CITALOPRAM 10MG TABLETS
CITALOPRAM 20MG TABLETS
CITALOPRAM 40MG TABLETS
PL 12762/0187-9

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Goldshield Pharmaceuticals Limited Marketing Authorisations for the medicinal products Citalopram 10mg, 20mg and 40mg Tablets (PL 12762/0187-9) on 25 February 2011. Citalopram Tablets are only available on prescription from your doctor and are used to treat:
- major depression or anxiety disorders in adults
- panic disorders, with or without fear of wide open spaces, crowds, or uncontrolled social conditions.

Citalopram Tablets contain the active ingredient citalopram (as citalopram hydrobromide), which belongs to a group of antidepressants called Selective Serotonin Reuptake Inhibitors (SSRIs).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Citalopram 10mg, 20mg and 40mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Goldshield Pharmaceuticals Limited Marketing Authorisations for the medicinal products Citalopram 10mg, 20mg and 40mg Tablets (PL 12762/0187-9) on 25 February 2011. The products are prescription-only medicines for the treatment of:

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

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Seropam 10 mg, 20 mg and 40 mg Tablets (H Lundbeck, Denmark), which were first authorised in January 1989. The corresponding reference products in the UK are Cipramil 10 mg, 20 mg and 40 mg film-coated tablets (Lundbeck Limited, UK), which were first authorised in March 1995.

The active ingredient citalopram hydrobromide is a potent Selective Serotonin Reuptake Inhibitor (SSRI), with no or minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A single-dose, three-way crossover bioequivalence study was submitted to support these applications, comparing the test products Citalopram 20mg Tablets (Goldshield Pharmaceuticals Limited, UK) and Citalopram 40mg Tablets (Goldshield Pharmaceuticals Limited, UK) with the reference product Seropam 20 mg Tablets (Lundbeck SA, France) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Citalopram 10mg, 20mg and 40mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
**PHARMACEUTICAL ASSESSMENT**

**ACTIVE SUBSTANCE**

INN: Citalopram hydrobromide  
Chemical Name: (RS)-1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-5-phthalalcarboxonitrile hydrobromide;  
1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide  
Molecular Formula: C_{20}H_{21}N_{2}OF.HBr  
Structure

![Structure of Citalopram](image)

Molecular weight: 405.31  
Appearance: White crystalline powder, soluble in methanol, chloroform and dichloromethane, sparingly soluble in water and anhydrous ethanol, and insoluble in ether.

Citalopram hydrobromide is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An in-house specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.
DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely maize starch, lactose monohydrate, croscarmellose sodium, glycerol, copovidone, magnesium stearate, microcrystalline cellulose, hypromellose type E5, macrogol 400 and titanium dioxide E171. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Seropam 10 mg, 20 mg and 40 mg Tablets (H Lundbeck, Denmark).

Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution and impurity profiles have been provided for these products and their respective reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packaged in polyvinylchloride/aluminium blisters. These are packed into cardboard cartons with patient information leaflets in pack sizes of 28 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions “Store in the original package.”

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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 it contains.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of citalopram hydrobromide are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of citalopram hydrobromide is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics
In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, three-treatment, three-period, three-way crossover study to compare the pharmacokinetics of a 40mg dose of the test products Citalopram 20mg Tablets (Goldshield Pharmaceuticals Limited, UK) and Citalopram 40mg Tablets (Goldshield Pharmaceuticals Limited, UK), and the reference product Seropam 20 mg Tablets (Lundbeck SA, France) in healthy adult male and female subjects under fasting conditions.

The subjects were given 40mg (one or two tablets) of either the test or reference products with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to 168 hours after each administration. The washout period between the treatment arms was 28 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (arithmetic mean±standard deviation) of citalopram hydrobromide

<table>
<thead>
<tr>
<th></th>
<th>Citalopram 2 x 20mg (Test A)</th>
<th>Citalopram 40mg (Test B)</th>
<th>Seropam 2 x 20 mg (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-ₜ (ng h/ml)</td>
<td>2245±670</td>
<td>2256±723</td>
<td>2196±631</td>
</tr>
<tr>
<td>AUC₀-∞ (ng h/ml)</td>
<td>2406±815</td>
<td>2413±844</td>
<td>2339±724</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>61.3±12.2</td>
<td>64.4±13.9</td>
<td>61.8±13.3</td>
</tr>
</tbody>
</table>

AUC₀-ₜ area under the plasma concentration-time curve from time zero to t hours
AUC₀-∞ area under the plasma concentration-time curve from time zero to infinity
Cmax maximum plasma concentration

Pharmacokinetic parameters (ratio and confidence intervals [CI]) of citalopram hydrobromide

<table>
<thead>
<tr>
<th></th>
<th>Test A/Ref Ratio(%)</th>
<th>Test B/Ref Ratio(%)</th>
<th>90% CI</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-ₜ (ng h/ml)</td>
<td>102</td>
<td>98.1-105</td>
<td>101</td>
<td>97.8-105</td>
</tr>
<tr>
<td>AUC₀-∞ (ng h/ml)</td>
<td>102</td>
<td>98.3-106</td>
<td>101</td>
<td>97.8-105</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>99.4</td>
<td>94.4-105</td>
<td>104</td>
<td>98.9-110</td>
</tr>
</tbody>
</table>

The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits as 80% to 125% for Cmax and AUC values. The
90% confidence intervals of the test/reference ratio of arithmetic means for AUC$_{0-t}$, AUC$_{0-\infty}$ and C$_{max}$ lie within the acceptable limits. Thus, the data support the claim that the test product Citalopram 20mg Tablets (Goldshield Pharmaceuticals Limited, UK) is bioequivalent to the reference product Seropam 20mg Tablets (Lundbeck SA, France). Furthermore, as Citalopram 40mg Tablets (Goldshield Pharmaceuticals Limited, UK) has been shown to be bioequivalent to 2 x Seropam 20mg Tablets (Lundbeck SA, France), it can also be considered to be bioequivalent to Seropam 40mg Tablets (Lundbeck SA, France).

As the 10mg, 20mg and 40mg strength products meet the criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 20mg and 40mg tablet strengths can be extrapolated to the 10mg tablet strength.

**Efficacy**

The efficacy of citalopram hydrobromide is well-known. No new efficacy data have been submitted and none are required for applications of this type.

**Safety**

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of applications. No new or unexpected safety issues were raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

**Clinical Expert Report**

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Citalopram 10mg, 20mg and 40mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of citalopram hydrobromide are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 20mg and 40 mg strength tablets and their respective reference products. As the 10mg, 20mg and 40mg strengths of the product meet the criteria specified in the Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions from the bioequivalence study with the 20mg and 40mg tablet strengths can be extrapolated to the 10mg tablet strength.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Seropam 10 mg, 20 mg and 40 mg Tablets (H Lundbeck, Denmark). Extensive clinical experience with citalopram hydrobromide is considered to have demonstrated the therapeutic value of the products. The benefit-risk is, therefore, considered to be positive.
STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 21 September 2004.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 07 October 2004.


4 The applicant responded to the MHRA’s requests, providing further information on the dossier on 29 November 2007, 28 August 2008, 20 July 2009 and 16 February 2010.

5 The applications were determined and granted on 25 February 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Citalopram 10mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 12.49mg of Citalopram hydrobromide equivalent to 10mg of Citalopram.

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM
Film coated tablets.
Round, biconvex, white film coated tablets with marking 10 on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For 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
Major Depressive Episodes
The recommended dose is 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.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Treating Panic Disorder
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect.

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

**Reduced hepatic function**
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.

Monoamine Oxidase Inhibitors: 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 in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some case 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.

### 4.4 Special warnings and precautions for use

**Suicide/suicidal thoughts or clinical worsening**
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Citalopram is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of
suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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
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.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as haemorrhagic manifestations e.g. gastrointestinal haemorrhage with SSRIs. The risk of gastrointestinal haemorrhage may be increased in elderly people during treatment with SSRIs. 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.

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. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted.
As with most antidepressants, citalopram should be discontinued if the patient enters a manic phase. There is little clinical experience of concurrent use of citalopram and ECT.

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.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 40% of patients treated with 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 and headache are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see “Withdrawal symptoms seen on discontinuation of citalopram”, Section 4.2 Posology and Method of Administration).

Citalopram tablets contain a small amount of glycerol. At high doses glycerol can be harmful and can cause headache, stomach ache and diarrhea.

This medicine contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications).

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2 D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80%). These properties give citalopram a low potential for clinically significant drug interactions.

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

Serotonergic drugs – Co administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.

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

In a pharmacokinetic study no affect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased. In animal studies cimetidine had little or no influence on citalopram kinetics.

Dynamic interactions between citalopram and herbal remedy St John's Wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects.

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.

Oral anticoagulants enhance haemorrhagic risk; monitoring of the coagulation parameters should be more frequent.

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, 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.

Lactation

Citalopram is known to be excreted in breast milk. Its effects on the nursing infant have not been established. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, increased sweating and tremor. The incidence of each in excess over placebo is low (<10%).

In comparative clinical trials with tricyclic antidepressants the incidence of adverse events occurring with citalopram was found to be lower in all cases.
Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs), including Citalopram. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Citalopram should be avoided. The majority of symptoms experienced on withdrawal of SSRIs are non-serious and self-limiting.

Frequent (5 - 20%)
Increased sweating, headache, tremor, dizziness, abnormal accommodation, somnolence, insomnia, agitation, nervousness, nausea, dry mouth, constipation, diarrhoea, palpitation, asthenia.

Less frequent (1 - <5%)
Rash, pruritus, paraesthesia, migraine, abnormal vision, taste perversion, sleep disorder, decreased libido, impaired concentration, abnormal dreaming, amnesia, anxiety, increased appetite, anorexia, apathy, impotence, suicide attempt, confusion, dyspepsia, vomiting, abdominal pain, flatulence, increased salivation, weight decrease, weight increase, postural hypotension, tachycardia, rhinitis, micturition disorder, polyuria, ejaculation failure, female anorgasmia, fatigue.

Rare (<1%)
Myalgia, movement disorders, convulsions, tinnitus, euphoria, increased libido, coughing, malaise. Psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use)

Post Marketing - The following adverse reactions apply to the therapeutic class of SSRIs
Skin Disorders: Angiodema; ecchymoses. Photosensitivity reactions have been reported very rarely.
Disorders of metabolism and nutrition: Rare cases of hyponatraemia and inappropriate ADH secretion have been reported and appear to be reversible on discontinuation. The majority of the reports were associated with the older patients.
Gastrointestinal disorders: Gastrointestinal bleeding.
General disorders: Anaphylactoid reactions.
Hepato-biliary disorders: Abnormal LFT's.
Musculoskeletal disorders: Arthralgia.
Neurological disorders: Serotonin syndrome.
Psychiatric disorders: Hallucinations; mania; depersonalisation; panic attacks (these symptoms may be due to the underlying disease).
Cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).
Reproductive disorders: Galactorrhoea.

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 and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).
Some unwanted effects are likely linked to the very nature of the depressive illness: “switch effect”: transition from depression to hypomanic or manic excitement and suicidal risk upon initiation of treatment.

Reactivation of delirium in psychotic patients.
In patients with panic attacks, increase of the trouble upon initiation of treatment.

4.9 Overdose
Fatal dose is not known. Patients have survived ingestion of more than 2 g citalopram. The effects may be potentiated by alcohol taken at the same time. Potential interaction with TCAs, MAOIs and other SSRIs. Post marketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920mg and 2800mg), as well as non-fatal overdoses of unto 6000mg.

Symptoms
Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included nausea, dizziness, Sinus tachycardia, tremor, drowsiness and somnolence may occur. At higher doses convulsions may occur within a few hours after ingestion.

Hyperventilation, hyperpyrexia and coma have been reported.

In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, and cyanosis.

ECG changes including nodal rhythm ventricular arrhythmia and one possible case of Torsades de pointes, prolonged QT intervals and wide QRS complexes may occur and rarely rhabdomyolysis. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported.

Rarely, features of the "serotonin syndrome" may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment
There is no specific antidote.

An ECG should be taken.

Gastric evacuation by lavage and Consider use of 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%.

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.

Due to the large volume of distribution of citalopram, forced diuresis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing over dosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.
5  PHARMACOLOGICAL PROPERTIES
5.1  Pharmacodynamic properties

ATC-code: N 06 AB 04

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT)-uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.

Citalopram is the most Selective Serotonin Reuptake Inhibitor (SSRI) yet described, with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

Tolerance to the inhibition of 5 HT uptake is not induced by long term (14 day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5 HT reuptake by citalopram is primarily due to the (S)-enantiomer.

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-HT 1A, 5-HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the 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%. Citalopram, a highly lipophilic molecule, is well absorbed from the gut. There is accumulation of the drug during repeated dosing, however the mean
steady-state plasma concentrations are proportional to the dose between 10 and 60 mg, with a high interindividual variability; this finding indicates linear kinetics.

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

Citalopram is 80% protein bound, somewhat less than other SSRIs, therefore it is less likely to be involved in drug interactions resulting from protein binding displacement. Citalopram crosses the blood-brain barrier, this is probably mediated by a carrier mechanism, but no active efflux systems appear to be involved and there is no stereo specificity in the brain penetration.

Biotransformation
Citalopram undergoes an intense biotransformation through first-pass hepatic metabolism. Citalopram is metabolized in the liver by 2 N-demethylation steps, to the active demethylcitalopram (DCT) via CYP2C19 and 3A4, and to, didemethylcitalopram (DDCT) via CYP2D6, 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. These metabolites can be further conjugated as glucuronides.

The impact of metabolizer status on Citalopram metabolism is considered to be clinically insignificant.

In human brain the local cerebral metabolism of Citalopram occurred mainly through mitochondrial monoamine oxidases A and B and not, as in the liver through cytochromes P450.

Elimination
The elimination half-life (T½) is about 1.5 days and the systemic citalopram plasma clearance (Clss) is about 0.33 L/min, and oral plasma clearance (C1 oral) is about 0.41 L/min. This long half-life allows the drug to be administered once daily.

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.

Citalopram, 12% as DCT, 1.5% as DDCT and 4, 3% as conjugated propionic acid derivative; more than 65% of the dose was unaccounted for, suggesting significant fecal elimination and/or metabolism via pathways other than demethylation and oxidation.

However, when radioactive 14C-Citalopram was used, the urinary excretion appeared to be higher: healthy volunteers, received 40 mg Citalopram as an oral solution and urine and faeces were collected during 17 days; 85% of the radioactivity were recovered in the urine and 10% in the faeces; in the urine the relative amounts of Citalopram and metabolites were as follows: Citalopram glucuronide 14%, DDCT glucuronide: 6% and glucuronide of propionic acid metabolite:12% (Dalgaard et al.19%).

In healthy volunteers given Citalopram 40mg/day orally for 21 days: t1/2 was definitely higher for R-Citalopram and metabolites than for their S-counterparts (47 and 35S for R-and S-Citalopram respectively; total oral clearance was higher for S-Citalopram, essentially due to non renal clearance; the S-enantiomers of Citalopram, DCT and DDCT were eliminated faster than their antipodes; thus, the enantiospecificity was apparently more related to clearance than to distributional mechanisms. Citalopram is excreted into human breast milk; the milk/breast ratio is # 1, 50; in this condition the dose recovered by the infant would be 1, 8% of the weight adjusted maternal dose.

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.

In elderly subjects compared to young subjects, the elimination process was reduced: plasma AUC augmented by 23-30%, elimination, half-life was prolonged by 50 to 150%; the systemic clearance fell from 24 to 5-18 L/h; the DCT/Citalopram ratio was significantly decreased.

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.

In patients with hepatic impairment, the oral clearance of Citalopram was decreased by 37%, the $t_{1/2}$ was doubled, and there was not modification of $C_{\text{max}}$.

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).

In combination with imipramine, there can be a 50% increase in AUC of imipramine metabolite; desipramine. Combined treatment with clomipramine may result in increased plasma level of Citalopram.

5.3 Preclinical safety data
Citalopram has low acute toxicity. According to the results of acute toxicity, a safety margin was calculated as the minimal dose affecting ECG/maximal therapeutic human dose: this ration was > 33; comparatively it was 0, 3 for amitryptyline, 2, 4 for imipramine and 4, 3 for clomipramine.

Sub acute or chronic toxicity
In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. In rats that have been treated with Citalopram, there was a dose-dependent fatty infiltration in the liver of male rats only.

In a three months oral toxicity study in dogs of either sex, no hepatotoxicity was observed.

Complementary experiences were performed in rats. Fatty acid liver infiltration was enhanced in male rats by enzymatic induction, indicating that hepatotoxic effect is probably caused by a metabolite or intermediate which is formed in toxic amounts during the first hepatic hepatic passage. However no such effects were observed in female rats.

Teratogenicity
Citalopram is not teratogenic in rat or rabbit.

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
Maize Starch
Lactose Monohydrate
Crocarmellose sodium
Glycerol
Copovidone
Magnesium Stearate
Microcrystalline Cellulose

Film Coating:-
Hypermellose type E5
Macrogol 400
Titanium Dioxide E171

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
No special precautions for storage. Store in the original package.

6.5 Nature and contents of container
PVC/aluminum foil blister packs containing 14 tablets. The 2 blisters are packed in a carton with a leaflet.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Goldshield Pharmaceuticals Ltd.,
NLA Tower,
12-16 Addiscombe Road,
Croydon,
Surrey CRO OXT,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 12762/0187

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Citalopram 20mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 24.98mg of Citalopram hydrobromide equivalent to 20mg of Citalopram.

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM
Film coated tablets.

Oval, biconvex, white colour, film coated tablets, scored on one side and with marking 20 on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For 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
Major Depressive Episodes
The recommended dose is 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.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Treating Panic Disorder
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. 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 and adolescents (< 18 years of age)
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Reduced hepatic function
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.

Monoamine Oxidase Inhibitors: 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 in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some case 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.

4.4 Special warnings and precautions for use
Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Citalopram is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of
suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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
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.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as haemorrhagic manifestations e.g. gastrointestinal haemorrhage with SSRIs. The risk of gastrointestinal haemorrhage may be increased in elderly people during treatment with SSRIs. 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.

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. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted.
As with most antidepressants, citalopram should be discontinued if the patient enters a manic phase. There is little clinical experience of concurrent use of citalopram and ECT.

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.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 40% of patients treated with 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 and headache are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see “Withdrawal symptoms seen on discontinuation of citalopram”, Section 4.2 Posology and Method of Administration).

Citalopram tablets contain a small amount of glycerol. At high doses glycerol can be harmful and can cause headache, stomach ache and diarrhea.

This medicine contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications).

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2 D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80%). These properties give citalopram a low potential for clinically significant drug interactions.

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

Serotonergic drugs – Co administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.

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

In a pharmacokinetic study no affect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased. In animal studies cimetidine had little or no influence on citalopram kinetics.

Dynamic interactions between citalopram and herbal remedy St John's Wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects.

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.

Oral anticoagulants enhance haemorrhagic risk; monitoring of the coagulation parameters should be more frequent.

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, hypertoniaz, hypertonia, 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.

Lactation

Citalopram is known to be excreted in breast milk. Its effects on the nursing infant have not been established. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, increased sweating and tremor. The incidence of each in excess over placebo is low (<10%).

In comparative clinical trials with tricyclic antidepressants the incidence of adverse events occurring with citalopram was found to be lower in all cases.
Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs), including Citalopram. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Citalopram should be avoided. The majority of symptoms experienced on withdrawal of SSRIs are non-serious and self-limiting.

Frequent (5 - 20%)
Increased sweating, headache, tremor, dizziness, abnormal accommodation, somnolence, insomnia, agitation, nervousness, nausea, dry mouth, constipation, diarrhoea, palpitation, asthena.

Less frequent (1 - <5%)
Rash, pruritus, paraesthesia, migraine, abnormal vision, taste perversion, sleep disorder, decreased libido, impaired concentration, abnormal dreaming, amnesia, anxiety, increased appetite, anorexia, apathy, impotence, suicide attempt, confusion, dyspepsia, vomiting, abdominal pain, flatulence, increased salivation, weight decrease, weight increase, postural hypotension, tachycardia, rhinitis, micturition disorder, polyuria, ejaculation failure, female anorgasmia, fatigue.

Rare (<1%)
Myalgia, movement disorders, convulsions, tinnitus, euphoria, increased libido, coughing, malaise. Psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use)

Post Marketing - The following adverse reactions apply to the therapeutic class of SSRIs
Skin Disorders: Angiodema; ecchymoses. Photosensitivity reactions have been reported very rarely.

Disorders of metabolism and nutrition: Rare cases of hyponatraemia and inappropriate ADH secretion have been reported and appear to be reversible on discontinuation. The majority of the reports were associated with the older patients.

Gastrointestinal disorders: Gastrointestinal bleeding.

General disorders: Anaphylactoid reactions.

Hepato-biliary disorders: Abnormal LFT's.

Musculoskeletal disorders: Arthralgia.

Neurological disorders: Serotonin syndrome.

Psychiatric disorders: Hallucinations; mania; depersonalisation; panic attacks (these symptoms may be due to the underlying disease).

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

Reproductive disorders: Galactorrhoea.

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 and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).
Some unwanted effects are likely linked to the very nature of the depressive illness: “switch effect”: transition from depression to hypomanic or manic excitement and suicidal risk upon initiation of treatment.

Reactivation of delirium in psychotic patients.
In patients with panic attacks, increase of the trouble upon initiation of treatment.

4.9 Overdose
Fatal dose is not known. Patients have survived ingestion of more than 2 g citalopram. The effects may be potentiated by alcohol taken at the same time. Potential interaction with TCAs, MAOIs and other SSRIs. Post marketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920mg and 2800mg), as well as non-fatal overdoses of unto 6000mg.

Symptoms
Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included nausea, dizziness, Sinus tachycardia, tremor, drowsiness and somnolence may occur. At higher doses convulsions may occur within a few hours after ingestion.

Hyperventilation, hyperpyrexia and coma have been reported.
In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, and cyanosis.

ECG changes including nodal rhythm ventricular arrhythmia and one possible case of Torsades de pointes, prolonged QT intervals and wide QRS complexes may occur and rarely rhabdomolysis. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported. Rarely, features of the “serotonin syndrome” may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment
There is no specific antidote.
An ECG should be taken.
Gastric evacuation by lavage and Consider use of 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%.

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.
Due to the large volume of distribution of citalopram, forced diuresis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing over dosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: N 06 AB 04

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5 HT).

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT)-uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.

Citalopram is the most Selective Serotonin Reuptake Inhibitor (SSRI) yet described, with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

Tolerance to the inhibition of 5 HT uptake is not induced by long term (14 day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5 HT reuptake by citalopram is primarily due to the (S)-enantiomer.

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-HT 1A, 5-HT2, DA D1 and D2 receptors, α1-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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%. Citalopram, a highly lipophilic molecule, is well absorbed from the gut. There is accumulation of the drug during repeated dosing, however the mean
steady-state plasma concentrations are proportional to the dose between 10 and 60 mg, with a high interindividual variability; this finding indicates linear kinetics.

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

Citalopram is 80% protein bound, somewhat less than other SSRIs, therefore it is less likely to be involved in drug interactions resulting from protein binding displacement. Citalopram crosses the blood-brain barrier, this is probably mediated by a carrier mechanism, but no active efflux systems appear to be involved and there is no stereo specificity in the brain penetration.

Biotransformation
Citalopram undergoes an intense biotransformation through first-pass hepatic metabolism. Citalopram is metabolized in the liver by 2 N-demethylation steps, to the active demethylcitalopram (DCT) via CYP2C19 and 3A4, and to, didemethylcitalopram (DDCT) via CYP2D6, 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. These metabolites can be further conjugated as glucuronides.

The impact of metabolizer status on Citalopram metabolism is considered to be clinically insignificant.

In human brain the local cerebral metabolism of Citalopram occurred mainly through mitochondrial monoamine oxidases A and B and not, as in the liver through cytochromes P450.

Elimination
The elimination half-life (T½β) is about 1.5 days and the systemic citalopram plasma clearance (ClS) is about 0.33 L/min, and oral plasma clearance (Cl oral) is about 0.41 L/min. This long half-life allows the drug to be administered once daily.

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.

Citalopram, 12% as DCT, 1.5% as DDCT and 4, 3% as conjugated propionic acid derivative; more than 65% of the dose was unaccounted for, suggesting significant fecal elimination and/or metabolism via pathways other than demethylation and oxidation.

However, when radioactive 14C-Citalopram was used, the urinary excretion appeared to be higher: healthy volunteers, received 40 mg Citalopram as an oral solution and urine and faeces were collected during 17 days; 85% of the radioactivity were recovered in the urine and 10% in the faeces; in the urine the relative amounts of Citalopram and metabolites were as follows: Citalopram glucuronide 14%, DDCT glucuronide: 6% and glucuronide of propionic acid metabolite:12% (Dalgaard et al.19%).

In healthy volunteers given Citalopram 40mg/day orally for 21 days: t1/2 was definitely higher for R-Citalopram and metabolites than for their S-counterparts (47 and 35th for R-and S-Citalopram respectively; total oral clearance was higher for S-Citalopram, essentially due to non renal clearance; the S-enantiomers of Citalopram, DCT and DDCT were eliminated faster than their antipodes; thus, the enantiospecificity was apparently more related to clearance than to distributional mechanisms. Citalopram is excreted into human breast milk; the milk/breast ratio is # 1, 50; in this condition the dose recovered by the infant would be 1, 8% of the weight adjusted maternal dose.

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.
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.

In elderly subjects compared to young subjects, the elimination process was reduced: plasma AUC augmented by 23-30%, elimination, half-life was prolonged by 50 to 150%; the systemic clearance fell from 24 to 5-18 L/h; the DCT/Citalopram ratio was significantly decreased.

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.

In patients with hepatic impairment, the oral clearance of Citalopram was decreased by 37%, the t½ was doubled, and there was not modification of Cmax.

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).

In combination with imipramine, there can be a 50% increase in AUC of imipramine metabolite; desipramine. Combined treatment with clomipramine may result in increased plasma level of Citalopram.

5.3 Preclinical safety data
Citalopram has low acute toxicity. According to the results of acute toxicity, a safety margin was calculated as the minimal dose affecting ECG/maximal therapeutic human dose: this ration was > 33; comparatively it was 0, 3 for amitryptyline, 2, 4 for imipramine and 4, 3 for clomipramine.

Sub acute or chronic toxicity
In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. In rats that have been treated with Citalopram, there was a dose-dependent fatty infiltration in the liver of male rats only.

In a three months oral toxicity study in dogs of either sex, no hepatotoxicity was observed.

Complementary experiences were performed in rats. Fatty acid liver infiltration was enhanced in male rats by enzymatic induction, indicating that hepatotoxic effect is probably caused by a metabolite or intermediate which is formed in toxic amounts during the first hepatic hepatic passage. However no such effects were observed in female rats.

Teratogenicity
Citalopram is not teratogenic in rat or rabbit.

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
Maize Starch
Lactose Monohydrate
Croscarmellose sodium
Glycerol
Copovidone
Magnesium Stearate
Microcrystalline Cellulose

Film coating:-
Hypromellose type E5
Macrogol 400
Titanium Dioxide E171

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
No special precautions for storage. Store in the original package.

6.5 Nature and contents of container
PVC/aluminum foil blister packs containing 2 x 14 tablets. The blisters are packed in a carton with a leaflet.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Goldshield Pharmaceuticals Ltd.,
NLA Tower,
12-16 Addiscombe Road,
Croydon,
Surrey CRO OXT,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 12762/0188

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
1 NAME OF THE MEDICINAL PRODUCT  
Citalopram 40mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION  
Each film-coated tablet contains 49.96mg of Citalopram hydrobromide equivalent to 40mg of Citalopram.  

For full list of excipients, see 6.1

3 PHARMACEUTICAL FORM  
Film coated tablets.  
Oval, biconvex, white colour, film coated tablets, scored on one side and with marking 40 on the other side.

4 CLINICAL PARTICULARS  
4.1 Therapeutic indications  
For 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  
Major Depressive Episodes  
The recommended dose is 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.  
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.  
Treatting Panic Disorder  
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect.  
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 and adolescents (< 18 years of age)
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Reduced hepatic function
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.

Monoamine Oxidase Inhibitors: 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 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.

4.4 Special warnings and precautions for use
Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Citalopram is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients
with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age
Citalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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
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.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as haemorrhagic manifestations e.g. gastrointestinal haemorrhage with SSRIs. The risk of gastrointestinal haemorrhage may be increased in elderly people during treatment with SSRIs. 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.

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. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted.

As with most antidepressants, citalopram should be discontinued if the patient enters a manic phase. There is little clinical experience of concurrent use of citalopram and ECT.
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.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 40% of patients treated with 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 and headache are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see “Withdrawal symptoms seen on discontinuation of citalopram”, Section 4.2 Posology and Method of Administration).

Citalopram tablets contain a small amount of glycerol. At high doses glycerol can be harmful and can cause headache, stomach ache and diarrhea.

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications).

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80%). These properties give citalopram a low potential for clinically significant drug interactions.

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

Serotonergic drugs – Co administration with serotonergic drugs (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.

Lithium & tryptophan – There is no pharmacokinetic interaction between lithium and citalopram. However there are have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these drugs should be undertaken with caution. Routine monitoring of lithium levels need not be adjusted.
In a pharmacokinetic study no affect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased. In animal studies cimetidine had little or no influence on citalopram kinetics.

Dynamic interactions between citalopram and herbal remedy St John's Wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects.

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.

Oral anticoagulants enhance haemorrhagic risk; monitoring of the coagulation parameters should be more frequent.

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, 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.

Lactation

Citalopram is known to be excreted in breast milk. Its effects on the nursing infant have not been established. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea, somnolence, dry mouth, increased sweating and tremor. The incidence of each in excess over placebo is low (<10%).

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

Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs), including Citalopram. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Citalopram should be
avoided. The majority of symptoms experienced on withdrawal of SSRIs are non-serious and self-limiting.

Frequent (5 - 20%)
Increased sweating, headache, tremor, dizziness, abnormal accommodation, somnolence, insomnia, agitation, nervousness, nausea, dry mouth, constipation, diarrhoea, palpitation, asthena.

Less frequent (1 - <5%)
Rash, pruritus, paraesthesia, migraine, abnormal vision, taste perversion, sleep disorder, decreased libido, impaired concentration, abnormal dreaming, amnesia, anxiety, increased appetite, anorexia, apathy, impotence, suicide attempt, confusion, dyspepsia, vomiting, abdominal pain, flatulence, increased salivation, weight decrease, weight increase, postural hypotension, tachycardia, rhinitis, micturition disorder, polyuria, ejaculation failure, female anorgasmia, fatigue.

Rare (<1%)
Myalgia, movement disorders, convulsions, tinnitus, euphoria, increased libido, coughing, malaise. Psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use)

Post Marketing - The following adverse reactions apply to the therapeutic class of SSRIs
Skin Disorders: Angiodema; ecchymoses. Photosensitivity reactions have been reported very rarely.

Disorders of metabolism and nutrition: Rare cases of hyponatraemia and inappropriate ADH secretion have been reported and appear to be reversible on discontinuation. The majority of the reports were associated with the older patients.

Gastrointestinal disorders: Gastrointestinal bleeding.

General disorders: Anaphylactoid reactions.

Hepato-biliary disorders: Abnormal LFT's.

Musculoskeletal disorders: Arthralgia.

Neurological disorders: Serotonin syndrome.

Psychiatric disorders: Hallucinations; mania; depersonalisation; panic attacks (these symptoms may be due to the underlying disease).

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

Reproductive disorders: Galactorrhoea

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 and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

Some unwanted effects are likely linked to the very nature of the depressive illness: “switch effect”: transition from depression to hypomanic or manic excitement and suicidal risk upon initiation of treatment.
Reactivation of delirium in psychotic patients.

In patients with panic attacks, increase of the trouble upon initiation of treatment.

4.9 Overdose

Fatal dose is not known. Patients have survived ingestion of more than 2 g citalopram. The effects may be potentiated by alcohol taken at the same time. Potential interaction with TCAs, MAOIs and other SSRIs. Post marketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920mg and 2800mg), as well as non-fatal overdoses of unto 6000mg.

Symptoms

Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included nausea, dizziness, Sinus tachycardia, tremor, drowsiness and somnolence may occur. At higher doses convulsions may occur within a few hours after ingestion.

Hyperventilation, hyperpyrexia and coma have been reported.

In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, and cyanosis.

ECG changes including nodal rhythm ventricular arrhythmia and one possible case of Torsades de pointes, prolonged QT intervals and wide QRS complexes may occur and rarely rhabdomyolysis. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported. Rarely, features of the "serotonin syndrome" may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment

There is no specific antidote.

An ECG should be taken.

Gastric evacuation by lavage and Consider use of 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%.

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. Due to the large volume of distribution of citalopram, forced diuresis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing over dosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: N06AB04

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5 HT).

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT)-uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.
Citalopram is the most Selective Serotonin Reuptake Inhibitor (SSRI) yet described, with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

Tolerance to the inhibition of 5 HT uptake is not induced by long term (14 day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5 HT reuptake by citalopram is primarily due to the (S)-enantiomer.

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-HT 1A, 5-HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the 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%. Citalopram, a highly lipophilic molecule, is well absorbed from the gut. There is accumulation of the drug during repeated dosing, however the mean steady-state plasma concentrations are proportional to the dose between 10 and 60 mg, with a high interindividual variability; this finding indicates linear kinetics.

**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.

Citalopram is 80% protein bound, somewhat less than other SSRIs, therefore it is less likely to be involved in drug interactions resulting from protein binding displacement. Citalopram crosses the blood-brain barrier, this is probably mediated by a carrier mechanism, but no active efflux systems appear to be involved and there is no stereo specificity in the brain penetration.
Biotransformation
Citalopram undergoes an intense biotransformation through first-pass hepatic metabolism. Citalopram is metabolized in the liver by 2 N-demethylation steps, to the active demethylcitalopram (DCT) via CYP2C19 and 3A4, and to, didemethylcitalopram (DDCT) via CYP2D6, 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. These metabolites can be further conjugated as glucuronides.

The impact of metabolizer status on Citalopram metabolism is considered to be clinically insignificant.

In human brain the local cerebral metabolism of Citalopram occurred mainly through mitochondrial monoamine oxidases A and B and not, as in the liver through cytochromes P450.

Elimination
The elimination half-life (T½β) is about 1.5 days and the systemic citalopram plasma clearance (Cls) is about 0.33 L/min, and oral plasma clearance (Cl oral) is about 0.41 L/min. This long half-life allows the drug to be administered once daily.

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.

Citalopram, 12% as DCT, 1.5% as DDCT and 4, 3% as conjugated propionic acid derivative; more than 65% of the dose was unaccounted for, suggesting significant fecal elimination and/or metabolism via pathways other than demethylation and oxidation.

However, when radioactive 14C-Citalopram was used, the urinary excretion appeared to be higher: healthy volunteers, received 40 mg Citalopram as an oral solution and urine and faeces were collected during 17 days; 85% of the radioactivity were recovered in the urine and 10% in the faeces; in the urine the relative amounts of Citalopram and metabolites were as follows: Citalopram glucuronide 14%, DDCT glucuronide: 6% and glucuronide of propionic acid metabolite:12% (Dalgaard et al.19%).

In healthy volunteers given Citalopram 40mg/day orally for 21 days: t½ was definitely higher for R-Citalopram and metabolites than for their S-counterparts (47 and 35th for R-and S-Citalopram respectively; total oral clearance was higher for S-Citalopram, essentially due to non renal clearance; the S-enantiomers of Citalopram, DCT and DDCT were eliminated faster than their antipodes; thus, the enantiospecificity was apparently more related to clearance than to distributional mechanisms. Citalopram is excreted into human breast milk; the milk/breast ratio is # 1, 50; in this condition the dose recovered by the infant would be 1, 8% of the weight adjusted maternal dose.

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.

In elderly subjects compared to young subjects, the elimination process was reduced: plasma AUC augmented by 23-30%, elimination, half-life was prolonged by 50 to 150%; the systemic clearance fell from 24 to 5-18 L/h; the DCT/Citalopram ratio was significantly decreased.
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.
In patients with hepatic impairment, the oral clearance of Citalopram was decreased by 37%, the \( t_{1/2} \) was doubled, and there was not modification of \( C_{\text{max}} \).

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).
In combination with imipramine, there can be a 50% increase in AUC of imipramine metabolite, desipramine. Combined treatment with clomipramine may result in increased plasma level of Citalopram.

5.3 Preclinical safety data
Citalopram has low acute toxicity. According to the results of acute toxicity, a safety margin was calculated as the minimal dose affecting ECG/maximal therapeutic human dose: this ration was > 33; comparatively it was 0, 3 for amitryptiline, 2, 4 for imipramine and 4, 3 for clomipramine.

Sub acute or chronic toxicity
In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram. In rats that have been treated with Citalopram, there was a dose-dependent fatty infiltration in the liver of male rats only.
In a three months oral toxicity study in dogs of either sex, no hepatotoxicity was observed.
Complementary experiences were performed in rats. Fatty acid liver infiltration was enhanced in male rats by enzymatic induction, indicating that hepatotoxic effect is probably caused by a metabolite or intermediate which is formed in toxic amounts during the first hepatic hepatic passage. However no such effects were observed in female rats.

Teratogenicity
Citalopram is not teratogenic in rat or rabbit.

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
Maize Starch
Lactose Monohydrate
Crocarmellose sodium
Glycerol
Copovidone
Magnesium Stearate
Microcrystalline Cellulose

Film coating:-
Hypermellose type E5
Macrogol 400
Titanium Dioxide E171
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
No special precautions for storage. Store in the original package.

6.5 Nature and contents of container
PVC/aluminum foil blister packs containing 14 tablets. Such 2 blisters are packed in a carton with a leaflet.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Goldshield Pharmaceuticals Ltd.,
NLA Tower,
12-16 Addiscombe Road,
Croydon,
Surrey CRO OXT,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 12762/0189

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
Citalopram 10mg, 20mg and 40mg Tablets (citalopram hydrobromide)

Goldshield

INFORMATION LEAFLET

Citalopram 10mg, 20mg and 40mg Tablets are used to treat:

- Major depression or anxiety disorders in adults.
- Olanzapine or quetiapine tablets (for depression or anxiety in adults).

Citalopram tablets are taken with a glass of water, usually at the same time every day. If you experience any side effects, please contact your doctor or pharmacist.

Citalopram tablets are not recommended for children or adolescents under 18 years old.

If you are pregnant or breast-feeding, please contact your doctor or pharmacist before taking Citalopram tablets.

Before taking Citalopram tablets, please contact your doctor or pharmacist if you:

- Are pregnant or breast-feeding.
- Have any other medical conditions.
- Are taking any other medications.
- Have had any other allergies or adverse reactions.

Keep all of the tablets out of reach of children.

If you experience any side effects, please contact your doctor or pharmacist.

If you are taking any other medications, please contact your doctor or pharmacist before taking Citalopram tablets.

If you are pregnant or breast-feeding, please contact your doctor or pharmacist before taking Citalopram tablets.

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Taking Citalopram tablets with food and drink:
Do not drink alcohol while taking Citalopram tablets as alcohol may make the symptoms of depression worse.
Driving and using machinery:
Citalopram tablets may make you feel dizzy, confused or affect your judgment. If this happens to you, do not drive or operate machinery.

Important information about some of the ingredients in Citalopram tablets:
Citalopram tablets contain lactose which is a type of sugar. If you have been told by your doctor that you are intolerant of sugar, contact your doctor before taking this medicine.

3. HOW TO TAKE CITALOPRAM TABLETS

Always take Citalopram tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Your doctor will tell you how much to take when you first start taking it. Most people start to feel better after 2 to 4 weeks.

If you do not feel any better after this time, talk to your doctor. He or she may tell you to take more of the medicine several times a day.

How much you take is decided by your doctor:
Major depression: The usual dose is 10 to 20 mg a day. Your doctor may decide to gradually increase the dose up to a maximum of 40 mg a day. Treatment should be for at least 6 months. Dependence on antidepressants can take 2 to 3 weeks to develop, so you should start taking your medicine gradually, in consultation with your doctor.

Other people should usually not take more than 20 mg of Citalopram each day.

Patients with liver or kidney problems are likely to be given lower doses of Citalopram than usual. Taking Citalopram tablets:
- Follow the directions and instructions how and when to take the tablets.
- Swallow the tablets whole. Avoid chewing or crushing the tablets unless you are told to do so by your doctor.

How to take more Citalopram tablets than you should:
- If you take more Citalopram tablets than you should, contact your doctor or pharmacist or go to the nearest hospital casualty department immediately. In some areas, there are no specific drug overdoses which could be treated.

Whether you have a fever, a cold or the flu, you should not take Citalopram tablets:
- Do not take Citalopram tablets if you have a cold or the flu. A cold or the flu can cause a fever which makes your medicines less effective.

If you take too many Citalopram tablets:
- You may have a wide range of side effects that can be harmful. You should call your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Skin and muscle:
Like most medicines, Citalopram can cause side effects, although everybody gets them.
Sleeping tablets can irritate the stomach and cause a frequent or dry cough. You should tell your pharmacist or doctor if you experience any of the following:

- Dry mouth
- Fainting
- Headaches
- Low mood or depression
- Mood swings
- Nausea
- Shivering
- Unusual mood changes

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- Unusual mood changes

When you are taking Citalopram tablets:
- You may feel a little tired or have a dry mouth.
- You may have unusual tiredness or drowsiness.
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The following side effects may also occur:
- Common: Feeling sick, nausea, vomiting, stomach pain, flatulence, diarrhea, constipation, dry mouth.
- Severe: Life-threatening allergic reactions (e.g., anaphylaxis, Stevens-Johnson syndrome).

5. STORED WATER-SOLUBLE TABLETS

Do not take Citalopram tablets while you are taking other medicines:
If you are taking any other medicines, you should tell your pharmacist or doctor.

Taking Citalopram tablets with alcohol:
Your doctor will tell you how much to take when you first start taking it. Most people start to feel better after 2 to 4 weeks.

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