Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains citalopram hydrobromide equivalent to 20mg of citalopram.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Citalopram 20mg film-coated tablets are oval, biconvex, scored, white, film-coated tablets marked with 'CI 20' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of major depressive episodes.
Treatment of panic disorder with or without agoraphobia.

4.2 Posology and method of administration

For the different dosage regimens suitable strengths should be prescribed.
Citalopram tablets are administered as a single daily dose. Citalopram tablets can be taken any time of the day without regard to food intake.

Treating Major Depressive Episodes

Citalopram should be administered as a single oral dose of 20mg daily. Dependent on individual patient response this may be increased to a maximum of 60mg daily.

Following treatment initiation, an antidepressant effect should not be expected for at least two weeks. A treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse.

Treating Panic Disorder

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 10mg daily is recommended for the first week before increasing the dose to 20mg daily. The dose may be further increased, up to a maximum of 60mg daily dependent on individual patient response, however an optimum dose is 20-30mg daily.

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

Elderly patients (>65 years old)

Treatment of major depressive episodes:
For elderly patients the dose should be reduced to 10-20 mg daily. Depending on individual patient response the dose may be increased to a maximum of 40 mg daily.

Treatment of panic disorder:
The initial dose is 10 mg once daily. After one week the dose may be increased to 20 mg daily. Depending on individual patient response the dose may be increased to a maximum of 40 mg daily.

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

Reduced hepatic function
Dosage should be restricted to the lower end of the dose range. Patients with hepatic impairment should receive a starting dose of 10 mg daily. The dose should not exceed 30 mg per day *(see section 4.4).* These patients should be clinically monitored.

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) *(see section 4.4).*

Interruption of therapy
To avoid withdrawal reactions citalopram should be withdrawn slowly. It is advised that the dose is gradually reduced over 1-2 week periods *(see section 4.8).*

4.3 Contraindications

Hypersensitivity to citalopram or to any of the excipients.

Monoamine oxidase inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving a selective serotonin reuptake inhibitor (SSRI) in combination with monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA) moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI *(see section 4.4).*

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 used in combination with a MAOI. Citalopram should not be given for fourteen days after discontinuing treatment with an irreversible MAOI or for the time specified after discontinuing treatment with a reversible MAOI (RIMA) as stated in the prescribing text of the RIMA. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

4.4 Special warnings and precautions for use

Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as tramadol, tryptophan, oxitriptan, sumatriptan or other triptans.

Diabetes - In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and 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.

Mania - Citalopram should be used with caution in patients with a history of mania / hypomania. 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 greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebocontrolled 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.

Haemorrhage - There have been reports of bleeding abnormalities such as ecchymoses, purpura, gynaecological haemorrhages, gastrintestinal bleedings and other cutaneous or mucous bleedings with SSRIs. Caution is advised in patients taking citalopram, particularly in concomitant use with oral anticoagulants, active substances known to affect platelet function or other active substances that may increase the risk of haemorrhage (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.

Serotonin syndrome - In rare cases a serotonin syndrome has been reported in patients using SSRIs.
A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Hyponatraemia - Hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has been reported rarely, predominantly in the elderly, and generally reverses on discontinuation of therapy.

St John's wort – An increase in serotoninergic effects, such as serotonin syndrome, may occur at 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.

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.

Consideration should be given to factors that may affect the disposition of a minor metabolite of citalopram

(didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in susceptible individuals. However, in ECG monitoring of patients in clinical trials, including those patients with pre-existing cardiac conditions, no clinically significant changes were noted.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see Posology) reduces the likelihood of this effect.

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

The use of citalopram in patients with severe renal impairment (creatinine clearance less than 20 ml/min.) is not recommended as no information is available on use in these patients *(see section 4.2).*

In cases of impaired hepatic function dose reduction is recommended *(see section 4.2)* and liver function has to be closely monitored.

Use in children and adolescents under 18 years of age- Citalopram should not be used for 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.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs) should not be used in combination with SSRIs *(see section 4.3).*

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2D6 and, 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.

Alcohol - The combination of citalopram and alcohol is not advisable. However, no adverse pharmacodynamic interactions between citalopram and alcohol have been noted.

Serotonergic drugs – Co-administration with serotonergic drugs (e.g. tramadol, tryptophan, oxitriptan, sumatriptan and other triptans) may lead to serotonin syndrome. In combination with triptans, there is a potential risk of coronary vasoconstriction and hypertension too. Therefore, the simultaneous use of citalopram and these active substances is not recommended *(see section 4.4).*

Lithium - There is no pharmacokinetic interaction between lithium and citalopram. However there have been reports of serotonin syndrome when SSRIs have been given with lithium and, therefore, the concomitant use of citalopram with lithium should be undertaken with caution and closer and more frequent clinical monitoring is required.

Caution is warranted for patients who are being treated simultaneously with oral anticoagulants, active substances known to affect platelet function, or other medicines that can increase the risk of haemorrhage (e.g. NSAIDs, acetylsalicylic acid, dipyridamol, ticlopidine, atypical antipsychotics, phenothiazines, most tricyclic depressants) *(see section 4.4).*

Co-administration of citalopram and metoprolol (CYP2D6 substrate) resulted in a two-fold increase in the plasma levels of metoprolol. No clinically significant effects on blood pressure or heart rate were observed.

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.

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.

Pharmacodynamic 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).*

In clinical studies no pharmacodynamic interactions have been noted when citalopram was given concomitantly with benzodiazepines, neuroleptics, analgesics, lithium, antihistamines, antihypertensive drugs, beta-blockers and other cardiovascular drugs.

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

4.6 Pregnancy and lactation

Pregnancy:
Based on a limited number of exposed pregnancies, available data do not give indication of an increased risk of congenital malformations in the newborn.

Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development *(see section 5.3).*

The following effects were reported in neonates with SSRIs administered to pregnant women until an imminent date of birth or until birth: irritability, tremor, hypertonia, increased muscle tone, constant crying, and difficulty in suckling or in sleeping. They may either indicate serotoninergic effects or withdrawal syndrome. The time to occur and the duration of these symptoms in theory depend on the elimination half-life of the product.

The use of citalopram may be considered during pregnancy when necessary, and neonate should be observed when prescribing until an imminent date of birth or until birth.

A treatment should never be abruptly stopped during pregnancy.

Lactation:
Citalopram is excreted in milk in small quantities. Benefits of breast-feeding should be weighed against the possible risks to the child.

4.7 Effects on ability to drive and use machines

Citalopram does not impair intellectual function and psychomotor performance. However, patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration either due to the illness itself, the medication or both and should be cautioned about their ability to drive a car and operate machinery.

4.8 Undesirable effects

Adverse 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.

In comparative clinical trials with tricyclic antidepressants the incidence of adverse events occurring with citalopram was found to be lower in all cases.

Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs), including citalopram. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with citalopram should be avoided *(see section 4.2).* The majority of symptoms experienced on

withdrawal of SSRIs are non-serious and self-limiting.

Adverse events reported in clinical trials with the following frequencies:

	Very common (>10%)	**Common (>1%, <10%)**	**Uncommon (>0.1%,<1%)**	**Very rare (<0.01%, including isolated reports)**	**Frequency not known**
Psychiatric disorders	Somnolence, insomnia, agitation, nervousness	Sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, Confusion	Euphoria, increased libido	Hallucinations, mania, depersonalisation, panic attack (these symptoms may be due to the underlying disease)	Suicidal ideation and suicidal behaviour*
Nervous system disorders	Headache, tremor, dizziness	Migraine, paraesthesia	Extrapyramidal disorder, convulsions	Serotonin syndrome, akathisia	
Cardiac disorders	Palpitations	Tachycardia	Bradycardia	Supraventricular & ventricular arrhythmias	
Vascular disorders		Postural hypotension, hypotension, hypertension			
Gastrointestinal disorders	Nausea, dry mouth, constipation, diarrhoea	Dyspepsia, vomiting, abdominal pain, flatulence, increased salivation			
Renal and urinary disorders		Micturition disorder, polyuria	Hyponatraemia		
Metabolism and nutrition disorders		Weight decrease, weight increase			
Hepato-biliary disorders			Increased liver enzyme values		
Respiratory		Rhinitis,	coughing		

disorders		Sinusitis		
Reproductive system disorders		Ejaculation failure, female anorgasmia, dysmenorrhoea, impotence		galactorrhoea
Skin disorders	Increased sweating	Rash, Pruritus	Photosensitivity	angiodema
Eye disorders	Abnormal accommodation	Abnormalities of vision		
Special senses Disorders		Taste Abnormalities		
Ear and labyrinth disorders			Tinnitus	
Musculoskeletal disorders			Myalgia	arthralgia
General disorders	asthenia	Fatigue, yawning	Allergic reactions, syncope, malaise, ecchymosis, purpura, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous membrane bleedings	Anaphylactoid reactions, prolactinaemia,

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

4.9 Overdose

Citalopram is given to patients at potential risk of suicide and some reports of attempted suicide have been received. Detail is often lacking regarding precise dose or combination with other drugs and/or alcohol.

Fatal dose 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.

Symptoms:
Nausea, vomiting, sweating, tachycardia, drowsiness, coma, dystonia, convulsions, hyperventilation and hyperpyrexia have been reported. Cardiac features that have been observed include nodal rhythm, 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:
There is no specific antidote. Treatment is symptomatic and supportive.

If the amount of medicine is large and ingestion very recent, gastric lavage can be considered (if the patient has lost consciousness, intubation must be performed first). Otherwise, it is essential to administer activated charcoal to reduce further absorption. Speeding up the passage using suitable laxatives, e.g., sodium sulphate can also be considered. Medical surveillance is advisable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors (SSRI)
ATC code: N 06 AB 04

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) yet described, with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the other SSRI's, citalopram has none 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.

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

Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics. There was potentiation of d-amphetamine-induced hyperactivity following administration of citalopram.

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the other SSRIs. The metabolites do not contribute to the overall antidepressant effect.

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 metabolised 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, the systemic citalopram plasma clearance (Cl_s) is about 0.33 L/min (330ml/min), and oral plasma clearance (Cl_{oral}) is about 0.41 L/min (410ml/min).

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12-23% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min (350ml/min) and renal clearance about 0.068 L/min (68ml/min).
The kinetics is linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Elderly patients (65 years)
Longer half-lives and decreased clearance values due to a reduced rate of metabolism 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

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. Phospholipidosis has been observed in several organs following multiple administration in rats. The effect was reversible at discontinuation. Accumulation of phospholipids has been observed in long term animal studies with many cation-amphophilic drugs. The clinical relevance of these results is not clear. Embryotoxicity studies in rats have shown skeletal anomalies at high maternal toxic doses. The effects may be related to the pharmacological activity or may be a consequence of maternal toxicity. Peri- and postnatal studies have revealed reduced survival in offspring during the lactation period. The potential risk for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Maize starch
Lactose monohydrate
Croscarmellose Sodium
Glycerol
Copovidone
Magnesium stearate
Microcystalline cellulose

Tablet coat:
Hypromellose
Macrogol
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

PVC/Alu blisters

Pack size: 10, 20, 28, 50 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited
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8 MARKETING AUTHORISATION NUMBER

PA 0585/018/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 2005

10 DATE OF REVISION OF THE TEXT

July 2008