

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Seropram

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg as citalopram hydrobromide.

Excipients with known effect: Lactose monohydrate.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, oval, scored, film-coated tablet marked "C" and "N" symmetrically around the score. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

"Major depression (ICD-10: *Moderate to severe depressive episodes*), including prevention of periodic depression".

Panic disorder.

4.2 Posology and method of administration

Posology

Depression

Adults:

Seropram should be administered as a single oral dose of 20 mg daily.

Depending on individual patient response, the dose may be increased to a maximum of 40 mg once daily.

Panic disorder:

Adults:

A single oral dose of 10 mg is recommended for the first week before increasing the dose to 20 mg daily. Depending on individual patient response, the dose may be increased to a maximum of 40 mg once daily.

Documentation is scarce as regards efficacy after more than 3-6 months of treatment.

Elderly patients (> 65 years of age):

For elderly patients the dose should be decreased to half of the recommended dose, e.g. 10-20 mg daily. The recommended maximum dose for the elderly is 20 mg daily.

Children and adolescents under the age of 18 years:

Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Reduced renal function:

Usual dosage may be administered in patients with mild to moderate renal impairment. No clinical experience is available in patients with severely reduced renal function (creatinine clearance < 20 ml/min), and caution should be exercised.

Reduced hepatic function:

An initial dose of 10 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function (see section 5.2).

Poor metabolisers of CYP2C19

An initial dose of 10 mg daily during the first two weeks of treatment is recommended to patients who are known to be poor metabolisers with respect to CYP2C19. The dose may be increased to a maximum of 20 mg daily depending on individual patient response (see Section 5.2).

Duration of treatment:

The antidepressant effect and the effect on panic disorder usually set in after 2 to 4 weeks of treatment. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time, usually up to six months or more after recovery, in order to prevent relapse.

Discontinuation symptoms seen when stopping SSRI treatment

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 discontinuation symptoms (see Sections 4.4 and 4.8). 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.

Method of administration:

Seropram is administered as one daily dosage. Seropram may be taken at any time of the day with or without food.

4.3 Contra-indications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.
- Concomitant treatment with linezolid, unless there are facilities for close observation and monitoring of blood pressure (see Section 4.5).
- Concomitant treatment of citalopram and selegilin (in doses exceeding 10 mg daily) (see Section 4.5).

- Citalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.
- Citalopram is contraindicated together with medicinal products that are known to prolong the QT interval (see section 4.5).
- Concomitant treatment with pimozide (see Section 4.5).

MAOIs (monoamine oxidase inhibitors)

Some cases presented with features resembling serotonin syndrome.

Citalopram should not be given to patients receiving Monoamine Oxidase Inhibitors (MAOIs) (including selegiline) in daily doses exceeding 10 mg/day.

Citalopram should not be given for fourteen days after discontinuation of an irreversible MAOI or for the time specified after discontinuation of a reversible MAOI (RIMA) as stated in the prescribing text of the RIMA. MAOIs should not be introduced for seven days after discontinuation of citalopram (see section 4.5).

4.4 Special warnings and precautions for use

Treatment of elderly patients and patients with functions, see section 4.2.

Use in children and adolescents under 18 years of age

Antidepressants should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately 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.

Paradoxical anxiety

Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect (see section 4.2).

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs and generally reverse on discontinuation of therapy. Elderly female patients seem to be at particularly high risk.

Suicide/suicidal thoughts or clinical worsening

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 Seropram 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, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared with placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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.

Mania

In patients with manic-depressive illness a change towards the manic phase may occur. Should the patient enter a manic phase citalopram should be discontinued

Seizures

Seizures are a potential risk with antidepressant drugs. Citalopram 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.

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Serotonin syndrome

In rare cases, serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus, and hyperthermia may indicate the development of this condition. Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines

Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as triptans (including sumatriptan and oxitriptan), opioids (including tramadol) and tryptophan.

Haemorrhage

There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings with SSRIs (see section 4.8). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking SSRIs, particularly with concomitant use of active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see Section 4.5).

ECT (electroconvulsive therapy)

There is limited clinical experience of concurrent administration of SSRIs and ECT; therefore caution is advisable.

St. John's Wort

Undesirable effects may be more common during concomitant use of citalopram and herbal preparations containing St John's wort (*Hypericum perforatum*). Therefore citalopram and St John's wort preparations should not be taken concomitantly (see section 4.5).

Adjustment of dosage when initiating treatment

In the early treatment phase the patient may suffer from insomnia and restlessness which may be relieved by adjusting the dosage administered.

Psychosis

When treating psychotic patients suffering from depressive episodes the psychotic symptoms may increase.

Sexual dysfunction

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

Discontinuation symptoms seen when stopping SSRI treatment Discontinuation symptoms when stopping treatment are common,, particularly if discontinuation is abrupt (see section 4.8). In a recurrence prevention clinical trial with citalopram, adverse events after discontinuation of active treatment were seen in 40% of patients versus 20% in patients continuing citalopram.

The risk of discontinuationsymptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

The symptomsusually 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 transient 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 of SSRI, Section 4.2).

QT interval prolongation

Citalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1).

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with citalopram is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac arrhythmia occur during treatment with citalopram, the treatment should be withdrawn and an ECG should be performed.

Angle-Closure Glaucoma

SSRIs including citalopram may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Citalopram should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma

Hypersensitivity to lactose

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and medicinal products of interaction

PHARMACODYNAMIC INTERACTIONS

Contraindicated combinations

MAO inhibitors (monoamine oxidase inhibitors)

Concomitant treatment with MAO inhibitors are contraindicated (both non-selective and selective MAO-A (moclobemide)) due to the risk of severe undesirable effects including serotonin syndrome (see Section 4.3).

Serious and sometimes fatal reactions have been reported in patients treated with an SSRI concomitantly with an MAO inhibitor, including the irreversible MAO inhibitor selegiline and the reversible MAO inhibitors linezolid and moclobemide and in patients who have recently finalised an SSRI treatment and have initiated a treatment with an MAO inhibitor. In some cases symptoms corresponding to serotonin syndrome have been reported. Symptoms of an active substance 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 (see Section 4.3).

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between citalopram and other medicinal products that prolong the QT interval have not been performed. An additive effect of citalopram and these medicinal products cannot be excluded. Therefore, co-administration of citalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. fentiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.

Pimozide

Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QT_c interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Selegiline (selective MAO-B inhibitor)

A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered citalopram (20 mg daily) and selegiline 10 mg daily (a selective MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10 mg daily) is contraindicated (see section 4.3).

Combinations requiring precaution for use

Serotonergic medical products

Co-administration with serotonergic drugs may cause serotonin syndrome.

Lithium and tryptophan

No pharmacodynamic interactions have been found in clinical studies in which citalopram has been given concomitantly with lithium. 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 medical products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

Concomitant administration of serotonergic medical products e.g. opioids (including tramadol) and triptans (including sumatriptan and oxitriptan) may lead to enhancement of

5-HT associated effects.

Until further information is available, the simultaneous use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

St John's wort

Dynamic interactions between SSRIs and herbal remedies containing St John's wort (*Hypericum perforatum*) can occur, resulting in an increase in undesirable effects (see Section 4.4). Pharmacokinetic interactions have not been investigated.

Haemorrhage

Caution is warranted for patients who are being treated simultaneously with anticoagulants, medicinal products that affect the platelet function, such as non steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, dipyridamol, and ticlopidine or other medicines (e.g. atypical antipsychotics,) that can increase the risk of haemorrhage (see section 4.4).

ECT (electroconvulsive therapy)

There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and citalopram (see section 4.4).

Alcohol

No pharmacodynamic or pharmacokinetic interactions have been demonstrated between citalopram and alcohol. However, the combination of citalopram and alcohol is not advisable.

Medicinal products inducing hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias (see section 4.4)

Medicinal products lowering the seizure threshold

SSRIs may lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g antidepressants [SSRIs], neuroleptics [thioxanthenes and butyrophenones], mefloquin, bupropion and tramadol).

PHARMACOKINETIC INTERACTIONS

The metabolism of citalopram to demethyl citalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%) isozymes of the cytochrome P450 system. The fact that citalopram is metabolised by more than one CYP means that inhibition of its biotransformation is less likely as inhibition of one enzyme may be compensated by another. Therefore co-administration of citalopram with other medicinal products in clinical practice has very low likelihood of producing pharmacokinetic drug interactions in clinical practice.

Food

The absorption and other pharmacokinetic properties of citalopram have not been reported to be affected by food.

EFFECT OF OTHER MEDICINAL PRODUCTS ON THE PHARMACOKINETICS OF CITALOPRAM

Co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of citalopram.

A pharmacokinetic interaction study of lithium and citalopram did not reveal any pharmacokinetic interactions (see also above).

Cimetidine (a potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram. Caution is advised when administering citalopram in combination with cimetidine.

Coadministration of escitalopram (the active enantiomer of citalopram) 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, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. Dose adjustment may be warranted.

No pharmacokinetic interactions due to plasma protein binding are expected.

EFFECTS OF CITALOPRAM ON OTHER MEDICINAL PRODUCTS

A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram and metoprolol (a CYP2D6 substrate) showed a twofold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and heart rate in healthy volunteers. Caution is recommended when metoprolol and citalopram are co-administered. Dose adjustment may be warranted.

Citalopram is a weak inhibitor of CYP2D6. Caution is recommended when citalopram is coadministered with medicinal products that are mainly metabolised by CYP2D6, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol.

Caution should be exercised when citalopram is administered with antidepressants (e.g. clomipramine, imipramine, nortriptyline and amitriptyline) or antipsychotics (e.g. risperidone, thioridazine and haloperidol) that are mainly metabolised by CYP2D6. Dose adjustment may be warranted.

Citalopram and demethyl citalopram are insignificant inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2 and CYP2C19 as compared with other SSRIs established as significant inhibitors.

Levomepromazine, digoxin, carbamazepine

No change or only very small changes of clinical importance were observed when citalopram was given with CYP1A2 substrates (clozapine and theophylline), CYP2C9 (warfarin), CYP2C19 (imipramine and mephenytoin), CYP2D6 (sparteine, imipramine, amitriptyline, risperidone) and CYP3A4 (warfarin, carbamazepine (and its metabolite carbamazepine epoxid) and triazolam).

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induce nor inhibit P-glycoprotein).

Desipramine, imipramine

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. When desipramine is combined with citalopram, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Published data on pregnant women (more than 2500 exposed outcomes) indicate no malformative fetoneonatal toxicity.

However, citalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of risk/benefit.

In reproductive toxicity studies (segments I, II and III) no signs of fetotoxic or teratogenic effects were found. However, in 1 study (not in repeated study) performed in rats, teratogenic effects were observed in high doses causing maternal toxicity (see Section 5.3). The potential risk in humans is unknown.

Using SSRIs in the third trimester may result in e.g. neurobehavioral disturbances in the newborn infant.

Cases of withdrawal symptoms have been reported in neonates if the mother has been treated with SSRIs during the later stages of pregnancy.

The following symptoms may occur in the neonates 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 discontinuation symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

The neonate should be observed if the mother has continued her citalopram treatment during the later stages of pregnancy. Abrupt discontinuation should be avoided during pregnancy.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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

Lactation:

Should not be used when breast feeding. Citalopram is excreted into breast milk. The dose ingested by the sucking infant is estimated to be approx. 5% of the daily maternal dose (in mg/kg). Only few or no side effects have been observed in neonates, but the existing data are insufficient to estimate the risk to the infant.

Fertility

Animal data have shown that citalopram may affect sperm quality (see section 5.3).

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

Citalopram has minor or moderate influence on the ability to drive and use machines.

Psychoactive medicinal products can reduce the ability to make judgements and to react to emergencies. Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 Undesirable effects

Adverse reactions are most frequent during the first 1 to 2 weeks of treatment and most adverse events usually disappear with continued treatment.

A dose-response relationship has been observed for the following adverse events: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue. The table shows the percentage of adverse drug reactions associated with SSRIs and/or citalopram seen in either $\geq 1\%$ of patients in double-blind, placebo-controlled trials or seen as post-marketing events. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $\leq 1/100$); rare ($\geq 1/10000$ to $\leq 1/1000$); very rare ($\leq 1/10000$), not known (cannot be estimated from available data).

System organ class	Frequency	Undesirable effect
Blood and lymphatic disorders	Not Known	Thrombocytopenia
Immune system disorders	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Hypersensitivity
	Very rare ($< 1/10,000$)	Anaphylactic reaction
Endocrine disorders	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Vasopressin hypersecretion (Schwartz-Bartters syndrome/SIADH).
Metabolism and nutrition disorders	Common	Appetite decreased, weight decreased, appetite increased.
	Uncommon	weight increased
	Rare	Hyponatraemia
	Not Known	Hypokalaemia
Psychiatric disorders	Very common	Agitation, nervousness.
	Common	Libido decreased, anorgasmia (female), anxiety, confusion, apathy, impaired concentration, abnormal dreams, memory impairment.
	Uncommon	Aggression, depersonalization, hallucinations,

		mania, euphoria, libido increased.
	Not Known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour ¹
Nervous system disorders	Very common	Somnolence, insomnia, tremor, dizziness, headache
	Common	Paraesthesia, sleep disorders, migraine, dysgeusia, disturbance in attention
	Uncommon	Syncope, convulsions, extrapyramidal disorders.
	Rare	Seizures (grand mal), dyskinesia, Psychomotor restlessness/akathisia (see section 4.4) .
	Not Known	Serotonin syndrome, movement disorders.
Eye disorders	Very common	Accommodation abnormal
	Common	Vision abnormal
	Uncommon	Mydriasis
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Very common	Palpitations
	Common	Tachycardia
	Uncommon	Bradycardia
	Not Known	Electrocardiogram QT prolonged, ventricular arrhythmia including torsade de pointes
Vascular disorders	Common	Hypotension, hypertension, orthostatic hypotension.
	Rare	Haemorrhage
Respiratory thoracic and mediastinal disorders	Common	Yawning, rhinitis, sinusitis
	Uncommon	Coughing
	Not Known	Epistaxis (nose-bleeding).
Gastrointestinal disorders	Very common	Dry mouth, nausea, constipation
	Common	Diarrhoea vomiting, dyspepsia, stomach ache, flatulence.
	Not Known	Gastro-intestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis
	Not Known	Liver function test abnormal
Skin and	Very common	Sweating increased

subcutaneous tissue disorders	Common	Pruritus,rash.
	Uncommon	Urticaria, alopecia, purpura, photosensitivity.
	Very rare	Angioedemas.
	Not Known	Ecchymosis.
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Common	Dysuria
	Uncommon	Urinary retention
Reproductive system and breast disorders	Common	Impotence, ejaculation disorders, ejaculation failure, dysmenorrhea.
	Uncommon	Female: Menorrhagia
	Very rare	Galactorrhoea
	Not Known	Female: Metrorrhagia, portpartum haemorrhage ²⁾ Male: Priapism,
General disorders and administration site conditions	Very common	Asthenia
	Common	Fatigue,pyrexia
	Uncommon	Oedema, malaise

Number of patients: citalopram / placebo = 1346 / 545

¹ Cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).

² This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

QT Prolongation

Cases of QT prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

Class effect – Bone Fractures

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Discontinuation symptoms seen when stopping SSRI treatment

Discontinuation of Citalopram (particularly when abrupt) often leads to discontinuation symptoms.

Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor,

confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally, these 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 Sections 4.2 and 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to Pharmaceutical Services, Ministry of Health, CY-1475, website: www.moh.gov.cy/phs Fax: + 357 22608649

4.9 Overdose

Toxicity

Clinical data on citalopram overdose are limited, and many cases involve concomitant overdoses of other drugs/alcohol. Fatal cases of citalopram overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medications.

Symptoms

The following symptoms have been reported in overdose cases of citalopram: convulsions, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, hypertension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, and atrial and ventricular arrhythmia.

Treatment

There is no 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.

ECG monitoring is advisable in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification

N 06 AB 04. Antidepressants, selective serotonin reuptake inhibitors.

5.1 Pharmacodynamic properties

Citalopram is a potent and the most selective serotonin (5-HT) re-uptake inhibitor (SSRI) with no, or minimal, effect on the reuptake of noradrenaline, dopamine, and gamma aminobutyric acid (GABA).

Citalopram has no or very low affinity to a number of receptors including 5-HT_{1A}, 5-HT₂, DA

D₁ and D₂ receptors α₁-, α₂-, β-adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors.

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

The main metabolites of citalopram are all SSRIs, although their potency is lower than that of citalopram. The metabolites do not contribute to the overall antidepressant effect.

Citalopram does not impair the cognitive / intellectual function and the psychomotor performance and has no, or minimal, sedative properties.

In studies with healthy volunteers citalopram had no influence on cardiovascular parameters.

Citalopram has no influence on the serum levels of prolactin and growth hormone.

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 7.5 (90%CI 5.9-9.1) msec at the 20 mg/day dose and 16.7 (90%CI 15.0-18.4) msec at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

5.2 Pharmacokinetic properties

Absorption

Citalopram tablets are quickly absorbed (T_{max} mean after approx. 3 hours), almost completely and independently of food intake. Oral bioavailability is about 80%.

Distribution

The apparent volume of distribution (V_d)_β is approx. 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 and 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. The concentrations of demethylcitalopram and didemethylcitalopram are usually 30-50% and 5-10% of the citalopram concentration, respectively. The biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31 %) and CYP2D6 (approx.31 %).

Elimination

The elimination half-life (T_{1/2β}) is approx. 1½ days; systemic plasma clearance (Cl_s) is approx. 0.33 L/min, and oral plasma clearance (Cl_{oral}) is approx. 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 is about 0.068 L/min.

Linearity

The kinetics is linear. Steady-state plasma levels are achieved in 1-2 weeks. Average plasma concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg.

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 in patients with reduced hepatic function. The half-life of citalopram is about twice as long, and steady-state plasma concentrations at a given dose will be about twice as high as in patients with normal hepatic function.

Reduced renal function

Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function after administration of a single dose of 20 mg. However, this has no significant influence on the kinetics of citalopram. At present no information is available as regards the treatment of patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Polymorphism

In vivo investigations have shown that the metabolism of citalopram exhibits no clinically important polymorphism of the sparteine/debrisoquine oxidation (CYP2D6). For CYP2C19, as a precaution, an initial dose of 10 mg should be considered for known poor metabolisers of CYP2C19 (see Section 4.2).

5.3 Preclinical safety dataAcute toxicity

Citalopram has low acute toxicity.

Chronic toxicity

In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram.

Reproduction studies

Based on data from reproduction toxicity studies (segments I, II, and III) there is no reason to have special concern for the use of citalopram in women of childbearing age.

Embryotoxicity studies in rats with doses of 56 mg/kg/day, which cause maternal toxicity showed bone anomalies in the region of the vertebral column and ribs. The maternal plasma level was then 2-3 times the therapeutic concentration in man. In rats citalopram did not have any effect on fertility, pregnancy and postnatal development but diminished the birth weight of the pups. Citalopram and its metabolites reach foetal concentrations, which are 10-15 times the maternal plasma level

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

Mutagenic and carcinogenic potential

Citalopram has no mutagenic or carcinogenic effect

6. PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Tablet core:

Maize starch. Lactose monohydrate. Cellulose, microcrystalline. Copovidone. Glycerol (85 per cent). Croscarmellose sodium. Magnesium stearate.

Coating:

Hypromellose 5. Macrogol 400. Titanium dioxide (E 171).

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

7 and 14 tablets in PVC/PVdC blister with aluminium foil.

6.6 Instructions for use and handling

Packaging material and any unused medicinal product should be returned to the pharmacy or disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lundbeck Hellas A.E.

Spyrou Kyprianou, 20 CHAPO CENTRAL, 3rd floor P.C 1075, Nicosia, Cyprus

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