1. NAME OF THE MEDICINAL PRODUCT

Citalopram 20 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg citalopram, as citalopram hydrobromide.

*Excipient(s) with known effect:*
Each 20 mg tablet contains 26.7 mg of lactose monohydrate

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, oval, biconvex, film-coated tablet with a score line on one 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

_Treating Depression:

*Adults:*

Citalopram should be administered as a single oral dose of 20 mg 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 antidepressant 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 up to a maximum of 40 mg a day (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.

A treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse.

**Treating Panic disorder:**

**Adults:**

In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. 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, however an optimum dose of 20-30 mg daily was indicated in a clinical study.

Maximum effectiveness of citalopram in treating panic disorder is reached after about 3 months and the response is maintained during continued treatment. Dependent on individual patient response it may be necessary to continue treatment for several months.

**Elderly patients (> 65 years of age):**

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

**Children:**

Citalopram 20 mg Tablets are not recommended for use in children and adolescents who are aged under 18 years. They must not be used in the treatment of major depression in children and adolescents under 18 years as one out of two controlled clinical studies failed to demonstrate efficacy.

**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).

**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 < 20 ml/min).
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).

Withdrawal symptoms seen on discontinuation of citalopram

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 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.

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

4.3 Contraindications

Hypersensitivity to citalopram or to any of the excipients (see section 6.1).

Monoamine oxidase inhibitors: 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 selective MAOI selegiline and the reversible MAOI (RIMA), 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 a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Citalopram should not be given to patients receiving MAOI including selegiline in daily doses exceeding 10 mg/day (see section 4.5).

Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

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

Citalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.

Citalopram is contraindicated together with medicinal products that are known to prolong the QT-interval (see section 4.5).

Concomitant treatment with pimozide (see section 4.5).
4.4 Special warnings and precautions for use

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

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

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

Electroconvulsive Therapy (ECT)
There is little clinical experience of concurrent administration of citalopram and ECT, therefore caution is advisable.

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

Mania
Citalopram should be used with caution in patients with a history of mania/hypomania. As with most antidepressants, citalopram should be discontinued in any patient entering a manic phase.

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 with drugs known to affect platelet function or other active substances that can increase the risk of haemorrhage (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)), as well as in patients with a history of bleeding disorders (see section 4.5).

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.

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.

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, oxtitriptan and tryptophan.

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)

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.

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.

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.
Akathisia/psychomotor restlessness

The use of citalopram 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.

Paradoxical anxiety

Some patients with panic disorder experience an initial anxiogenic effect (intensified anxiety symptoms) when starting pharmacotherapy with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose (see Posology) reduces the likelihood of this effect.

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 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 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, diarrhoea, palpitations, emotional instability, irritability, visual disturbances and headache 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.

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 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.

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.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of citalopram to demethylcitalopram is mediated by isozymes CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%) 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 the inhibition of one enzyme may be compensated by another. Unlike some other SSRIs, citalopram is only a weak inhibitor of this important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80%). These properties give citalopram a low potential for clinically significant drug interactions.

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

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

MAO-inhibitors
The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including 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 derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.

Pimozide
Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and 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)
An interaction study with concomitantly administered citalopram (20 mg daily) and a selective MAO-B inhibitor, selegiline (10 mg daily) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10 mg daily) is not recommended.

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

Serotonergic drugs
Co-administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects. The simultaneous use of citalopram and 5-HT agonists such as sumatriptan and other triptans, is not recommended.

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

Imipramine, desipramine
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.

St. John’s Wort
Dynamic interactions between citalopram and herbal remedy St John’s Wort (*Hypericum perforatum*) can occur, resulting in an increase in undesirable effects (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, phenothiazines, tricyclic antidepressants) that can increase the risk of haemorrhage (see section 4.4).

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

Medicinal products inducing QT prolongation or hypokalaemia/ hypomagnesaemia
Caution is warranted for concomitant use of other QT interval prolonging medicines or hypokalaemia/hypomagnesaemia inducing drugs (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 [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.

*Influence of other medicinal products on the pharmacokinetics of citalopram*

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

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

**Metoprolol**
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.

**Other medicinal products**
Caution is recommended when citalopram is co-administered with medicinal products that are mainly metabolised by CYP2D6, 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 (see above), clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

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.

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).

No pharmacodynamic interactions have been noted in clinical studies in which citalopram has been given concomitantly with antihistamines.

### 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. Animal studies did not provide any evidence of teratogenicity, however the safety of citalopram during human pregnancy has not been established. As with all drugs, citalopram should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus and taking into account the following aspects:
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 neonate 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 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 reversible. Impact on human fertility has not been observed so far.

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. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered. The existing information is insufficient for assessment of the risk to the child. Caution is recommended.

4.7 Effects on ability to drive and use machines

Citalopram has minor or moderate influence on the ability to drive and use machines as psychoactive medicinal products can reduce the ability to make judgements and to react to emergencies. Patients who are prescribed psychotrophic 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 effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves. The 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 $\geq 1\%$ of patients in double-blind placebo-controlled trials or in the post-marketing period. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ to $< 1/1000$); very rare ($< 1/10000$), not known (can not be estimated from available data).

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>Frequency</th>
<th>Preferred term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic disorders</td>
<td>Not Known</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not Known</td>
<td>Hypersensitivity, Anaphylactic reaction</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Not Known</td>
<td>Inappropriate ADH secretion</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Appetite decreased, Weight decreased</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Increased appetite, Weight increased</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Hypokalaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very common</td>
<td>Sleep disorder</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Agitation, Libido decreased, Anxiety, Nervousness, Confusional state, Abnormal orgasm (female), Abnormal dreams, Apathy.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Aggression, Depersonalization, Hallucination, Mania, Increased libido.</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Panic attack, Bruxism, Restlessness, Suicidal ideation, Suicidal behaviour²</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Somnolence, Insomnia, Headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Tremor, Paraesthesia, Dizziness, Disturbance in attention, Migraine, Amnesia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Syncope</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Convulsion grand mal, Dyskinesia, Taste disturbance</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Convulsions, Serotonin syndrome, Extrapyramidal disorder, Akathisia, Movement disorder</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4</td>
</tr>
</tbody>
</table>

Special warnings and precautions for use.
<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>Incidence</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Not Known</td>
<td>Visual disturbance,</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Tinnitus</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Bradycardia, Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>QT-prolongation ¹, Ventricular arrhythmia including torsade de pointes</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td>Common</td>
<td>Yawning, Rhinitis</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Coughing</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Common</td>
<td>Impotence, Ejaculation disorder, Ejaculation failure</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Female: Menorrhagia</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Female: Metrorrhagia, Male: Priapism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Galactorrhoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Nausea, Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dyspepsia, Vomiting, Abdominal pain, Flatulence, Increased salivation, Diarrhoea, Constipation</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Gastro-intestinal bleeding (including rectal haemorrhage)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Oedema</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Pyrexia, Malaise</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Rare</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Abnormal liver function tests</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>Myalgia, Arthralgia</td>
</tr>
</tbody>
</table>
Number of patients: Citalopram / placebo = 1346 / 545

1 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).

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

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

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).

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
The fatal dose is not known. Patients have survived ingestion of up to 2 g citalopram. The effects will be potentiated by alcohol taken at the same time. Potential interaction with tricyclic antidepressants and MAOIs. 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**
Nausea, vomiting, sweating, tachycardia, hypertension, mydriasis, drowsiness, cardiac arrest, bundle branch block, torsade de pointes, cyanosis, coma, stupor, dystonia, convulsions, tremor, hyperventilation, dizziness, somnolence, agitation, serotonin syndrome and hyperpyrexia have been reported. Cardiac features that have been observed include nodal rhythm, atrial and ventricular arrhythmia, prolonged QT intervals and wide QRS complexes. Prolonged bradycardia with severe hypotension and syncope has also been reported.

Rarely, features of the “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**
An ECG should be taken. Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within one 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.

If consciousness is impaired the patient should be intubated.

Control convulsions with intravenous diazepam if they are frequent or prolonged. There is no known specific antidote to citalopram. Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. 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: N06 AB04*

Mechanism of action
Biochemical and behavioural studies have shown that 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 a very 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 SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT1A, 5-HT2, DA, D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, 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 SSRIs 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\text{max} average/mean 3.8 hours). Oral bioavailability is about 80%.
Distribution
The apparent volume of distribution ($V_d$) 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 ($T_{1/2}$) is about 1½ 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 ($\geq 65$ 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 < 20 mL/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
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Maize starch
Glycerol
Copovidone
Magnesium stearate

Tablet film-coating
Hypermellose
Microcrystalline cellulose
Polyoxyethylene stearate
Titanium dioxide (E171)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

60 months

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Blister packs (PVC/PVDC/aluminium) containing 28 tablets.

6.6. Instruction for use and handling (use, and disposal)

No special requirements.

No Data Held
7. MARKETING AUTHORISATION HOLDER

Waymade plc trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 06464/1972

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th February 2005

10 DATE OF REVISION OF THE TEXT

02/09/2016