Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Citalopram Pfizer 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg citalopram as citalopram hydrobromide.

Excipient:
Each film-coated tablet contains 45.72 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, biconvex, capsule shaped, film-coated tablets debossed with ‘A’ on one side and with a score line in between ‘0’ and ‘6’ on the other side.
The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Major depressive episodes.
- Panic disorder with or without agoraphobia.

4.2 Posology and method of administration

Major depressive episodes:
Following treatment initiation, an antidepressant effect should not be expected for at least two weeks. Patients with depression should be treated for a sufficient period of time and treatment should be continued 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 Citalopram should be withdrawn slowly: it is advised that the dose is gradually reduced over 1-2 week periods (see section 4.4)

Adults: The recommended starting dose is 20 mg per day. If necessary, the dose can be increased up to 40 mg per day, depending on the individual response of the patient.
The maximum dose is 60 mg per day.

Panic disorder:
Initial dose is 10 mg daily. A week later, the dose should be increased to 20 mg daily.
The optimum dosage is 20 - 30 mg daily. If the individual patient’s response to treatment is insufficient, the dose may be increased gradually up to a maximum of 60 mg daily.

Full therapeutic response may take up to 3 months to develop. It may be necessary to continue treatment for several months.

Elderly patients (> 65 years of age):
The recommended daily dose is 20 mg. Dependent on individual patient response this 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
A starting dose of 10 mg per day during the first 2 weeks of treatment is recommended for patients with mild to moderate liver impairment. Depending on the individual this response may be increased to 30 mg per day. Prudence and extra careful dose titration is advised in patients with severely reduced liver function (see section 5.2).

Reduced renal function
Adjustment of dose is not required when the patient has mild to moderate renal impairment. Caution is advised in patients with severe renal impairment (creatinine clearance less than 30 mL/min, see section 5.2), because there are no clinical data available for this group of patients.

Withdrawal symptoms seen on discontinuation
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 unacceptable 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.

Poor metabolisers of CYP2C19
In patients with known poor metabolism of CYP2C19, an initial daily dose of 10 mg for the first two weeks is recommended. Depending on the result of treatment, the dose can subsequently be increased to 20 mg (see section 5.2).

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.

4.3 Contraindications

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

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 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

Treatment of elderly patients and patients with reduced renal and hepatic function, see 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.

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.

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.

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.

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

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

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

Serotonin syndrome
In rare cases, serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus, aid 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.

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

ECT (electroconvulsive therapy)
There is limited clinical experience of concurrent administration of citalopram; therefore caution is advisable.

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 MAOinhibitors 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).

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 SSRI”, Section 4.2).

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

QT *prolongation*
Elevated levels of a minor metabolite of citalopram (didemethylcitalopram) could theoretically prolong the QT interval in susceptible patients, patients with suspected congenitally prolonged QT syndrome or in patients with hypokalaemia/hypomagnesiaemia. ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Contraindicated combinations
MAO-inhibitors
The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including the serotonin syndrome (see section 4.3).
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline and the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued and SSRI and have been started on a MAOI.
Some cases presented with features resembling serotonin syndrome.
Symptoms of an active substance interaction with a MAOI include: agitation, tremor, myoclonus, and hyperlhermia.

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 citaloprarn and selegiline (in doses above 10 mg daily) is not recommended.

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

Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.
Until further information is available, the simultaneous use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

St. John's Wort
Dynamic interactions between SSRIs and herbal 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 haemorrhage (see section 4.4).

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

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

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

Desipramine, imipramine
In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine was increased. When desipramine is combined with citalopram, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

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, a known enzyme-inhibitor, caused a slight rise in the average steady-state citalopram levels. Caution is therefore recommended when administering high doses of citalopram in combination with high doses of cimetidine. 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
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 CYPlA2, 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 Pglycoprotein).

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. Citalopram can be used during pregnancy 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, particular in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonates alter 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.

Lactation
Citalopram is excreted into breast milk. It is estimated that the sucking 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.

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 effects 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-controlledtrials 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
	Not known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Not known	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
1 Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with preexisting cardiac disease
2 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 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 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

4.9 Overdose

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

Symptoms
The following symptoms have been seen in reported overdose of citalopram:
convulsion, tachycardia, somnolence, QT 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.

Treatment
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant, Selective serotonin reuptake inhibitors
ATC-code: N06AB04

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.

5.2 Pharmacokinetic properties

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 metabolising enzyme is CYP2C19. Some contribution from CYP3A4 and CYP2D6 is possible.

Elimination:
The plasma half-life is approximately 1.5 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 300nmol/l is reached. There is no clear relationship between citalopram plasma levels and therapeutic response or undesirable effects.

Special populations
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:
In patients with a mildly to moderately reduced renal function a longer half-life and a small increase in the exposure of citalopram has been observed. Citalopram is eliminated more slowly, without an important effect on the pharmacokinetics of citalopram. There is no information available about the pharmacokinetics in patients suffering from serious kidney function dysfunction.

Polymorphism:
Slow metabolisers of CYP2C19 have been observed to have plasma concentrations of escitalopram twice as high as those of rapid metabolisers. No significant alteration in exposure has been observed in slow metabolisers of CYP2D6 (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans. These data are from conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.
Phospholipidosis has been observed in various organs following multiple dosing of rats. The effect was reversible after discontinuation. Accumulation of phospholipids has been observed in long-term animal studies with many cation-amphophilic drugs. The clinical relevance this is not clear.

Reproductive toxicity studies in rats have shown skeletal abnormalities in offspring, but no increased frequency of malformations. These effects can related to the pharmacological effect, but can also be caused by maternal toxicity. Peri-and postnatal studies have a decreased survival of the offspring during lactation demonstrated. The potential risk for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Blister Pack: Clear PVC/PVDC aluminium blister.
Package sizes: 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112 or 120 tablets.

White opaque HDPE container with white opaque polypropylene closure:
20 mg tablets: 30, 100 and hospital packs of 200, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 822/34/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 September 2011

10 DATE OF REVISION OF THE TEXT