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CITALOPRAM 10 MG, 20 MG AND 40 MG TABLETS
PL 36390/0024-6

LAY SUMMARY

On 18th November 2011, the MHRA granted STD Chemicals Limited Marketing Authorisations (licences) for Citalopram 10 mg, 20 mg and 40 mg Tablets (PL 36390/0024-6).

Citalopram 10 mg, 20 mg and 40 mg Tablets contain citalopram hydrobromide.

Citalopram Tablets belong to a group of medicines called selective serotonin reuptake inhibitors (SSRIs).

Citalopram Tablets are used to treat symptoms of:
- Depression (feelings of sadness, tearfulness, inability to sleep or enjoy life as you once used to) including the accompanying symptoms of anxiety;
- Panic attacks - citalopram can help relieve symptoms in people who are prone to panic attacks.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Citalopram 10 mg, 20 mg and 40 mg Tablets outweigh the risks; hence these Marketing Authorisations have been granted.
CITALOPRAM 10 MG, 20 MG AND 40 MG TABLETS
PL 36390/0024-6

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Citalopram 10 mg, 20 mg and 40 mg Tablets (PL 36390/0024-6) to STD Chemicals Limited on 18th November 2011. These products are prescription-only medicines (POM) and are indicated for the treatment of:

- depressive illness in the initial phase and as maintenance against potential relapse/recurrence.
- panic disorder with or without agoraphobia.

Citalopram 10 mg, 20 mg and 40 mg Tablets are not recommended for use in children and adolescents below 18 years of age.

These applications for Citalopram 10 mg, 20 mg and 40 mg Tablets are submitted according to Article 10c of Directive 2001/83/EC as amended, cross-referring to Citalopram 10 mg, 20 mg and 40 mg (PL 08137/0075-7), which were approved to Neolab Limited on 17th September 2002. These licences recently underwent a change of ownership to Fannin (UK) Limited on 15th August 2011 (PL 20417/0022-4).

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

A Risk Management Plan (RMP) was not submitted and is not required for applications of this type.

No new data were submitted nor were they necessary for these “simple” applications, as the data are identical to that of the previously granted cross-reference products.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 36390/0024-6
PROPRIETARY NAME: Citalopram 10 mg, 20 mg and 40 mg Tablets
ACTIVE(S): Citalopram hydrobromide
COMPANY NAME: STD Chemicals Limited
E.C. ARTICLE: Article 10c
LEGAL STATUS: POM

1. INTRODUCTION
These are “simple” applications for Citalopram 10 mg, 20 mg and 40 mg Tablets (PL 36390/0024-6) submitted under Article 10c of Directive 2001/83/EC as amended. The proposed MA holder is STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The applications cross-refer to Citalopram 10 mg, 20 mg and 40 mg (PL 08137/0075-7), which were approved to Neolab Limited on 17th September 2002. These licences recently underwent a change of ownership to Fannin (UK) Limited on 15th August 2011 (PL 20417/0022-4).

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 NAME(S)
The proposed names of the products are Citalopram 10 mg, 20 mg and 40 mg Tablets. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products are film-coated tablets that contain 10mg, 20mg and 40mg of citalopram (as the hydrobromide) as the active ingredient. The finished products are packaged in blister strips composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVdC) and aluminium and then enclosed in outer cartons.

Pack sizes are 28 and 30 tablets.

The proposed shelf-life is 2 years with no special storage instructions. This is consistent with the details registered for the cross-reference products.

2.3 Legal status
Prescription only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition
The composition is consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size for each product is stated.

2.8 Finished product/shelf-life specification
The finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
The excipients used are identical to those in the cross-reference products and none contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin.

This information is consistent with the cross-reference products.

3. EXPERT STATEMENTS
The applicant has included expert statements in Module 2 of the applications. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)
At the time of assessment, the SmPCs were consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING
PIL
The PIL has been prepared in-line with the details registered for the cross-reference product. This PIL is similar to the PIL for Sertraline Hydrochloride 50 mg and 100 mg Tablets, licensed to Neolab Limited on 24th September 2007 (PL 08137/0141-2). A satisfactory bridging statement has been provided.

The results of consultations with target patient groups ("user testing") are in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.
Labelling
At the time of assessment, the artwork was comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In-line with current legislation, the applicant has included the name of the product in Braille on the packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the applications are acceptable. The grant of these Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

An Environmental Risk Assessment was not submitted and is not required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously approved for the cross-reference products and, as such, has been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications Citalopram 10 mg, 20 mg and 40 mg (PL 08137/0075-7), which were approved to Neolab Limited on 17th September 2002. These licences recently underwent a change of ownership to Fannin (UK) Limited on 15th August 2011 (PL 20417/0022-4).

No new or unexpected safety concerns arise from these applications.

At the time of assessment, the SmPCs, PIL and labelling were satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with citalopram hydrobromide is considered to have demonstrated the therapeutic value of the compound. The risk:benefit ratio is therefore considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 23rd June 2011.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 27th June 2011.</td>
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<td>Following assessment of the application further information was requested regarding the quality section of the dossiers on 14th September 2011.</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 18th October 2011 for the quality section of the dossiers.</td>
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<td>The applications were determined on 18th November 2011.</td>
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CITALOPRAM 10 MG, 20 MG AND 40 MG TABLETS
PL 36390/0024-6

STEPS TAKEN AFTER ASSESSMENT

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Citalopram 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Citalopram 10 mg (as the hydrobromide).
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White round tablet.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.
Citalopram is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology
Major Depressive Episode:
Citalopram should be administered as a single oral dose of 20 mg daily. In general improvement in patients starts after one week but may only become evident from the second week of therapy.

As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased up to a maximum of 60 mg a day in 20 mg steps according to the patient's response (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.

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

Treating Panic Disorder:
Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. The recommended dose is 20-30 mg daily. A low initial starting dose is recommended to minimise the potential worsening of panic symptoms, which is generally recognised to occur early in the treatment of this disorder. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg/day (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.

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

Elderly patients (>65 years of age):
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children (< 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:
Dosage should be restricted to the lower end of the dose range.

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

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

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

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

MAOIs (monoamine oxidase inhibitor):
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and linezolid 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 used in combination with a MAOI. Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Treatment of elderly patients and patients with reduced kidney and liver function, see section 4.2.

Use in children and adolescents under 18 years of age:
Citalopram Tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with depressive illness, obsessive-compulsive disorder, bulimia nervosa or PMDD. 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 some 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 angiogenic 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.
**Diabetes:**
In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

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

**ECT (electroconvulsive therapy):**
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 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.

- **Haemorrhage:**
- There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as other haemorrhagic manifestations e.g. gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings with SSRIs (see section 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.

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.

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.

**Glaucoma:**
SSRIs may infrequently cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.
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.

Serotonin Syndrome:
If citalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan, caution is advisable. Rarely, the occurrence of “serotonin syndrome” has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia, may indicate the development of this condition (see section 4.5). Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

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

For information on concomitant treatment with non-selective, irreversible MAO-inhibitors 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:
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In a recurrence prevention clinical trial with citalopram, adverse events after 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:
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 susceptible individuals such as patients with congenitally prolonged QT syndrome, or in patients with hypokalaemia/hypomagnesaemia. 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.

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.
No pharmacodynamic interactions have been noted in clinical studies in which citalopram has been given concomitantly with benzodiazepines, neuroleptics, analgesics, lithium, alcohol, antihistamines, antihypertensive drugs, beta-blockers and other cardiovascular drugs.

**Contraindicated combinations**

**MAO-inhibitors:**
Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications).

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.

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.

**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 10mg daily) is not recommended.

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

**Serotonergic drugs:**
Co administration with serotonergic 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).

**Lithium and tryptophan:**
There is no pharmacokinetic interaction between lithium and citalopram. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

**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.
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.

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).

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).

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
In animal studies cimetidine had little or no influence on citalopram kinetics.

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 significantly increase the effect of metoprolol on the blood pressure and cardiac rhythm.

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

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

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

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induce nor inhibit P-glycoprotein).

### 4.6 PREGNANCY AND LACTATION

**Pregnancy:**
Animal studies did not provide any evidence of teratogenicity, however the safety of citalopram during human pregnancy has not been established. As with all drugs citalopram should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Neonates should be observed if maternal use of citalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonates after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, 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 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.

### 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 judgments and to react to emergencies.

Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.
4.8 UNDESIRABLE EFFECTS

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves. The adverse reactions are presented at the MedDRA Preferred Term Level.

For the following reactions a dose-response was discovered: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue. The table shows the percentage of adverse drug reactions associated with SSRIs and/or citalopram seen in either ≥1% of patients in double-blind placebo-controlled trials or in the post-marketing period.

Frequencies are defined as: very common (≥1/10); common (≥1/100, ≤1/10); uncommon (≥1/1000, ≤1/100); rare (≥1/10000, ≤1/1000); very rare (≤1/10000), not known (cannot be estimated from available data).

| Medical Condition                        | Very Common | Common | Uncommon | Rare | Not Known
<table>
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</thead>
<tbody>
<tr>
<td>Blood and lymphatic disorders</td>
<td></td>
<td>Purpura</td>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity, Anaphylactic reaction</td>
<td></td>
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<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td>Inappropriate ADH secretion</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Appetite decreased</td>
<td>Increased appetite</td>
<td>Hyponatremia</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td>Agitation, libido decreased, anxiety, nervousness, confusional state</td>
<td>Aggression, depersonalisation, hallucination, mania</td>
<td>Panic attack, bruxism, restlessness, suicide ideation and suicidal behaviour</td>
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</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence, insomnia</td>
<td>Tremor</td>
<td>Syncope</td>
<td>Convulsion grand mal, dyskinesia</td>
<td>Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4 Special warnings and precautions for use)</td>
<td>Visual disturbance</td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
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<td></td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Bradycardia, tachycardia</td>
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<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td>Orthostatic hypotension</td>
<td></td>
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<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td>Yawning</td>
<td></td>
<td>Epistaxis</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth, Nausea</td>
<td>Diarrhoea, vomiting</td>
<td>Gastrointestinal haemorrhage (including</td>
<td></td>
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</tbody>
</table>
### Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rectal haemorrhage)</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td></td>
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<td></td>
<td>Hepatitis</td>
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<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
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<tr>
<td>Renal and urinary disorders</td>
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<td>Urinary retention</td>
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<tr>
<td>Reproductive system and breast disorders</td>
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<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
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<td></td>
<td></td>
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<tr>
<td>Investigations</td>
<td></td>
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</tbody>
</table>

### Number of patients: Citalopram / placebo = 1346 / 545

1 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.

The following adverse events have been reported in clinical trials:

**Very common:** Headache, asthenia, sleep disorder

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

**Rare:** increase libido, coughing malaise and photosensitivity

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

*Withdrawal symptoms seen on discontinuation of SSRI treatment.*
Discontinuation of citalopram (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precaution for use).
4.9 OVERDOSE
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 and other SSRIs.

Nausea, vomiting, sweating, dizziness, tachycardia, tremor, 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.

Management
There is no specific antidote.

Observe for a minimum of 4 hours due to the long half life of citalopram.
An ECG should be taken.

Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal, given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50%. An 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.

Control convulsions with intravenous diazepam if they are frequent or prolonged.

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC-code: N 06 AB 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 newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT1A, 5-HT2, DA D1 and D2 receptors, α1-, α2- and β-adrenoceptors, histamine H1, muscarinic 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 newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.
In humans citalopram does not impair cognitive (intellectual function) and psychomotor performance and has no or minimal sedative properties, either alone or in combination with alcohol.

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

**Dose Response**
In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

### 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 ($V_d$) is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

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

**Elimination:**
The elimination half-life ($T_{1/2}$) is about 1.5 days and the systemic citalopram plasma clearance ($Cl_p$) is about 0.33 L/min, and oral plasma clearance ($Cl_{oral}$) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side-effects.

**Elderly patients (≥ 65 years):**
Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

**Reduced hepatic function:**
Citalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of citalopram is about twice as long and steady state citalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

**Reduced renal function:**
Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min).

### 5.3 PRECLINICAL SAFETY DATA
Citalopram has low acute toxicity. In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. Based on data from reproduction toxicity studies (segment I, II and III) there is no reason to have special concern for the use of citalopram in women of child-bearing potential. Citalopram has no mutagenic or carcinogenic potential.
6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core
Mannitol
Colloidal anhydrous silica
Microcrystalline cellulose
Magnesium stearate

Coating
Macrogol
Hypromellose
Titanium dioxide (E171)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Not applicable.

6.5 NATURE AND CONTENTS OF CONTAINER
Blistter strip comprising of PVC/PVdC/Aluminium foil enclosed in an outer carton. Pack sizes of 28 and 30 tablets (not all packs may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/11/2011

10 DATE OF REVISION OF THE TEXT
18/11/2011
1 NAME OF THE MEDICINAL PRODUCT
Citalopram 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Citalopram 20 mg (as the hydrobromide).
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White round tablet with a score mark on one side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.
Citalopram is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Major Depressive Episode:
Citalopram should be administered as a single oral dose of 20 mg daily. In general improvement in patients starts after one week but may only become evident from the second week of therapy.

As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased up to a maximum of 60 mg a day in 20 mg steps according to the patient's response (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.
A treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse.

Treating Panic Disorder:
Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. The recommended dose is 20-30 mg daily. A low initial starting dose is recommended to minimise the potential worsening of panic symptoms, which is generally recognised to occur early in the treatment of this disorder. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg /day (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.
Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer.

Elderly patients (>65 years of age):
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children (< 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:
Dosage should be restricted to the lower end of the dose range.

Reduced renal function:
Dosage adjustment is not necessary in cases of mild or moderate renal impairment. No information is available in cases of severe renal impairment (creatinine clearance <20 mL/min).
Withdrawal symptoms seen on discontinuation of citalopram:
Abrupt discontinuation should be avoided. When stopping treatment with citalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 Special Warnings and Special Precautions for Use and section 4.8 Undesirable Effects). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

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

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

MAOIs (monoamine oxidase inhibitor):
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and linezolid 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 used in combination with a MAOI. Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Treatment of elderly patients and patients with reduced kidney and liver function, see section 4.2.

Use in children and adolescents under 18 years of age:
Citalopram Tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with depressive illness, obsessive-compulsive disorder, bulimia nervosa or PMDD. 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 some 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 angiogenic 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.

Diabetes:
In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and or oral hypoglycaemic dosage may need to be adjusted.
Seizures:
Seizures are a potential risk with antidepressant drugs. The drug should be discontinued in any patient who develops seizures. Citalopram should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

ECT (electroconvulsive therapy):
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 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.

- Haemorrhage:
- There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as other haemorrhagic manifestations e.g. gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings with SSRIs (see section 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.

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.

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.

Glaucoma:
SSRIs may infrequently cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

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.
**Serotonin Syndrome:**
If citalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan, caution is advisable. Rarely, the occurrence of “serotonin syndrome” has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia, may indicate the development of this condition (see section 4.5). Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

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

For information on concomitant treatment with non-selective, irreversible MAO-inhibitors 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:**
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In a recurrence prevention clinical trial with citalopram, adverse events after 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:**
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 susceptible individuals such as patients with congenitally prolonged QT syndrome, or in patients with hypokalaemia/hypomagnesaemia. 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.

### 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.

No pharmacodynamic interactions have been noted in clinical studies in which citalopram has been given concomitantly with benzodiazepines, neuroleptics, analgesics, lithium, alcohol, antihistamines, antihypertensive drugs, beta-blockers and other cardiovascular drugs.
Contraindicated combinations

MAO-inhibitors:
Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications).

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.

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.

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 10mg daily) is not recommended.

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

Serotonergic drugs:
Co administration with serotonergic 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).

Lithium and tryptophan:
There is no pharmacokinetic interaction between lithium and citalopram. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

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.

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.

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).

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).

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
In animal studies cimetidine had little or no influence on citalopram kinetics.

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 significantly increase the effect of metoprolol on the blood pressure and cardiac rhythm.

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

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

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

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induce nor inhibit P-glycoprotein).

4.6 PREGNANCY AND LACTATION

Pregnancy:
Animal studies did not provide any evidence of teratogenicity, however the safety of citalopram during human pregnancy has not been established. As with all drugs citalopram should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Neonates should be observed if maternal use of citalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonates after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, 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 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.

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 judgments and to react to emergencies.

Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 UNDESIRABLE EFFECTS

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves. The adverse reactions are presented at the MedDRA Preferred Term Level.

For the following reactions a dose-response was discovered: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue. The table shows the percentage of adverse drug reactions
associated with SSRIs and/or citalopram seen in either ≥1% of patients in double-blind placebo-controlled trials or in the post-marketing period.

Frequencies are defined as: very common (≥1/10); common (≥1/100, ≤1/10); uncommon (≥1/1000, ≤1/100); rare (≥1/10000, ≤1/1000); very rare (≤1/10000), not known (cannot be estimated from available data).

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic disorders</td>
<td>Purpura</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity, Anaphylactic reaction</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td>Inappropriate ADH secretion</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Appetite decreased</td>
<td>Increased appetite</td>
<td>Hyponatremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation, libido decreased, anxiety, nervousness, confusional state</td>
<td>Aggression, depersonalisation, hallucination, mania</td>
<td></td>
<td>Panic attack, bruxism, restlessness, suicide ideation and suicidal behaviour</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence, insomnia</td>
<td>Tremor</td>
<td>Syncope</td>
<td>Convulsion grand mal, dyskinesia</td>
<td>Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td>Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4 Special warnings and precautions for use</td>
<td>Visual disturbance</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
<td></td>
<td></td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td>Epistaxis</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td>Yawning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth, Nausea</td>
<td>Diarrhoea, vomiting</td>
<td></td>
<td>Gastrointestinal haemorrhage (including rectal haemorrhage)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Sweating increased</td>
<td>Pruritus</td>
<td>Urticaria, alopecia, rash</td>
<td>Ecchymosis, angioedemas</td>
<td></td>
</tr>
</tbody>
</table>
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.

The following adverse events have been reported in clinical trials:

Very common: Headache, asthenia, sleep disorder

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

Rare: increase libido, coughing malaise and photosensitivity

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

Withdrawal symptoms seen on discontinuation of SSRI treatment.
Discontinuation of citalopram (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precaution for use).

4.9 OVERDOSE
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 and other SSRIs.

Nausea, vomiting, sweating, dizziness, tachycardia, tremor, 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.

Management
There is no specific antidote.

Observe for a minimum of 4 hours due to the long half life of citalopram. An ECG should be taken.

Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal, given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50%. An 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.

Control convulsions with intravenous diazepam if they are frequent or prolonged.

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC-code: N 06 AB 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 newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT1A, 5-HT2, DA D1 and D2 receptors, α1, α2 and β-adrenoceptors, histamine H1, muscarinic 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 newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.

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

Citalopram did not reduce saliva flow in a single dose study in human volunteers and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters. Citalopram has no effect on the serum levels of prolactin and growth hormone.
Dose Response
In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

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) is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

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

Elimination:
The elimination half-life (T_{1/2}) is about 1.5 days and the systemic citalopram plasma clearance (Cl) is about 0.33 L/min, and oral plasma clearance (Cl_{oral}) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side-effects.

Elderly patients (≥ 65 years):
Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function:
Citalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of citalopram is about twice as long and steady state citalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

Reduced renal function:
Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min).

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

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core
Mannitol
Colloidal anhydrous silica
Microcrystalline cellulose
Magnesium stearate
6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Not applicable.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister strip comprising of PVC/PVdC/Aluminium foil enclosed in an outer carton. Pack sizes of 28 and 30 tablets (not all packs may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/11/2011

10 DATE OF REVISION OF THE TEXT
18/11/2011
1 NAME OF THE MEDICINAL PRODUCT
Citalopram 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Citalopram 40 mg (as the hydrobromide).
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White round tablet with a score mark on one side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

Citalopram is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Major Depressive Episode:
Citalopram should be administered as a single oral dose of 20 mg daily. In general improvement in patients starts after one week but may only become evident from the second week of therapy.

As with all antidepressant medicinal products, dosage should be reviewed and adjusted if necessary within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased up to a maximum of 60 mg a day in 20 mg steps according to the patient's response (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.

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

Treating Panic Disorder:
Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. The recommended dose is 20-30 mg daily. A low initial starting dose is recommended to minimise the potential worsening of panic symptoms, which is generally recognised to occur early in the treatment of this disorder. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased gradually up to a maximum of 60 mg /day (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.

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

Elderly patients (>65 years of age):
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children (< 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:
Dosage should be restricted to the lower end of the dose range.

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

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

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

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

MAOIs (monoamine oxidase inhibitor):
Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and linezolid 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 used in combination with a MAOI. Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Treatment of elderly patients and patients with reduced kidney and liver function, see section 4.2.

Use in children and adolescents under 18 years of age:
Citalopram Tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with depressive illness, obsessive-compulsive disorder, bulimia nervosa or PMDD. 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 some 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 angiogenic 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.

Diabetes:
In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and or oral hypoglycaemic dosage may need to be adjusted.
Seizures:
Seizures are a potential risk with antidepressant drugs. The drug should be discontinued in any patient who develops seizures. Citalopram should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

ECT (electroconvulsive therapy):
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 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.

- Haemorrhage:
- There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as other haemorrhagic manifestations e.g. gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings with SSRIs (see section 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.

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.

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.

Glaucoma:
SSRIs may infrequently cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

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.
Serotonin Syndrome:
If citalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan, caution is advisable. Rarely, the occurrence of “serotonin syndrome” has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia, may indicate the development of this condition (see section 4.5). Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

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

For information on concomitant treatment with non-selective, irreversible MAO-inhibitors 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:
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In a recurrence prevention clinical trial with citalopram, adverse events after 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:
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 susceptible individuals such as patients with congenitally prolonged QT syndrome, or in patients with hypokalaemia/hypomagnesaemia. 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.

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.

No pharmacodynamic interactions have been noted in clinical studies in which citalopram has been given concomitantly with benzodiazepines, neuroleptics, analgesics, lithium, alcohol, antihistamines, antihypertensive drugs, beta-blockers and other cardiovascular drugs.
Contraindicated combinations

MAO-inhibitors:
Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications).

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.

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.

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 10mg daily) is not recommended.

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

Serotonergic drugs:
Co administration with serotonergic 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).

Lithium and tryptophan:
There is no pharmacokinetic interaction between lithium and citalopram. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

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.

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.

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).

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).

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
In animal studies cimetidine had little or no influence on citalopram kinetics.

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 significantly 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 concurrent administration of citalopram and metoprolol (a CYP2D6 substrate) showed a twofold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol on blood pressure and heart rate in healthy volunteers.

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

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

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induce nor inhibit P-glycoprotein).

4.6 PREGNANCY AND LACTATION
Pregnancy:
Animal studies did not provide any evidence of teratogenicity, however the safety of citalopram during human pregnancy has not been established. As with all drugs citalopram should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Neonates should be observed if maternal use of citalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonates after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, 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, particularly 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 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.

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 judgments and to react to emergencies.

Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 UNDESIRABLE EFFECTS
Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves. The adverse reactions are presented at the MedDRA Preferred Term Level.

For the following reactions a dose-response was discovered: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue. The table shows the percentage of adverse drug reactions...
associated with SSRIs and/or citalopram seen in either $\geq 1\%$ of patients in double-blind placebo-controlled trials or in the post-marketing period.

Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$, $\leq 1/10$); uncommon ($\geq 1/1000$, $\leq 1/100$); rare ($\geq 1/10000$, $\leq 1/1000$); very rare ($\leq 1/10000$), not known (cannot be estimated from available data).

<table>
<thead>
<tr>
<th>Medical Disorders</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic disorders</td>
<td></td>
<td>Purpura</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity, Anaphylactic reaction</td>
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<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inappropriate ADH secretion</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Appetite decreased</td>
<td>Increased appetite</td>
<td></td>
<td>Hyponatremia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation, libido decreased, anxiety, nervousness, confusional state</td>
<td>Aggression, depersonalisation, hallucination, mania</td>
<td></td>
<td>Panic attack, bruxism, restlessness, suicide ideation and suicidal behaviour</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence, insomnia</td>
<td>Tremor</td>
<td>Syncope</td>
<td>Convulsion grand mal, dyskinesia</td>
<td>Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4 Special warnings and precautions for use</td>
<td></td>
<td>Visual disturbance</td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td>Tinnitus</td>
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<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Bradycardia, tachycardia</td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td>Orthostatic hypotension</td>
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<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td></td>
<td>Yawning</td>
<td></td>
<td>Epistaxis</td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Dry mouth, Nausea</td>
<td>Diarrhoea, vomiting</td>
<td>Gastrointestinal haemorrhage (including rectal haemorrhage)</td>
<td></td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Sweating increased</td>
<td>Pruritus</td>
<td>Urticaria, alopecia, rash</td>
<td>Ecchymosis, angioedemas</td>
<td></td>
</tr>
</tbody>
</table>
Very Common | Common | Uncommon | Rare | Not Known
--- | --- | --- | --- | ---
Musculoskeletal, connective tissue and bone disorders | Myalgia, arthralgia |  |  |  
Renal and urinary disorders | Urinary retention |  |  |  
Reproductive system and breast disorders | Impotence, ejaculation disorder, ejaculation failure, abnormal orgasm (female) | Female: Menorrhagia |  | Female: Metrorrhagia Male: Priapism, galactorrhoea 
General disorders and administration site conditions | Fatigue, dizziness, paraesthesia | Oedema |  |  
Investigations | Weight decreased | Weight increased | Liver function test abnormal |  

Number of patients: Citalopram / placebo = 1346 / 545

1 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.

The following adverse events have been reported in clinical trials:

Very common: Headache, asthenia, sleep disorder

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

Rare; increase libido, coughing malaise and photosensitivity

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

Withdrawal symptoms seen on discontinuation of SSRI treatment:
Discontinuation of citalopram (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhea, 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 Precaution for use).

4.9 OVERDOSE

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 and other SSRIs.

Nausea, vomiting, sweating, dizziness, tachycardia, tremor, 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.

**Management**

There is no specific antidote.

Observe for a minimum of 4 hours due to the long half life of citalopram. An ECG should be taken.

Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal, given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50%. An 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.

Control convulsions with intravenous diazepam if they are frequent or prolonged.

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

**ATC-code**: N 06 AB 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 newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT1α, 5-HT2, DA D1 and D2 receptors, α1- and β-adrenoceptors, histamine H1, muscarinic 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 newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.

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

Citalopram did not reduce saliva flow in a single dose study in human volunteers and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters. Citalopram has no effect on the serum levels of prolactin and growth hormone.
Dose Response
In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption:
Absorption is almost complete and independent of food intake (Tmax average/mean 3.8 hours). Oral bioavailability is about 80%.

Distribution:
The apparent volume of distribution (Vd)β is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

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

Elimination:
The elimination half-life (T½ β) is about 1.5 days and the systemic citalopram plasma clearance (Cl) is about 0.33 L/min, and oral plasma clearance (Cloral) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side-effects.

Elderly patients (≥ 65 years):
Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function:
Citalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of citalopram is about twice as long and steady state citalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

Reduced renal function:
Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min).

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Core
Mannitol
Colloidal anhydrous silica
Microcrystalline cellulose
Magnesium stearate
6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Not applicable.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister strip comprising of PVC/PVdC/Aluminium foil enclosed in an outer carton. Pack sizes of 28 and 30 tablets (not all packs may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/11/2011

10 DATE OF REVISION OF THE TEXT
18/11/2011
PATIENT INFORMATION LEAFLET
CITALOPRAM 10 mg, 20 mg & 40 mg TABLETS
(citalopram hydrobromide)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet you may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Citalopram Tablets are and what they are used for
2. Before you take Citalopram Tablets
3. How to take Citalopram Tablets
4. Possible side effects
5. How to store Citalopram Tablets
6. Further information

1. WHAT CITALOPRAM TABLETS ARE AND WHAT THEY ARE USED FOR

Citalopram is one of a group of medicines called selective serotonin reuptake inhibitors (SSRIs). These work by bringing the level of serotonin in the brain back up to normal. Low levels of serotonin are thought to be a cause of depression and related disorders.

Citalopram is used to treat symptoms of:
- Depression (feelings of sadness, tearfulness, inability to sleep or enjoy life as you once used to) including the accompanying symptoms of anxiety;
- Panic attacks - citalopram can help relieve symptoms in people who are prone to panic attacks.

2. BEFORE YOU TAKE CITALOPRAM TABLETS

Do not take Citalopram Tablets if you are:
- allergic (hypersensitive) to citalopram hydrobromide or any of the other ingredients in the tablets (these are listed in Section 6, Further Information). If you develop a rash or other allergic reactions (like itching, swollen lips or face, shortness of breath), stop taking the tablets straight away and contact your doctor immediately.
- taking a monoamine oxidase inhibitor drug (MAOI) for depression or reversible monoamine oxidase inhibitors type A (MAOIs), since serious or even fatal reactions can occur. Examples of MAOIs include selegiline, moclobemide and linezolid. Treatment with citalopram should only be started 2 weeks after discontinuation of an irreversible MAOI.
- also taking a medicine containing pimozide.

Take special care with Citalopram Tablets

Before you take Citalopram Tablets you should tell your doctor if you:
- are receiving ECT (electroconvulsive therapy)
- have epilepsy or fits (seizures). If you experience an increase in seizure frequency, contact your doctor immediately as treatment with Citalopram Tablets may need to be discontinued
- have mania now or in the past, if you have a manic episode, contact your doctor immediately as treatment with Citalopram Tablets may need to be discontinued
- suffer from diabetes, as your insulin/medication may need adjusting
- have liver, kidney or heart problems
- have a bleeding disorder or have suffered from bleeding in the stomach or intestine
- suffer with problems with your eyes, such as certain kinds of glaucoma
- have low levels of sodium in the blood
- start to experience fever, muscle stiffness or tremor; changes in your mental state, like confusion, irritability and extreme agitation as you may be suffering from serotonin-syndrome or neuroleptic malignant syndrome. Although this syndrome occurs rarely it may result in potentially life threatening conditions. You should contact your doctor immediately as treatment with citalopram may need to be discontinued.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Some patients with manic-depressive illness may enter into a manic phase. This is characterised by unusual and rapidly changing ideas, inappropriate happiness and excessive physical activity. If you experience this consult your doctor.

Symptoms such as restlessness or difficulty in sitting or standing still can also occur during the first weeks of the treatment. Tell your doctor immediately if you experience these symptoms.

Special information relating to this medicine

As with other medicines used to treat depression or related diseases, an improvement is not achieved immediately. After the start of treatment with Citalopram Tablets, it may take several weeks before you experience any improvement. At the beginning of the treatment certain patients may experience increased anxiety, which will disappear during continued treatment. Therefore, it is very important that you follow your doctor's orders exactly and do not stop the treatment or change the dose without consulting your doctor.
Important information about Citalopram Tablets and thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:
- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to hospital straight away.

You may find it helpful to talk to a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about change in your behaviour.

Use in children and adolescents under 18 years of age

Citalopram Tablets should normally not be used for children and adolescents under 18 years. Patients under 18 have an increased risk of side effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Citalopram for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Citalopram Tablets for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Citalopram Tablets. Also, the long-term safety effects of this medicine concerning growth, maturation and cognitive and behavioural development of this age group, have not yet been demonstrated.

Taking other medicines

You should tell your doctor if you are taking or have recently taken any of the following medicines as they may decrease or increase the effect of your Citalopram Tablets. This includes medicines obtained without a prescription:

- certain MAO-inhibitors (used to treat depression). Non-selective MAO-inhibitors and MAO-inhibitors type A ( moclobemide) must not be used with Citalopram Tablets as serious or even fatal reactions (serotonin syndrome) can occur (see section 'Do not take Citalopram Tablets').
- sumatriptan (used to treat migraine) or tramadol (a pain killer). If you feel unwell when using these medicines with Citalopram Tablets you should see your doctor.
- lithium or tryptophan for the treatment of depression, anxiety and other mental disorders
- pimozide (a neuroleptic). This should not be taken at the same time as Citalopram Tablets (see section 'Do not take Citalopram Tablets')
- medicines known to affect the blood platelets (e.g. anticoagulant drugs used to treat or prevent blood clots; aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac used as painkillers and some antipsychotic drugs and tricyclic antidepressants)
- metoprolol, a beta blocker used to treat migraine, some heart conditions and high blood pressure. The effects of either drug could be increased, decreased or altered.
- cimetidine used to treat heartburn and stomach ulcers
- St Johns Wort (Hypericum perforatum), a herbal remedy

It may still be all right for you to take Citalopram Tablets and your doctor will be able to decide what is suitable for you.

Taking your medicine with food and alcohol

Citalopram Tablets can be taken with or without food. Drinking alcohol while being treated with citalopram is not recommended.

Pregnancy

If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before taking this medicine and your doctor will decide if this medicine is right for you. If you take this group of medicines (antidepressants) during the last 3 months of your pregnancy and until the days of birth you should be aware that the following effects may be seen in your newborn: trouble with breathing, a bluish skin, stiff or floppy muscles, jitters or being too hot or cold. If your newborn baby gets any of these symptoms please contact your doctor.

Make sure your midwife and/or doctor know you are on Citalopram Tablets. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Citalopram Tablets may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the new born (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are breast-feeding, ask your doctor for advice. You should not breast-feed your baby when taking Citalopram Tablets because small amounts of the medicine can pass into the breast milk.

Driving and using machines

These tablets may make you feel drowsy or affect your concentration. You should not drive or operate machinery if affected.
3. HOW TO TAKE CITALOPRAM TABLETS

Method of Administration:
Citalopram Tablets should be taken every day as a single dose. They should be swallowed whole with a drink of water, preferably at the same time each day. Do not crush or chew your tablets.

Dosage:
Your doctor will decide on the right starting dose for you and on any increase in the dose depending on your condition and whether you are taking any other medicines.
Always take Citalopram Tablets exactly as your doctor has told you to do so. You should check with your doctor or pharmacist if you are not sure. The label on the carton will tell you how many tablets you should take and when.

The usual doses for Citalopram Tablets are as follows:

Adults:
Depression (including accompanying symptoms of anxiety): The usual starting dose is 20 mg daily. This may be increased to a maximum of 60 mg daily, depending on your condition.

Panic disorders: The usual starting dose is 10 mg daily for the first week, increasing to 20-30 mg daily. This dose may be increased to a maximum of 80 mg daily, depending on your condition.

Elderly patients (above 65 years of age):
The usual starting dose is 20 mg daily, and this can be increased to a maximum of 40 mg daily, depending on response to treatment.

Use in children and adolescents under 18 years of age:
Citalopram Tablets are not recommended for children or adolescents. For further information, please see section 2 'Before you take Citalopram Tablets'.

Patients with special risks
Patients with liver problems should not receive more than 30 mg per day

Treatment duration:
You may not start to feel better when you first start taking this medicine. It may take several weeks for your symptoms to improve, so keep taking the tablets. Tell your doctor if you feel worse after starting the medication.

Even when you start to feel better you should continue to take this medicine. If you suffer from depression this may be for 4 to 6 months or longer. Tell your doctor if you have taken all your tablets and you still feel unwell.

If you take more Citalopram Tablets than you should:
If you have accidentally taken more than your prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist immediately. Remember to take the pack and any remaining Citalopram Tablets with you. The most common signs and symptoms of overdose are nausea, a forceful and rapid heartbeat, tremor, agitation, drowsiness and dizziness.

If you forget to take Citalopram Tablets:
It is important that you take your medicine every day. If you forget to take your medicine, just take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Citalopram Tablets:
If you stop taking Citalopram Tablets suddenly, you may experience withdrawal/discontinuation symptoms. These can include headaches, feeling dizzy, shaby, sick, anxious, agitated or confused. Some people experience tingling sensations, pins and needles, burning sensations, electric-shock like sensations or they find that they sweat more. Difficulty in sleeping and strange dreams can also occur.

If you are troubled by any of these withdrawal symptoms, your doctor may advise you to reduce the amount of medicine gradually by taking smaller amounts or taking the medicine less frequently for some time before stopping the tablets completely. Do not stop taking your medicine abruptly and do not stop taking your medicine without talking to your doctor first.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Citalopram Tablets can cause side effects although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after taking these tablets, you should stop taking the tablets and contact your doctor immediately:
- Any sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat
- Rash or itching (especially affecting your whole body)

If you notice any of the following you should contact your doctor immediately as your dose may need to be reduced or stopped:
- you start having fits (convulsions) for the first time or fits that you suffered from in the past have become more frequent
- your behaviour changes because you feel elated or over excited
- a combination of symptoms (known as 'serotonin syndrome') including unexplained fever with faster breathing or heart rate, sweating, muscle stiffness or tremor, confusion, extreme agitation or sleepiness (only rarely)

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to the hospital straight away.
Very common side effects (affects more than 1 user in 10):
- sleepiness; insomnia
- dry mouth
- nausea
- increased sweating

Common side effects (affects 1 to 10 users in 100):
- decrease in appetite; decrease in weight
- agitation; anxiety; nervousness; confusional state; abnormal dreams
- decrease in sex drive; impotence; ejaculation disorder; ejaculation failure; abnormal orgasm (female)
- tremor; dizziness; tingling or numbness (paraesthesia)
- tinnitus
- yawning; fatigue
- attention disturbance
- diarrhoea; vomiting; constipation
- pruritus
- muscle pain (myalgia); joint pain (arthralgia)

Uncommon side effects (affects 1 to 10 users in 1,000):
- red blotches or discoloration of the skin (purpura); hives (urticaria); rash; skin sensitivity to light
- hair loss
- increased appetite
- aggression; vague or dreamlike state (depersonalisation); hallucination; mania
- tinnitus
- unusually large pupils (the dark centre of the eye)
- slow heart beat; palpitations
- difficulty in passing urine
- swelling of the skin
- heavy or irregular periods
- increase in weight

Rare side effects (affects 1 to 10 users in 10,000):
- low blood sodium (hyponatraemia)
- tonic-clonic seizures
- taste disturbances
- bleeding
- fever
- inflammation of the liver (hepatitis)

Side effects of unknown frequency:
- reduction in blood platelets which increases the risk of bleeding or bruising
- low levels of blood potassium which can cause muscle weakness, twitching or abnormal heart rhythm
- hypersensitivity reactions; allergic reactions
- panic attack; grinding of the teeth; disturbed sleep; restlessness; thoughts of suicide or harming yourself; convulsions; movement disorder
- disturbed vision
- irregular heartbeat; hypotension (feeling faint or light-headed on standing)
- nosebleeds: bleeding of the stomach or intestines
- abnormal liver test
- bruising
- prolonged or painful erection; production of milk unassociated with childbirth
- an increased risk of bone fractures has been observed in patients taking this type of medicine

If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CITALOPRAM TABLETS

Do not take this medicine after the expiry date shown on the carton. The expiry date is the last day of that month.

Keep all medicines out of the reach and sight of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Citalopram Tablets contain:
The active substance is citalopram (as hydrobromide). Each tablet contains 10 mg, 20 mg or 40 mg of citalopram (as hydrobromide).

The other ingredients are mannitol, colloidial anhydrous silica, microcrystalline cellulose, magnesium stearate, macrogol, hypromellose and titanium dioxide (E171).

What Citalopram Tablets look like and the contents of the pack:
Citalopram 10 mg Tablets are white, round, film coated without a score line.
Citalopram 20 mg and 40 mg Tablets are white, round, film coated with a score line on one side.
Your medicine is available in blister packs of 28 or 30 tablets (not all packs may be marketed).

Marketing Authorisation Holder and Manufacturer:
The Product Licence holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.
The manufacturer responsible for batch release is Neclab Ltd, 57 High Street, Odilham, Hants, RG20 1LF.

This leaflet was last revised in February 2011.
The labelling below are the label mock-ups for the 28 tablet pack sizes for each strength. The marketing authorisation holder has stated that it does not intend to market the 30 tablet pack sizes at this time; therefore no labelling mock-ups for the 30 tablet pack sizes have been submitted. The marketing authorisation holder has committed to submit the UK labelling for the 30 tablet pack sizes to the regulatory authority for review before marketing the 30 tablet pack sizes.
Each tablet contains: Citalopram 20mg (as the hydrobromide).
Also contains mannitol.
Film-coated tablets for oral use. To be taken as directed by a physician.
Please read the enclosed leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Distributor;
Neo lab Ltd, 57 High Street, Oldham, Hants, RG29 1LF.
PL 36390/0025
MA Holder: STD Chemicals Ltd. Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.
Each tablet contains Citalopram 40mg (as the hydrobromide). Also contains mannitol.
Film-coated tablets for oral use. To be taken as directed by a physician. Please read the enclosed leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN