SUMMARY OF PRODUCT CHARACTERISTICS

AUROPRAM

Citalopram Hydrobromide Tablets 10 mg, 20 mg & 40 mg

RX Only

1. NAME OF DRUG PRODUCT: Citalopram Hydrobromide Tablets 10 mg
Citalopram Hydrobromide Tablets 20 mg
Citalopram Hydrobromide Tablets 40 mg

(TRADE) NAME OF PRODUCT: AUROPRAM 10
AUROPRAM 20
AUROPRAM 40

STRENGTH: 10 mg, 20 mg & 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Citalopram Hydrobromide Tablets 10 mg:
Each film-coated tablet contains Citalopram Hydrobromide equivalent to 10 mg of Citalopram base.
Excipients with known effect:
Each film-coated tablet contains 22.86 mg lactose monohydrate.
Citalopram Hydrobromide Tablets 20 mg:
Each film-coated tablet contains Citalopram Hydrobromide equivalent to 20 mg of Citalopram base.
Excipients with known effect:
Each film-coated tablet contains 45.72 mg lactose monohydrate.
Citalopram Hydrobromide Tablets 40 mg:
Each film-coated tablet contains Citalopram Hydrobromide equivalent to 40 mg of Citalopram base.
Excipients with known effect:
Each film-coated tablet contains 91.44 mg lactose monohydrate.

3. PHARMACEUTICAL FORM

Film Coated Tablets
Citalopram Hydrobromide Tablets 10 mg: White coloured, biconvex, round shaped film coated tablets debossed with ‘A’ on one side and ‘05’ on the other side.

Citalopram Hydrobromide Tablets 20 mg: White coloured, biconvex, capsule shaped film coated tablets debossed with 'A' on one side and with a score line in between '0' and '6' on the other side.

Citalopram Hydrobromide Tablets 40 mg: White coloured, biconvex, capsule shaped film coated tablets debossed with 'A' on one side and with a score line in between '0' and '7' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Citalopram is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 Posology and method of administration

Citalopram should be administered as a single oral dose, either in the morning or in the evening. The tablets can be taken with or without food, but with fluid.
Following treatment initiation, an antidepressant effect should not be expected for at least two weeks. Treatment should continue until the patient has been free of symptoms for 4-6 months. Citalopram should be withdrawn slowly, it is advised that the dose is gradually reduced over a period of at least one to two weeks.

Adults

The recommended starting dose is 20 mg citalopram per day. If necessary, the dose can be increased to a maximum of 40 mg per day, depending on the individual response of the patient.

Older people (>65 years of age)

For older people the dose should be decreased to half of the recommended dose, e.g 10-20 mg per day. Depending on the individual response of the patient, the dose can be increased to a maximum of 20 mg/day.

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).

Reduced renal function

Dosage adjustment is not required if the patient has mild to moderate renal impairment. No information is available on treatment of patients with severe renal impairment (creatinine clearance less than 20 ml/min).

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 regarding CYP2C19

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 of SSRI

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 and section 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 section4.5).

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).

Citalopram is contraindicated in the combination with linezolid unless there are facilities for close observation and monitoring of blood pressure (see section 4.5).

4.4 Special warnings and precautions for use

Treatment of older people and patients with reduced kidney and liver function, 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 (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.

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. Older female people 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.

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 to 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.

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.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment

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

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation of citalopram" section 4.2).

Diabetes

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

ECT (electroconvulsive therapy)

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

Haemorrhage

There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymosis, gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings with SSRIs (see section 4.8).Caution is advised in patients taking SSRIs, particularly in concomitant use with 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).

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

Serotonin syndrome

In rare cases a 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 sumatriptan or other triptans, tramadol, oxitriptan and tryptophan.

Psychosis

Treatment of psychotic patients with depressive episodes may increase psychotic symptoms.

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).

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 hypokalaemia, 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.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

At the pharmacodynamic level cases of serotonin syndrome with citalopram and moclobemide and buspirone have been reported.

Contraindicated combinations

MAO-inhibitors

The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including the serotonin syndrome (see section 4.3).

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

Some cases presented with features resembling serotonin syndrome. Symptoms of an active substance interaction with a MAOI include: agitation, tremor, myoclonus, and hyperthermia.

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. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), 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 QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Combinations requiring precaution for use

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).

Serotonergic medicinal products

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 medicinal products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

Co administration with serotonergic medicinal products (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HTassociated 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).

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).

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 can 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 butyrophenones], mefloquin, bupropion and tramadol).

St. John's Wort
Dynamic interactions between SSRIs and herbal remedy 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.

ECT (electroconvusive 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.

Pharmacokinetic interactions
Biotransformation of citalopram to demethylcitalopram 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 medicinal product interactions.

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

Influence 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 in the average steady-state citalopram levels. Caution is when administering citalopram in combination with cimetidine. Dose adjustment may be warranted.
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, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine.
Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when citalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have an arrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted. Co-administration with metoprolol resulted in a twofold increase in the plasma levels of metoprolol, but did not statistically significant increase the effect of metoprolol on the blood pressure and cardiac rhythm.

Effects of citalopram on other medicinal products
A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram and metoprolol (aCYP2D6 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.
Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6 as compared to other SSRIs established as significant inhibitors.
Thus no change or only very small changes of no 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).
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 Pregnancy and lactation

Pregnancy

Published data on pregnant women (more than 2500 exposed outcomes) indicate no malformative feto/ neonatal toxicity. However, citalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/ benefit.

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

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1,000 pregnancies. In the general population 1 to 2 cases of PPHN per 1,000 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

Citalopram is excreted into breast milk. It is estimated that the suckling infant will receive about 5% of the weight related maternal daily dose (in mg/kg). No or only minor events have been observed in the infants. However, the existing information is insufficient for assessment of the risk to the child. Caution is recommended.

Male 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 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 either due to the illness itself, the medication or both and should be cautioned about their ability to drive a car and operate machinery.

4.8 Undesirable effects

Adverse reactions observed with citalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually attenuate subsequently. The adverse reactions are presented at the MedDRA Preferred Term Level.

For the following reactions a dose-response was discovered: 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 ≥ 1%of patients in double-blind placebo-controlled trials or in the post-marketing period.

	very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**uncommon (≥ 1/1,000 to < 1/100)**	**rare (≥ 1/10,000 to <1/1,000)**	**not known (frequency cannot be estimated from available data)**
Blood and lymphatic system disorders					
					Thrombocytopeni
Immune system disorders					
					Hypersensitivi Anaphylactic reaction
Endocrine disorders					
					inappropriate AI secretion
Metabolism and nutrition disorders					
		Appetit decreased, wei decreased	increase appetite weigh increased	hyponatrem	hypokalaemia
Psychiatric disorders					

		agitatio nervousness, sle disorder abnormal dreams amnesia, anxie decreased libi anorexia, apat confusional sta abnormal orga (female)	Aggressio depersonalis tion, euphori increase libido, hallucinatio mania		bruxism restlessness, pa attack, suicic ideation, suicic behaviour*
Nervous system disorders					
	Headache, Somnolence, insomnia,	tremor, dizzine migraine paraesthesi disturban inattention	syncope	Convulsior grandma dyskinesia tast disturbance	convulsion seroton syndrom extrapyramic disorder, akathis movement disord
Eye disorders					
	Abnorma accommodation		mydriasis		visual disturbanc
Ear and labyrinth disorders					
		tinnitus			
Cardiac disorders					
	Palpitations		Bradycardia achycardia		Electro cardiogra QT prolonge ventricul arrhythmia including torsa de pointes
Vascular disorders					
		hypotension, hypertension		Haemorrha e	orthostat hypotension,
Respiratory, thoracic and mediastinal disorders					
		rhinitis, sinusit yawning	coughing		epistaxis
Gastrointestinal disorders					
	nausea, dry mouth,	dyspepsi vomiting abdominal pa flatulenc increase salivatio constipatio diarrhoea			
Hepatobiliary disorders					

				hepatitis	liver function t abnormal
Skin and subcutaneous tissue disorders					
	Increase sweating	Pruritus	urticaria alopecia rash, purpur photo sensitivit reaction		ecchymosi angiodemas
Musculoskeletal and connective tissue disorders					
		Myalgia, arthralg			
Renal and urinary disorders					
		Micturition disord polyuria	urinar retention		
Reproductive system and breast disorders					
		ejaculation failu ejaculatio disorder, fema anorgasmi dysmenorrhoe impotence	female menorrhagia		Postpartu haemorrhage[2] female metrorrhagia male: priapis galactorrhoea
General disorders and administration site conditions					
	asthenia	fatigue, tasteabnormalitie	oedema malaise	pyrexia	

* 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, 4.6).

Class effects

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.

QT interval 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 hypokalaemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via TMDA ADR reporting tool; website: https://imis.tmda.go.tz/arrt or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store";

Withdrawal symptoms seen on discontinuation of SSRI treatment

Discontinuation of citalopram (particularly when abrupt) commonly leads to withdrawal 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 section 4.2 and section 4.4).

4.9 Overdose

Toxicity

Comprehensive 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 seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT interval prolongation, coma, vomiting, tremor, hypotension, 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.

Management

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.

ECG monitoring is advised 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant, Selective serotonin reuptake inhibitors.

ATC code: N06A B04

Citalopram is a potent inhibitor of 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 SSRI's, citalopram has not very low affinity for a series of receptors including 5-HT $_{1A,}$ 5-HT $_{2}$, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. 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.

Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Like tricyclic antidepressants, other SSRI's and MAO inhibitors, citalopram suppresses REM-sleep and increases deep slow-wave sleep.

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 are higher than those of 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 and has no or minimal sedative properties, either alone or in combination with alcohol.

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 $(V_d)_\beta$ is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

Biotransformation

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

Elimination

The elimination half-life ($T_{½\beta}$) 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 are 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 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 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.

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 high maternal toxic doses. The effects could possibly be related to the pharmacological activity or could be an indirect effect to maternal toxicity. Peri- and postnatal studies have revealed reduced survival in offspring during the lactation period. The potential risk for humans is unknown. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Lactose monohydrate, Maize starch, Copovidone, Croscarmellose sodium, Cellulose microcrystalline and Magnesium stearate

Tablet film coat: Opadry White 03B58902 (Contains Hypromellose, Macrogol 400 & Titanium dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30ºC

6.5 Nature and contents of container

PVC/PVdC/ Aluminium blisters in a carton of pack size 2x14 film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited.,

Plot No.: 2, Maitrivihar,

Ameerpet, Hyderabad-500 038,

Telangana State, India.

8. Marketing authorisation number (s)

TAN 21 HM 0332

9. Date of first authorisation

2021-08-20

10. date of revision of the text