SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 40mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 40mg film-coated tablet contains citalopram hydrobromide equivalent to citalopram 40mg;
Also contains Lactose monohydrate 94.540mg

3 PHARMACEUTICAL FORM

Film-coated Tablets

White to off white, oval, biconvex, film-coated tablets with BL embossed on one side and 40 on the other.

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

4.2.1 Posology

MAJOR DEPRESSIVE EPISODES Adults:

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

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

In general improvement in patients starts after one week but may only become evident from the second week of therapy.

As with all anti-depressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses,

if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased to a maximum of 40mg daily (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at lowest effective dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Panic Disorder

Adults:

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

Patients should be started on 10mg/day and the dose gradually increased in 10mg steps according to the patient's response up to the recommended dose. A low initial starting dose is recommended to minimise the potential worsening of panic symptoms, which is generally recognised to occur early in the treatment of this disorder. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually up to a maximum of 40mg/day (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at lowest effective dose.

Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer.

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 20mg daily.

OCD

Adults:

An initial dose of 20mg daily is recommended.

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

Children and adolescents (< 18 years of age)

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

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 for 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).

Reduced renal function
Dosage adjustment is not necessary in cases of mild or moderate renal impairment. No information is available in cases of severe renal impairment (creatinine clearance <20mL/min).

Withdrawal symptoms seen on discontinuation of Citalopram Tablets
Abrupt discontinuation should be avoided. When stopping treatment with Citalopram, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.2.2 Method of administration
Citalopram tablets are administered as a single daily dose. Citalopram tablets can be taken any time of the day without regard to food intake.

4.3 Contraindications

Hypersensitivity tothe active substance or to any of the excipients (see section 6.1).

Monoamine Oxidase Inhibitors: Some cases presented with features resembling serotonin syndrome.

Citalopram should not be used in combination with a MAOI including selegiline in daily doses exceeding 10mg/day. Citalopram should not be given for fourteen days after discontinuation of an irreversible MAOI or for the time specified after discontinuing treatment with the 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).Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

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).

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

Citalopram should not be used concomitantly with pimozide (see also section 4.5).

4.4 Special warnings and precautions for use

Diabetes

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

Glaucoma

As with other SSRIs, citalopram can cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

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 sumatriptan or other triptans, tramadol, oxitriptan, and tryptophan.

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

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

Mania
In patients with manic-depressive illness a change towards the manic phase may occur. Citalopram should be discontinued in any patient entering a manic phase.

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

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior 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/SNRIshas 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

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

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.

ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

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

Paradoxical anxiety
Some patients with panic disorder experience an initial intensified anxiogenic effect when starting pharmacotherapy. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose reduces 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.

Reversible, selective MAO-A inhibitors
The combination of citalopram with MAO-A inhibitors is generally not recommended due to the risk of onset of a serotonin syndrome (see section 4.5).

For information on concomitant treatment with non-selective, irreversible MAO- see section 4.5.

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).

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

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

In a recurrence prevention clinical trial with citalopram, adverse events after treatment discontinuation 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).

Use in children and adolescents under 18 years of age
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years Suicide – related behaviours (suicide 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.

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

Elderly patients

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

Reduced kidney and liver function

Caution should be used in the treatment of patients with reduced kidney and liver function (see section 4.2).

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

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.

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.

Pimozide:

Co administration of a single dose of pimozide 2mg to subjects treated with racemic citalopram 40mg/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 10msec. 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 (20mg daily) and selegiline (10mg daily) (a selective MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10mg daily) is not recommended.

Alcohol
The combination of citalopram and alcohol is not advisable. No pharmacodynamic or pharmacokinetic interactions have been demonstrated between citalopram and alcohol.

Serotonergic medicinal products
Co administration with serotonergic drugs (e.g. tramadol, sumatriptan) 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).

Lithium & tryptophan
No pharmacodynamic interactions have been found in clinical studies in which citalopram has been given concomitantly with lithium. However there are have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Routine monitoring of lithium levelsshould be continued as usual.

Desipramine, imipramine
In a pharmacokinetic study no affect 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.

St John's Wort
Dynamic interactions between SSRIsand 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.

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, phenothiazines, tricyclic depressants) that can increase the risk of haermorrhage (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).

Medicinal products inducing hypokalaemia or hypomagnesaemia:
Caution is warranted for concomitant use of other hypokalaemia/hypomagnesaemia inducing drugs as they, like citalopram, potentially prolong the QT interval.

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 [tricyclics, SSRIs], neuroleptics [phenothiazines, thioxanthenes, and butyrophenones]), mefloquin, bupropion and tramadol).

Neuroleptics:
Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

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:
Cimetidine (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. Dose adjustment may be warranted. Co-administration of escitalopram (the active enantiomer of citalopram) with omeprazole 30mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram. Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine). A reduction in the dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.

Metoprolol:
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 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, carbamazepine:
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).

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 2500 exposed outcomes) indicate no malformative feto/ neonatal toxicity. As with all drugs citalopram canbe used duringpregnancy if clinically needed,taking into account the aspects mentioned below.

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 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.

Lactation

Citalopram is known to be excreted in 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. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

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 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

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 reversibl. 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.

Patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration due to the illness itself and 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 effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuatesubsequently. The adverse reactions are presented at the MedDRA preferred Term level.

For the following reactions a dose-response was discovered: nausea, somnolence, dry mouth, increased sweating, insomnia, diarrhoeaand 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, <1/10); uncommon (≥1/1000, ≤1/100); rare (≥1/10000, ≤1/1000); very rare (≤1/10000), not known (can not be estimated from available data).

MedDRA SOC	Frequency	Preferred term
Blood and lymphatic disorders	Not Known	Thrombocytopenia
Immune system disorders	Not Known	Hypersensitivity , anaphylactic reaction
Endocrine disorders	Not Known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Appetite decreased, weight decreased
	Uncommon	Increased appetite, weight increased
	Rare	Hyponatremia
	Not Known	Hypokalaemia
Psychiatric disorders	Common	Agitation, libido decreased, anxiety, nervousness, confusional state, abnormal orgasm (female), abnormal dreams
	Uncommon	Aggression, depersonalization, hallucination, mania
	Not Known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[2]
Nervous system disorders	Very common	Somnolence, insomnia
	Common	Tremor, paraesthesia, dizziness, disturbance in attention

	Uncommon	Syncope
	Rare	Convulsion grand mal, dyskinesia, taste disturbance
	Not Known	Convulsions , serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder
Eye disorders	Uncommon	Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4 special warnings and precautions for use)
	Not Known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Not Known	Ventricular arrhythmia including torsade de pointes, QT-prolongation[1]
Vascular disorders	Rare	Haemorrhage
	Not Known	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Common	Yawning
	Not Known	Epistaxis
Gastrointestinal disorders	Very common	Dry mouth, Nausea
	Common	Diarrhoea vomiting, Constipation
	Not Known	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis
	Not Known	Liver function test abnormal
Skin and subcutaneous tissue disorders	Very common	Sweating increased
	Common	Pruritus
	Uncommon	Urticaria, alopecia, rash, purpura, photosensitivity reaction
	Not Known	Ecchymosis, angioedemas
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Uncommon	Urinary retention

Reproductive system and breast disorders	Common	Impotence, ejaculation disorder, ejaculation failure
	Uncommon	Female: Menorrhagia
	Not Known	Female: Metrorrhagia Male: Priapism, galactorrhoea
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema
	Rare	Pyrexia

Number of patients: Citalopram / placebo = 1346 / 545

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)

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

The following additional adverse events have also been reported in clinical trials:

Very common: Headache, asthenia, sleep disorder.

Common: Migraine, palpitation, taste perversion, impaired concentration, amnesia, anorexia, apathy, dyspepsia, abdominal pain, flatulence, increased salivations, rhinitis.

Rare: Increased libido, coughing, malaise.

Class effects

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.

Withdrawal symptoms seen on discontinuation of Citalopram 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).

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 at: www.mhra.gov.uk/yellowcard.

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.

Fatal dose is not known. Patients have survived ingestion of more than 2 g citalopram.

The effects may be potentiated by alcohol taken at the same time.

Potential interaction with TCAs, MAOIs and other SSRIs.

Symptoms
The following symptoms have been seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT 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, hyperpyrexia, and atrial and ventricular arrhythmia.

ECG changes including nodal rhythm, prolonged QT intervals and wide QRS complexes may occur. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported.

Rarely, features of “Serotonin syndrome” may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment
There is no specific antidote.

Consider oral activated charcoal in adults and children who have ingested more than 5mg/kg body weight within 1 hour. Activated charcoal given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50%. Osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered. Control convulsions with intravenous diazepam if they are frequent or prolonged.

Treatmentshould be symptomatic and supportive and include the maintenance of a clear airway and monitoring of ECGand vital signs until stable.

If consciousness is impaired the patient should be intubated.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors.
ATC-code: N 06 AB 04

Mechanism of action:

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT)-uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.

Citalopram is the most Selective Serotonin Reuptake Inhibitor (SSRI), 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 or 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. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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.

Pharmacodynamic effects

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.

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

Citalopram did not reduce saliva flow in a single dose study in human volunteers and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters. Citalopram has no effect on the serum levels of prolactin and growth hormone.

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

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 demethylcitalopram, 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 250nmol/L (100-500nmol/L) are achieved at a daily dose of 40mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Elderly patients (≥65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

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

5.3 Preclinical safety data

Citalopram has low acute toxicity. In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. Based on data from reproduction toxicity studies (segment I, II and III) there is no reason to have special concern for the use of citalopram in women of child-bearing potential. Citalopram has no mutagenic or carcinogenic potential.

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
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Purified talc
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blisters: 4 years

HDPE containers: 3 years

6.4 Special precautions for storage

Blisters: Do not store above 25ºC. Store in the original package
Bulk: Do not store above 25ºC. Keep the container tightly closed

6.5 Nature and contents of container

Al /PVDC/PVC blister, pack sizes of 14, 28, 56 or 84 tablets
HDPE tablet containers, pack sizes of 1000 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road,
Berkhamsted
Herts
HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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12/06/2015