SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Citalopram Sandoz 40 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of citalopram (as hydrobromide)

Excipient with known effect
*E*ach film-coated tablet contains 43.7 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

White, oblong, biconvex film-coated tablet, scored on one side and embossed C40

The film-coated tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

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 Citalopram should be withdrawn slowly, it is advised that the dose is gradually reduced over a period of at least one to two weeks.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.
Elderly (>65 years of age)
For elderly 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 .

Renal impairment
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).

Hepatic impairment
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 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.

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 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).

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

Elderly
Caution should be used in the treatment of elderly patients (see section 4.2).

Renal and hepatic impairment
Caution should be used in the treatment of 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. 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.

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 medicinal products 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 pharmacotherapy 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 medicinal products. 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 medicinal products

Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as triptans (including sumatriptan and oxitriptan), opioids (including tramadol and buprenorphine) and tryptophan due to the risk of serotonin syndrome.

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.

Citalopram contains lactose and sodium

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

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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 an 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 derviatives, 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 Cmax 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. opioids (including tramadol and buprenorphine) 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).

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 medicinal products (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 moderate increase in the average steady-state citalopram levels. Caution is when administering citalopram in combination with cimetidine. Dose adjustment may be warranted.

Omeprazole and other CYP2C19 inhibitors
Co-administration 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.

Metoprolol
Caution is recommended when citalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow 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 (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.

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.

Levomepromazine, digoxin, and carfbamezaphine
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 induces nor inhibits 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 Fertility, 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).

Breast-feeding
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.

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 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. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10000 to ≤ 1/1000); very rare (≤ 1/10000), not known (cannot be estimated from available data).

	very common (≥1/10)	**common (≥1/100, < 1/10)**	**uncommon (≥1/1,000, < 1/100)**	**rare (≥1/10,000, ≤1/1,000)**	**not known (frequency cannot be estimated from available data)**
Blood and lymphatic system disorders					thrombocytopenia
Immune sytem disorders					hypersensitivity, anaphylactic reaction
Endocrine disorders					inappropriate ADH secretion Hyperprolactinaemia
Metabolism and nutrition disorders		appetite decreased, weight decreased	increased appetite, weight increased	hyponatremia	hypokalaemia

	very common (≥1/10)	**common (≥1/100, < 1/10)**	**uncommon (≥1/1,000, < 1/100)**	**rare (≥1/10,000, ≤1/1,000)**	**not known (frequency cannot be estimated from available data)**
Psychiatric disorders		agitation, nervousness, sleep disorders, abnormal dreams, amnesia, anxiety, decreased libido, anorexia, apathy, confusional state, abnormal orgasm (female)	Aggression, depersonalisa -tion, euphoria, increased libido, hallucination, mania		bruxism, restlessness,panic attack, suicidal ideation, suicidal behavior*

	very common (≥1/10)	**common (≥1/100, < 1/10)**	**uncommon (≥1/1,000, < 1/100)**	**rare (≥1/10,000, ≤1/1,000)**	**not known (frequency cannot be estimated from available data)**
Nervous system disorders	headache, somnolence, insomnia,	tremor, dizziness, migraine, paraesthesia, disturbance in attention	syncope	Convulsions grand mal, dyskinesia, taste disturbance,	convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	abnormal accommo-dation		mydriasis		visual disturbance
Ear and labyrinth disorders		tinnitus			
Cardiac disorders	palpitations		Bradycardia tachycardia		Electrocardiogram QT prolonged, ventricular arrhythmias including torsade de pointes
Vascular disorders		hypotension, hypertension		Haemorrhage	orthostatic hypotension,
Respiratory, thoratic and mediastinal disorders		rhinitis, sinusitis, yawning	coughing		epistaxis

	very common (≥1/10)	common (≥1/100, < 1/10)	uncommon (≥1/1,000, < 1/100)	rare (≥1/10,000, ≤1/1,000)	not known (frequency cannot be estimated from available data)
Gastrointestinal disorders	nausea, dry mouth,	dyspepsia, vomiting, abdominal pain, flatulence, increased salivation, constipation, diarrhoea			Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders				hepatitis	liver function test abnormal
Skin and subcutaneous tissue disorders	increased sweating	pruritus	urticaria, alopecia, rash, purpura, photosensitivity reaction		ecchymosis, angiodemas
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia			
Renal and urinary disorders		Urinary retention micturition disorder, polyuria			
Reproductive system and breast disorders		ejaculation failure, ejaculation disorder, female anorgasmia, dysmenorrhoea, impotence	female: menorrhagia		postpartum haemorrhage[2] female: metrorrhagia male: priapism, galactorrhoea
General disorders		Asthenia, fatigue, taste abnormalities	oedema, malaise	pyrexia	

* Cases of suicidal ideation and suicidal behaviour 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).

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 the Yellow Card Scheme: www.mhra.gov.uk/yellowcard.

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 medicinal products/alcohol. Fatal cases of citalopram overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medicinal products.

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 medicinal products 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 an antidepressant with a strong and selective inhibitory action on the uptake of
5-hydroxytryptamine (5-HT, serotonin).

Mechanism of action and pharmacodynamic effects
Tolerance to the inhibitory effect of citalopram on 5-HT uptake does not occur during long-term treatment.
The antidepressant effect is probably connected with the specific inhibition of serotonin uptake in the brain neurons.
Citalopram has almost no effect on the neuronal uptake of noradrenaline, dopamine and gamma-aminobutyric acid. Citalopram shows no affinity, or only very little, for cholinergic, histaminergic and a variety of adrenergic, serotonergic and dopaminergic receptors.
Citalopram is a bi-cyclic isobenzophurane-derivative that is chemically not related to tricyclic and tetracyclic antidepressants or other available antidepressants. The main metabolites of citalopram are also selective serotonin uptake inhibitors, though to a lesser degree. The metabolites are not reported to contribute to the overall antidepressant effect.

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).

Citalopram has no effect on the serum levels of growth hormone. Citalopram like other SSRIs may increase plasma prolactin, an effect secondary to the prolactin stimulating role of serotonin.

5.2 Pharmacokinetic properties

General characteristics of the active substance

Absorption
Citalopram is rapidly absorbed following oral administration: the maximum plasma concentration is reached on average after 4 (1-7) hours. Absorption is independent of food intake. Oral bioavailability is approximately 80%.

Distribution
The apparent distribution volume is 12-17 l/kg. The plasma-protein binding of citalopram and its metabolites is below 80%.

Bio-transformation
Citalopram is metabolised into demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and the deaminated propionic acid-derivative. The propionic acid-derivative is pharmacologically inactive. Demethylcitalopram, didemethylcitalopram and citalopram-N-oxide are selective serotonin uptake inhibitors, although weaker than the parent compound. The main metabolizing enzyme is CYP2C19. Some contribution from CYP3A4 and CYP2D6 is possible.

Elimination
The plasma half-life is approximately 1½ days. After systemic administration, the plasma clearance is approximately 0.3-0.4 l/min and after oral administration the plasma clearance is approximately 0.4 l/min.
Citalopram is mainly eliminated via the liver (85%), but also partly (15%) via the kidneys. Of the quantity of citalopram administered, 12-23 % is eliminated unaltered via the urine. Hepatic clearance is approximately 0.3 l/min and renal clearance is 0.05-0.08 l/min. Steady-state concentrations are reached after 1-2 weeks. A linear relationship has been demonstrated between the steady-state plasma level and the dose administered. At a dose of 40 mg per day, an average plasma concentration of approximately 300 nmol/l is reached. There is no clear relationship between citalopram plasma levels and therapeutic response or adverse reactions.

Characteristics relating to patients
Longer plasma half-life values and a smaller clearance have been found in older patients due to a reduced metabolism.
The elimination of citalopram progresses more slowly in patients with reduced liver function. The plasma half-life of citalopram is approximately twice as long and the steady-state plasma concentration approximately twice as high in comparison with patients with a normal liver function.
The elimination of citalopram progresses more slowly in patients with a mild to moderate renal function disorder. A longer half-life and a small increase in the exposure of citalopram have been observed without any major impact on the pharmacokinetics of citalopram. No information is available on treatment of patients with severe renal impairment (creatinine clearance less than 20 ml/min).

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

Core:
Cellulose, microcrystalline
Glycerol 85 %
Magnesium stearate
Maize starch
Lactose monohydrate
Copovidone
Sodium starch glycolate (type A)
Coating:
Macrogol 6000
Hypromellose
Talc
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The film-coated tablets are packed in
- PVDC-PVC / aluminium blisters or are packed in a HDPE bottle and inserted into a carton

Pack sizes
Blister: 10, 14, 20, 28, 30, 50, 56, 98, 100 film-coated tablets

Bottle: 250 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0978

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 March 2003

10 DATE OF REVISION OF THE TEXT

20/06/2024