (3 cases), erythema multiforme, hepatic necrosis (2 cases), hepatitis, cholestatic hepatitis, hyponatraemia, neuroleptic malignant syndrome, mania, pancreatitis, serotonin syndrome, spontaneous abortion, thrombocytopenia, ventricular arrhythmia, priapism, and withdrawal syndrome.

MEDICINE INTERACTIONS

MAOIs

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

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. Due to the interaction noted at a low dose of pimozole, concomitant administration of citalopram and pimozole is contraindicated (see CONTRAINDICATIONS).

Serotonergic drugs

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.

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.

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

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.

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.

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 haemostatis (NSAIDs, aspirin, warfarin, etc)

Serotonin release by platelets plays an important role in haemostatis. 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 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 (see DOSAGE AND ADMINISTRATION).

Alcohol

Neither pharmacodynamic nor pharmacokinetic interaction with alcohol has been shown. However, the combination of SSRIs and alcohol is not advisable.

Drugs that Prolong the QT interval

ECG monitoring is recommended with concomitant use of medicines that can cause QT prolongation and/or TdP (See Warnings – QT prolongation and Torsades 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.

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

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

OVERDOSAGE

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 5,200mg 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.

Gastric lavage should be carried out as soon as possible after oral ingestion.

Medical supervision is advisable.

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

PHARMACEUTICAL PRECAUTIONS

Storage

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

Shelf Life

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

MEDICINES CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

Blisters packs of 28, 56 or 84 tablets.

FURTHER INFORMATION

Citalopram 20mg Film-coated Tablets contain citalopram hydrobromide, a fine white to off-white, crystalline material. Citalopram hydrobromide is sparingly soluble in water, soluble in ethanol (96%), freely soluble in chloroform and very slightly soluble in diethylether. No polymorphic forms have been detected.

Excipients

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

Actions

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

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

In contrast to many tricyclic antidepressants and some of the newer 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.

Pharmacokinetics

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) 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.

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 μ 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 (0.08-0.3L/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

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

Preclinical safety

For comparison the recommended daily therapeutic dose is 0.3-0.9 mg/kg. Fatty infiltration of the liver was seen in male rats but not in females and was greater when citalopram was given by gavage (8 mg/kg/day for 3 months) than in a more sustained manner via the diet (32 mg/kg/day for 12 months). Citalopram (25 mg/kg/day for 28 days) given as infusion over 30 minutes did not induce signs of fatty infiltration. The fatty infiltrations, which are completely reversible, are therefore connected with excessive first-pass metabolic transformation in the male rat. This has no clinical parallel, since first-pass metabolism is modest in man. Induction of completely reversible phospholipidosis was seen in both male and female rodents receiving 60 and 120 mg/kg/day (rats, 52 weeks) and 100 and 240 mg/kg/day (mice, 26 weeks). There was no evidence of phospholipidosis in dogs. Citalopram has not shown any signs of phospholipidosis in humans. The ratio between the doses which caused phospholipidosis in rats and mice and the therapeutic dose is high (ratio rats/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.

Repeat 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.

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.

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.

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