Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellcital 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 50 mg of citalopram hydrobromide equivalent to 40 mg citalopram.

Each tablet also contains Lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

White to off-white circular biconvex film-coated tablet debossed with '40' on one side and a lip shaped scoreline on the other side.

The scoreline is a design feature, not to facilitate breaking: tablets do not divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Major depressive episodes.
Panic disorder with or without agoraphobia.

4.2 Posology and method of administration

Bellcital Tablets are not breakable.

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

Adults
Major depressive episodes*:* Citalopram should be administered as a single oral dose of 20 mg daily. If necessary, the dose can be increased gradually by 10 mg. Dependent on individual patient response, this may be increased to a maximum of 40 - 60 mg daily. Following treatment initiation, an antidepressant effect should not be expected for at least two weeks. A treatment duration of at least 4 - 6 months is usually necessary to provide adequate maintenance against the potential for relapse.

Panic disorder: A single dose of 10mg per day for the first week is recommended; after this the dose may be increased to 20 mg per day. The dose may continue to be increased up to a maximum dose of 40 - 60 mg per day depending on individual patient response. Maximum effect is reached after 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 this may be increased to a maximum of 30-40mg daily.

Treatment of Panic Disorder
The initial dose is 10mg once daily, after one week the dose may be increased to 20mg daily. Depending on individual patient response this may be increased to a maximum of 40mg daily.

Children and adolescents under the age of 18
Not recommended, as safety and efficacy have not been established in this population.

Reduced hepatic function
Patients with hepatic impairment should receive a starting dose of 10mg/day. The dose should not exceed 30mg for patients with hepatic impairment. These patients should be clinically monitored.

Reduced renal function
Dosage adjustment is not necessary in cases of mild or moderate renal impairment. Since there are no adequate data, use of Citalopram in patients with severe renal failure (creatinine clearance below 20 ml/min) is not recommended.

Citalopram should be withdrawn slowly. It is advised that the dose is gradually reduced over 1-2 week periods.

4.3 Contraindications

Citalopram is contraindicated in patients with hypersensitivity to the active substance, Citalopram or to any of the excipients (see section 6.1).

Monoamine oxidase inhibitors
Citalopram should not be used in combination with a monoamine oxidase inhibitors (MAOI). Citalopram should not be given to patients receiving MAOIs including selegiline in daily doses exceeding 10 mg/day.

Cases of serious and sometimes fatal reactions have been reported in patients receiving a selective serotonin reuptake inhibitor (SSRI) in combination with 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.

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 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 (see section 4.5).

5-HT-agonists
Sumatriptan's serotonergic effects are suspected to be enhanced by SSRI's. Until further evidence is available it is advised not to use citalopram simultaneously with 5-HT agonists eg Sumatriptan.

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

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

4.4 Special warnings and precautions for use

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 again 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
Bellcital Tablets should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms.

In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Paradoxical anxiety
Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose is advised to reduce the likelihood of of a paradoxical anxiogenic effect (see section 4.2)

Hyponatraemia
Hyponatraemia, probably due to inappropriate anti-diuretic 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 and it may be necessary to review the use of Citalopram.

Mania
Citalopram should be used with caution in patients with a history of mania/hypomania. In patients with manic-depressive illness a change towards the manic phase may occur. Citalopram should be discontinued in any patient entering a manic phase.

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.

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

Serotonergic medicines
Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as tramadol, tryptophan, oxitriptan, sumatriptan or other triptans (see section 4.3).

St John's Wort
An increase in serotoninergic effects, such as serotonin syndrome, may occur with 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

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

Haemorrhage
There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymoses and purpura, gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings with SSRIs (see section 4.8).
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 can increase the risk of haemorrhage (e.g. atypical antipsychotics and
phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), ticlopidine and dipyridamol, as well as in patients with a history of bleeding disorders (see section 4.5).

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

QT prolongation
Consideration should be given to factors which may affect the disposition of a minor metabolite of citalopram (didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in patients predisposed, patients with congenitally prolonged QT syndrome or in patients with hypokalaemia/hypomagnesiaemia. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted. ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

Monoamine Oxidase Inhibitors (MAOIs)
MAOIs should not be used in combination with SSRIs (see section 4.3).

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.

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.

Withdrawal symptoms seen on discontinuation of Citalopram 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 disturbance (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 month, according to the patient's needs (see "Withdrawal Symptoms Seen on Discontinuation of Citalopram", section 4.2).

Excipients
These tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take 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 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.

Pimozide
Co administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and Cmax of pimozide, although not consistently throughout the study. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Combinations requiring precaution for use

Selegiline (selective MAO-B inhibitor)
A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered citalopram (20 mg daily) and selegiline (10 mg daily) (a selective
MAO-B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10 mg daily) is 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, dextromethorphan, pethidine, tryptophan, oxitriptan, sumatriptan and other triptans) may lead to enhancement of 5-HT associated effects; 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 4.3).

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). Pharmacokinetic interactions have not been investigated.

Haemorrhage
Caution is warranted for patients who are being treated simultaneously with oral anticoagulants, medicinal products that affect platelet function, or other medicines that can increase the risk of haemorrhage (e.g. non steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, dipyridamol, ticlopidine, atypical antipsychotics, phenothiazines, tricyclic anti-depressants) (see section 4.4).

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

Alcohol
Clinical studies have revealed no pharmacodynamic or pharmacokinetic interactions 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 affect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased. When desipramine is combined with Citalopram, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

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. Protein binding is relatively low (<80%).
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 two-fold increase in the plasma levels of metoprolol, but did not statistically significant increase the effect of metoprolol on blood pressure and cardiac rhythm.

Effects of citalopram on other medicinal products

A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram and metoprolol (a CYP2D6 substrate) showed a twofold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and heart rate in healthy volunteers.

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6 as compared to other SSRIs established as significant inhibitors.

Levomepromazine, digoxin, carbamazepine
Thus no change or only very small changes of no clinical importance were observed when citalopram was given with CYP1A2 substrates (clozapine and theophylline), CYP2C9 (warfarin), CYP2C19 (imipramine and mephenytoin), CYP2D6 (sparteine, imipramine, amitriptyline, risperidone) and CYP3A4 (warfarin, carbamazepine (and its metabolite carbamazepine epoxid) and triazolam).

However, since carbamazepine is a microsomal enzyme inducer, the possibility that carbamazepine may increase the clearance of citalopram should be considered if the two drugs are given concomitantly.

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. 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).

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 after maternal SSRI /SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, difficulty in suckling or in sleeping, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence.

These symptoms could be due to either sertoninergic effects or withdrawal syndrome. 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.

Breastfeeding:
Citalopram is excreted into breast milk. It is estimated that the suckling infant will receive about 5% of the weight related maternal daily dose (in mg/kg). No or only minor events have been observed in the infants. However, the existing information is insufficient for assessment of the risk to the child. Caution is recommended.

The advantages of breastfeeding should outweigh the potential adverse effects for the child.

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 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 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 list below shows the percentage of adverse drug reactions associated with SSRIs and/or citalopram seen in either ≥ 1% of patients in double-blind placebo-controlled trials or in the post-marketing period.

Frequencies are defined as follows: Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (< 1/10000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Not known: Thrombocytopenia

Immune system disorders
Uncommon: Allergic reactions
Very rare: Anaphylactoid reactions
Not known: Hypersensitivity, anaphylactic reaction

Endocrine disorders
Very rare: Prolactinaemia
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
Very common: insomnia
Common: Agitation, nervousness, sleep disorders, abnormal orgasm (female), abnormal dreams, amnesia, anxiety, decreased libido, apathy and confusion.
Uncommon: Aggression, hallucinations, mania, depersonalisation, euphoria and increased libido
Not known: Panic attack (these symptoms may be due to the underlying disease), bruxism, restlessness, suicidal ideation, suicidal behaviour

Nervous system disorders
Very common: Somnolence, headache, dizziness
Common: Migraine, tremor, dizziness, disturbance in attention and paraesthesia
Uncommon: Syncope
Rare: Convulsion grand mal, dyskinesia, taste disturbance
Not known: Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder

Eye disorders
Very common: Abnormal accommodation
Common: Abnormalities of vision
Uncommon: Mydriasis
Not known: Visual disturbance

Ear and labyrinth disorders
Common: tinnitus

Cardiac disorders
Very common: Palpitations
Uncommon: Bradycardia, tachycardia
Very rare: Supraventricular and ventricular arrhythmia
Not known: QT-prolongation

Vascular disorders
Common: Hypotension, hypertension
Rare: Haemorrhage
Not known: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: Rhinitis, yawning and sinusitis
Uncommon: Coughing
Not known: Epistaxis

Gastrointestinal disorders
Very common: Nausea, dry mouth
Common: Dyspepsia, diarrhoea, vomiting, constipation, abdominal pain, flatulence and increased salivation
Not known: Gastrointestinal haemorrhage (including rectal haemorrhage)

Hepatobiliary disorders
Rare: Hepatitis
Not known: Liver function test abnormal

Skin and subcutaneous tissue disorders
Very common: Increased sweating
Common: Pruritus
Uncommon: Urticaria, alopecia, rash, purpura, photosensitivity reaction
Not known: Ecchymosis, angiodema

Musculoskeletal and connective tissue disorders
Common: Myalgia, arthralgia

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.

Renal and urinary disorders
Common: Micturition disorder and polyuria
Uncommon: Urinary retention

Reproductive system and breast disorders
Common: Ejaculation failure, ejaculation disorder, dysmenorrhoea and impotence
Uncommon: Female: Menorrhagia
Not known: Female: Metrorrhagia, Male: Priapism, galactorrhoea

General disorders and administration site conditions
Very common: Asthenia
Common: Fatigue
Uncommon: Malaise, oedema
Rare: Pyrexia

Number of patients: Citalopram / placebo = 1346 / 545

Cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).
Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease.

Withdrawal symptoms seen on discontinuation of citalopram treatment
Discontinuation of citalopram (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbance (include paraesthesia), sleep disturbance (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 sections 4.2 and section 4.4).

4.9 Overdose

Toxicity:
Comprehensive clinical data on citalopram overdose are limited and many cases involve concomitant overdoses of other drugs/alcohol. 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. Fatal cases of citalopram overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medications. Fatal dose is not known. Patients have survived ingestion of 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:
The following symptoms have been seen in reported overdose of citalopram: Nausea, drowsiness, dystonia, convulsions, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, hyperpyrexia and atrial and ventricular arrythmia. "Serotonin syndrome" 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 known specific antidote to citalopram. 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). The use of activated charcoal, to reduce further absorption, should be considered. Speeding up the passage using osmotically working laxatives, e.g., sodium sulphate can also be considered. ECG and vital signs should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Serotonin Reuptake Inhibitors
ATC-Code: N 06A B 04,

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 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 SSRIs, citalopram has no 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 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.

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 of citalopram is almost complete and independent of food intake (T_{max} average/mean 3.8 hours). Oral bioavailability is about 80%.

Distribution
The apparent volume of distribution ($V_d\beta$) is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

Biotransformation
Citalopram is metabolized to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated proprionic acid derivative. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma.

Elimination
The elimination half-life ($T_{½}\beta$) is about 1.5 days and the systemic citalopram plasma clearance (Cl_s) is about 0.33 L/min, and oral plasma clearance (Cl_{oral}) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12 – 23% 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 (≥ 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

In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. Citalopram has no mutagenic or carcinogenic potential. Embryotoxicity studies have shown skeletal anomalies at maternal toxic doses. The effects may be related to the pharmacological activity or could be an indirect effect due to maternal toxicity. Peri- and postnatal studies have revealed reduced survival in offspring during the lactation period. The potential risk for humans is unknown.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Tablets
Lactose monohydrate
Microcrystalline cellulose
Maize starch
Copovidone
Croscarmellose sodium
Magnesium stearate

Film Coating
Opadry White 20H 58983
Hypromellose
Titanium dioxide E171
Propylene glycol
Hydroxypropyl cellulose
Talc

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

1, 14, 20, 28, 30, 50, 56, 98, 100 or 250 film coated tablets in a PVC/PVdC/Aluminium blister

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy Ireland Limited
Spafield
Cork Road
Cashel
Co Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0408/061/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 February 2005
Date of last renewal: 8th September 2008

10 DATE OF REVISION OF THE TEXT

July 2011