

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0577/072/001

Case No: 2024541

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Citalopram 20mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/01/2007**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 20mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s):

53.28 mg Lactose Monohydrate

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet

A white, oval film coated tablet marked with “CM scoreline 20” on one side and “G” on the other. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Citalopram is indicated for the treatment of depressive illnesses in the initial stage and as maintenance against relapse or recurrence. Citalopram is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 Posology and method of administration

For treatment of depression

- Adults:

The usual dose is 20mg citalopram once daily, with a maximum recommended dose of 60mg per day; the maximum dose will be dependent on the response of the individual patient. The dose may be taken in the morning or evening, with or without food. A treatment period of at least 6 months is recommended to give adequate protection against the possibility of a relapse.

For treatment of panic disorder:

A single dose of 10mg per day for the first week is recommended; after this the dose may be increased to 20mg per day. The dose may continue to be increased to 60mg per day depending on individual patient response. Maximum effectiveness is reached after 3 months. It may be necessary to continue treatment for several months.

- Elderly:

The recommended daily dose is 20mg. This may be increased to a maximum of 40mg.

- Children and adolescents under the age of 18:

Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (See section 4.4 Special Warnings and Special Precautions for Use).

- Patients with hepatic dysfunction should be restricted to the lower end of the dose range.

- Dosage adjustment is not necessary for patients with mild to moderate renal dysfunction. No information is available for case of final stage impairment of renal function (creatinine clearance <20mL/minute).
- Poor CYP2C19 metabolisers:
For known poor CYP2C19 metabolisers an initial dose of 10 mg daily the first two weeks of treatment is recommended. Depending on the outcome of the treatment the dose can thereafter be increased to 20 mg (see section 5.2).
- Withdrawal symptoms seen on discontinuation:
Abrupt discontinuation should be avoided. When stopping treatment with citalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

- Hypersensitivity to citalopram
- Monoamine Oxidase Inhibitors:

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

Some cases presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Citalopram should not be used in combination with a MAOI. Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

4.4 Special warnings and precautions for use

Use in children & adolescents under 18 years of age-

Citalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Diabetes – In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and or oral hypoglycaemic dosage may need to be adjusted.

Seizures: - Seizures are a potential risk with antidepressant drugs. The drug should be discontinued in any patient who develops seizures. Citalopram should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

ECT – There is little clinical experience of concurrent administration of citalopram and ECT, therefore caution is advisable.

Mania – Citalopram should be used with caution in patients with a history of mania/hypomania. Citalopram should be discontinued in any patient entering a manic phase.

Suicide/suicidal thoughts – Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists 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.

Other psychiatric conditions for which citalopram is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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

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

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

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.

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.

Withdrawal symptoms seen on discontinuation- Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects).

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 and electric shock sensations), 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 have been reported following discontinuation of SSRIs/SNRIs. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation", Section 4.2 Posology and Method of Administration).

Consideration should be given to factors which may affect the disposition of a minor metabolite of citalopram (didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in susceptible individuals. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted.

As with most antidepressants, citalopram should be discontinued if the patient enters a manic phase. There is little clinical experience of concurrent use of citalopram and ECT.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see Posology) reduces the likelihood of this effect.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2 D6 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, TCAs and some SSRIs). Protein binding is relatively low (< 80%). These properties give citalopram a low potential for clinically significant drug interactions.

Alcohol – The combination of citalopram and alcohol is not advisable. However clinical studies have revealed no adverse pharmacodynamic interactions between citalopram and alcohol.

Serotonergic drugs – 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.

Lithium & tryptophan - There is no pharmacokinetic interaction between lithium and citalopram. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. The routine monitoring of lithium levels need not be adjusted.

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. In animal studies cimetidine had little or no influence on citalopram kinetics.

Dynamic interactions between citalopram and herbal remedy St John's wort (*Hypericum perforatum*) can occur, resulting in an increase in undesirable effects.

No pharmacodynamic interactions have been noted in clinical studies in which citalopram has been given concomitantly with benzodiazepines, neuroleptics, analgesics, lithium, alcohol, antihistamines, anti-hypertensive drugs, beta-blockers and other cardiovascular drugs.

QT prolongation - Caution is warranted for concomitant use of other QT interval prolonging medicines or hypokalaemia/hypomagnesaemia inducing drugs as they, like Citalopram, also prolong the QT interval.

Seizures - 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 and butyrophenones), mefloquin, bupropion and tramadol).

Escitalopram - The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram.

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.

4.6 Pregnancy and lactation

Pregnancy – There are limited data from the use of citalopram in pregnant women. Studies in rats have shown teratogenic effects at high doses which caused maternal toxicity (see section 5.3). The potential risk for humans is unknown. Citalopram should only be used in pregnancy if considered clearly necessary.

New born infants should be observed if maternal use of citalopram continues into the later stages of pregnancy, particularly the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the new-born infant after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Lactation – Citalopram is excreted in milk in small quantities. The advantages of breastfeeding should outweigh the potential undesirable effects for the child.

4.7 Effects on ability to drive and use machines

Patients prescribed psychotropic medication may have some impairment of concentration due to the illness, the medication, or both. Patients should be cautioned about their ability to drive a car and operate machinery. Citalopram itself does not cause any impairment to intellectual function or psychomotor performance.

4.8 Undesirable effects

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, increased sweating and tremor. The incidence of each in excess over placebo is low (<10%).

Withdrawal symptoms seen on discontinuation:

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), 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 have been reported. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥ 1/1,000 to ≤ 1/100	Rare (≥1/10,000 to ≤ 1/1000)	Not Known
Metabolism and nutrition disorders		Weight decrease, weight increase			
Psychiatric disorders	Somnolence, insomnia, agitation, nervousness	Sleep, disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, confusion	Euphoria, increased libido	Suicidal thoughts/ behaviour (see section 4.4)	
Nervous system disorders	Headache, tremor, dizziness	Migraine, paraesthesia	Convulsions	Akathisia (see section 4.4). Serotonin syndrome.	Choreoathetosis
Eye disorders	Abnormal accommodation	Abnormalities of vision			
Ear and labyrinth disorders			Tinnitus		
Cardiac disorders	Palpitations	Tachycardia		Cases of QT prolongation have been reported post- marketing.	
Vascular disorders		Postural hypotension			
Respiratory, thoracic and mediastinal disorders		Rhinitis	Coughing		
Gastrointestinal disorders	Nausea, dry mouth, constipation, diarrhoea	Dyspepsia, vomiting, abdominal pain, flatulence, increased salivation			
Hepato-biliary disorders					Cholestasis
Skin and subcutaneous tissue disorders	Increased sweating	Rash, pruritus			
Musculoskeletal, connective tissue and bone disorders			Myalgia	Movement disorders	
Renal and urinary disorders		Micturition disorder, polyuria			
Reproductive system and breast disorders		Ejaculation failure, female anorgasmi, impotence			Galactorrhoea
General Disorders	Asthenia	Fatigue, taste abnormalities	Malaise		

4.9 Overdose

Citalopram is given to patients at potential risk of suicide and some reports of attempted suicide have been received. Detail is often lacking regarding precise dose or combination with other drugs and/or alcohol.

Symptoms:

Somnolence, coma, stupor, seizures, ECG changes (e.g. prolonged QT interval), atrial and ventricular arrhythmia, nausea, vomiting, transpiration, cyanosis, hyperventilation. Features of serotonin syndrome may occur, particularly when other substances are co-ingested.

Treatment:

There is no known specific antidote to citalopram. Treatment should be symptomatic and supportive. Activated charcoal, osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered. If consciousness is impaired the patient should be intubated. ECG and vital signs should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective serotonin reuptake inhibitors

ATC code: N 06A B04.

Citalopram has been demonstrated to be a potent inhibitor of serotonin (5-HT)-uptake. Long-term treatment with citalopram does not induce tolerance to the inhibition of 5-HT-uptake.

Citalopram is the most Selective Serotonin Reuptake Inhibitor (SSRI) yet described, with minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. Citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT₂, dopamine D₁ and D₂ receptors, alpha₁-, alpha₂- and beta-adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors. This is in contrast to many tricyclic antidepressants and some of the newer SSRI's. Lack of receptor affinity has been confirmed using a series of functional in vitro tests in isolated organs as well as functional in vitro tests. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

Like tricyclic antidepressants, other SSRI's and MAO inhibitors, citalopram suppresses REM –sleep and increases deep slow-wave sleep. Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics. There was potentiation of d-amphetamine-induced hyperactivity following administration of citalopram.

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites for Citalopram are higher than many of the newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.

Citalopram does not impair cognitive (intellectual function) and psychomotor performance in humans and has no or minimal sedative properties, either alone or in combination with alcohol.

A single dose study in human volunteers showed that citalopram did not reduce saliva flow and 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.

5.2 Pharmacokinetic properties

Absorption: Absorption is almost complete and independent of food intake (T_{\max} average/mean 3.8 hours). Oral bioavailability is about 80%.

Distribution: The apparent volume of distribution ($(V_d)_B$) is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

Biotransformation: Citalopram is metabolised to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma. The main metabolising enzyme is CYP2C19. Some contribution from CYP3A4 and CYP2D6 is possible.

Elimination: The elimination half-life ($T_{1/2\beta}$) is about 1.5 days and the systemic citalopram plasma clearance (Cl_s) is about 0.33 L/min, and oral plasma clearance (Cl_{oral}) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min.

The kinetics is linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 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.

Elderly patients (=65 years): Longer half lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function: Citalopram is eliminated more slowly for 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. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min).

Preclinical safety data: 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.

5.3 Preclinical safety data

In laboratory animals no evidence for a special hazard for humans was found. This is based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Phospholipidosis in several organs was observed in repeated dose toxicity studies in rats. This reversible effect is known for several lipophilic amines and was not connected with morphological and functional effects. The clinical relevance is not clear.

Embryotoxicity studies in rats have shown skeletal anomalies at maternal toxic doses. The effects may be related to the pharmacological activity or could be an indirect effect due to maternal toxicity. Peri- and postnatal studies have revealed reduced survival in offspring during the lactation period. The potential risk for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Lactose monohydrate

Maize Starch

Microcrystalline Cellulose

Povidone

Crospovidone

Magnesium Stearate

Tablet Coat

Titanium Dioxide (E171)

Lactose monohydrate

Macrogol 4000

Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVdC blisters sealed with aluminium foil (also includes unit dose packs). Pack sizes of 12, 14, 20, 28, 30, 49, 50, 56, 60, 98, 100 or 500 tablets.

PVC/PVdC blisters sealed with aluminium foil. Calendar pack size of 28 tablets.

High Density Polyethylene (HDPE) tablet containers with polypropylene (PP) caps. Pack sizes of 12, 14, 20, 28, 50, 100 or 250 tablets.

Polypropylene tablet containers with polyethylene caps. Pack sizes of 12, 14, 20, 28, 50, 100 or 250 tablets.

Not all pack sizes may be available.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 577/72/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th October 2005
Date of last renewal: 9th January 2007

10 DATE OF REVISION OF THE TEXT

August 2007