



APO-CITALOPRAM

Citalopram hydrobromide, film coated tablets, 20mg

Presentation

APO-CITALOPRAM 20mg are white, oval, biconvex, film coated tablets, scored and engraved "20" on one side and "APO" on the other side. Each tablet typically weighs 122mg.

Uses

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

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including, 5-HT_{1A}, 5-HT₂, DA D₁ and 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 bladder disturbances, blurred vision, cardiotoxicity, dry mouth, gut disturbances, sedation 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 SSRI's, although their potency and selectivity ratios are lower than those of citalopram but higher than those of many of the newer SSRI's. 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.

The dose response curve is flat.



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Pharmacokinetics

Absorption: Absorption of citalopram is almost complete and independent of food intake (T_{max} mean 3 hours). Bioavailability from oral ingestion is approximately 80%.

Distribution: The apparent volume of distribution (Vd_{β}) is about 12-17L/kg. The plasma protein binding of citalopram and its main metabolites is below 80%.

Biotransformation: Citalopram is metabolised to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. All of the active metabolites are SSRIs, but these are weaker than the parent compound. The predominant compound in plasma is unchanged citalopram.

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

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

Use in Elderly (> 65 years): Longer half lives (1.5-3.75 days) and decreased clearance values (0.08-0.3L/min) due to a reduced metabolism rate have been shown in elderly patients. Steady state levels were about twice as high in elderly than in younger patients treated with the same dose.

Impaired Hepatic Function: In patients with reduced hepatic function, citalopram is eliminated slower. The half-life of citalopram is about twice as long and steady state citalopram concentrations as a given dose will be about twice as high in patients with normal liver function.

Impaired Renal Function: In patients with a mild to moderate reduction in renal function citalopram is eliminated slower, but this has no major impact on the pharmacokinetics of citalopram. Patients with a mean serum creatinine value of 278µmol/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 < 20mL/min).

Indications

APO-CITALOPRAM is indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.



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Dosage and Administration

APO-CITALOPRAM can be taken in the morning or evening with or without food. As the treatment result in general, can be evaluated only after 2-3 weeks treatment, a possible dose increase in 10mg increments should take place at 2-3 week intervals.

Adults

PO-CITALOPRAM 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 60mg daily.

Use in Elderly

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

Use in Children and Adolescents (under 18 years of age):

Safety and efficacy have not been established in this population. Consequently, APO-CITALOPRAM should not be used in patients under 18 years of age (see 'Warnings and Precautions').

Impaired Hepatic Function:

Patients with reduced hepatic function should receive no more than 30mg of APO-CITALOPRAM per day.

Impaired 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 < 20mL/min).

Duration of Treatment

The antidepressive effect of APO-CITALOPRAM usually sets in after 2 to 4 weeks. A treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse. Withdrawal phenomena were not reported in clinical trials. However, because other SSRIs have been associated with withdrawal phenomena the dose should be tapered over at least one week if discontinuation is contemplated.

Contraindications

APO-CITALOPRAM is contraindicated in patients with a known sensitivity to citalopram, or any of the components of this medicine.

Warnings and Precautions

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



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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 the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressive medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania 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. Although a causal link between emergence of such symptoms and either the worsening or depression and/or the 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 patients presenting symptoms.

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

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 for 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 citalopram is not approved for use in treating bipolar depression.

Monoamine Oxidase Inhibitors (MAOIs):

As with other SSRIs, APO-CITALOPRAM should not be given to patients receiving Monoamine Oxidase Inhibitors (MAOIs), or for 14 days after their discontinuation. MAOIs should not be given until 7 days after discontinuation with APO-CITALOPRAM.

Serotonin Syndrome:

"Serotonin syndrome" has been reported rarely in patients receiving SSRIs. A combination of symptoms, possibly including agitation, confusion, hyperthermia, myoclonus and tremor, may



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indicate the development of this condition (refer to “Interactions”). Sumatriptan's serotonergic effects are suspected to be enhanced by SSRIs. Until further evidence is available it is advised not to use APO-CITALOPRAM concurrently with 5-HT agonists, e.g. Sumatriptan (refer to “Interactions”).

Hyponatraemia:

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

There is little clinical experience of concurrent use of citalopram and ECT.

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 1116 patients who received citalopram in clinical trials was evaluated and the data indicated 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 to “Further Information”). Like other SSRIs, citalopram causes a small decrease in heart rate. Therefore, caution should be observed when citalopram is initiated in patients with pre-existing slow heart rate.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Therefore, caution is advised in patients taking SSRIs, especially in concomitant use with drugs known to affect platelet function (e.g. Atypical antipsychotics, phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs), as well as in patients with a history of bleeding disorders.

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 sedation, and suicidal ideation, especially early 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.

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 carcinogenic or mutagenic potential.

Use in Pregnancy and Lactation

Category C

Studies in animals have not shown any teratogenic potential and citalopram does not effect reproduction of perinatal conditions. Due to limited human data APO-CITALOPRAM should only be used during pregnancy if it is considered necessary and under the close supervision of a



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

Adverse Effects

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first 1 or 2 weeks of treatment and usually attenuate as the depressive state improves. The most commonly observed adverse effects associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were ($p=0.05$): diarrhoea, dry mouth, ejaculation disorder, increased sweating, nausea and tremor. 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 statistically significant differences between the groups were found.

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

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

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

SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM PLACEBO versus	
	(N = 1083)	(N = 486)
	CITALOPRAM PLACEBO	
	%	%
(100) SKIN AND APPENDAGES DISORDERS		
Pruritus	1.0	0.8
Rash	1.0	1.2
Sweating increased	11.3*	7.4



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SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM PLACEBO versus	
	(N = 1083)	(N = 486)
	CITALOPRAM PLACEBO %	
(200) MUSCULO-SKELETAL SYSTEM DISORDERS		
Myalgia	1.9	1.2
Arthralgia	1.8	0.8
(410) CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Dizziness	10.3	10.1
Extrapyramidal disorder ¹⁾	1.5	0.6
Headache	26.9	26.7
Paraesthesia	1.4	1.2
Tremor	8.8*	5.8

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

SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM %	PLACEBO %
(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



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SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM %	PLACEBO %
Suicide attempt	1.3	1.2
Yawning	2.0	-
(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	4.0	2.2
(CT ≤ 50 years: N = 447; PL ≤ 50 years: N = 180)		
(1810) BODY AS A WHOLE		
Asthenia	11.5	11.7
Back pain	2.0	2.3



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SYSTEM ORGAN CLASS Reaction (WHO Preferred Term)	CITALOPRAM %	PLACEBO %
Chest pain	1.2	0.6
Fatigue	4.9	3.3
Fever	2.3	0.4
Influenza-like symptoms	1.0	1.0
Pain	1.3	1.3

Dose Dependency of Adverse Events

The potential relationship between the dose of 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 60mg. Jonckheere's trend test revealed a positive dose response ($p < 0.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

Male and Female Sexual Dysfunction with SSRIs

While sexual dysfunction is often part of depression and other psychiatric disorders, there is increasing evidence that treatment with selective serotonin reuptake inhibitors (SSRIs) may induce sexual side effects. This is a difficult area to study because patients may not spontaneously report symptoms of this nature, and therefore, it is thought that sexual side effects with the SSRIs may be underestimated. In placebo-controlled clinical trials (table), the reported incidence of decreased libido for the whole population was 2.5%; ejaculation disorder (primarily ejaculatory delay), and impotence in male depressed patients receiving 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.



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Weight Changes

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

Laboratory Changes

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

ECG Changes

Electrocardiograms from citalopram (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. 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. There were no observed differences in QT or other ECG intervals.

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 Reactions 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 Reactions 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 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Skin and Appendages Disorders

Uncommon: photosensitivity reaction, urticaria, acne, eczema, skin discoloration, alopecia, dermatitis, skin dry, psoriasis.

Rare: hypertrichosis, decreased sweating, melanosis, keratitis, pruritus ani.

Musculo-skeletal 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.



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Rare: abnormal coordination, hyperesthesia, ptosis, stupor.

Vision Disorders

Common: abnormal accommodation.

Uncommon: conjunctivitis, eye pain.

Rare: mydriasis, photophobia, abnormal lacrimation, cataract, diplopia.

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.

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.

Liver and Biliary System Disorders

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

Rare: cholecystitis, cholelithiasis, bilirubinaemia, jaundice.

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, goiter, gynaecomastia.

Cardiovascular Disorders, General

Common: postural hypotension, hypotension.

Uncommon: hypertension, oedema (extremities), cardiac failure.

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.

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



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Uncommon: leucopenia, leukocytosis, lymphadenopathy.

Rare: granulocytopenia, lymphocytosis, lymphopenia.

Platelet, Bleeding & Clotting Disorders

Uncommon: purpura, epistaxis, haematoma.

Rare: pulmonary embolism, coagulation disorder, gingival bleeding.

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.

*% based on female subjects only: 2955

Body as a Whole

Uncommon: hot flushes, rigors, alcohol intolerance, syncope.

Rare: hayfever.

Other Events Observed During the Postmarketing Evaluation of Citalopram

Although no causal relationship to citalopram treatment has been found, the following adverse events have been reported to be temporally associated with citalopram treatment in at least 3 patients (unless otherwise noted) and not described elsewhere in the Adverse Reactions 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, Torsades de pointes, priapism, and withdrawal syndrome.

Interactions

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

Co-administration of a single dose of pimoziide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimoziide, although not consistently throughout the study. The co-administration of pimoziide 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 pimoziide, concomitant administration of APO-CITALOPRAM and pimoziide is contraindicated (see Contraindications).

SSRIs may theoretically interact with 5-HT agonists. Co-administration with serotonergic drugs (eg. 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.

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



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which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, tricyclic antidepressants and some SSRIs).

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, but did suggest that it is a weak inhibitor of CYP-1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on in vivo metabolism mediated by these isoenzymes. However, in vivo data to address this question are very limited.

Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4, e.g., ketoconazole, itraconazole, and macrolide antibiotics, and potent inhibitors of CYP2C19, e.g., omeprazole, might decrease the clearance of citalopram. Citalopram steady state levels were not significantly different in poor metabolisers and extensive 2D6 metabolisers after multiple dose administration of citalopram, suggesting that coadministration, with citalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism.

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

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 coadministration 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 1mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Warfarin - Administration of 40 mg/day citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

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



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Ciprofloxacin 250mg, 500mg and 750mg tablets

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, a documented enzyme inhibitor, caused a moderate increase in the average steady state levels of citalopram. It is therefore advised to exercise caution at the upper end of the dose range of citalopram when it is used concomitantly with high doses of cimetidine.

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

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. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

Overdosage

Citalopram is given to patients who are at the potential risk of suicide and some reports of attempted suicide have been received. Information is often lacking in regards to the precise dose or combination with other drugs and/or alcohol.

Symptoms:

Experience from cases considered to be due to citalopram alone comprised the following symptoms/signs: convulsions, cyanosis, drowsiness, nausea, somnolence, sweating, tachycardia, tremor, unconsciousness, vomiting and rarely ECG changes. Fatalities have been reported.

Treatment:

There is no specific antidote. Treatments should be symptomatic and supportive. Gastric lavage should be carried out as soon as possible after oral ingestion. Medical surveillance is advisable.

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

Pharmaceutical Precautions

Store below 25°C. Protect from heat, light and moisture.

Shelf life: 36 months from the date of manufacture.

Medicine Classification

Prescription Medicine



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Package Quantities

Blister packs of 120, 240 and 480 tablets

Further Information

APO-CITALOPRAM tablets contain Lactose.

Animal Toxicity

For comparison the recommended daily therapeutic dose is 0.3-0.9mg/kg. Fatty infiltration of the liver was seen in male rats but not in females and was greater when citalopram was given by gavage (8mg/kg/day for 3 months) than in a more sustained manner via the diet (32mg/kg/day for 12 months). Citalopram (25mg/kg/day for 28 days) given as an 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 60mg/kg/day and 120mg/kg/day (rats, 52 weeks) and 100mg/kg/day and 240mg/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 doses which caused phospholipidosis in rats and mice and the therapeutic dose is high (ratio rats/human 53 and ratio mice/human 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 80mg/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.

In dogs, convulsions and death occurred when plasma citalopram levels exceeded 6,000nmol/L (more than 20 times the average patient level). By preventing convulsive episodes with diazepam, intravenous infusion could be continued up to 70mg/kg resulting in plasma concentrations of up to 21,000nmol/L without indications of serious toxicity. Repeated dose toxicity studies demonstrated that fatal arrhythmias may occur at combined high levels of the didemethyl metabolite (which affects the heart) and citalopram (central nervous effects). Neither citalopram alone, nor the metabolite alone produce dangerous arrhythmias. The didemethyl metabolite, however, prolongs the QT interval – an action which can develop into fatal arrhythmia when coupled with centrally mediated effects induced by convulsive or near convulsive doses of citalopram. Fatal arrhythmias may occur in dogs simultaneously exposed to citalopram levels exceeding about 2,600nmol/L and didemethyl metabolite levels exceeding about 1,000nmol/L. However, the kinetics differ greatly between dogs and man and the didemethyl metabolite is much less prominent in man.



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Dose 40mg Citalopram per day	No. of patients in steady state	Mean (nmol/L)	SD (nmol/L)
Citalopram	2087	276	186
Dimethylcitalopram	2067	116	113
Didemethylcitalopram	2020	22	20

Pharmacokinetic data indicate that high levels of citalopram following an overdose will not be combined with immediate 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 140nmol/L was found 2-3 days after an overdose of 1200mg of citalopram and the citalopram level at that time was 1950nmol/L. The metabolite related cardiovascular findings in dogs are therefore of no concern for the clinical use of citalopram.

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