CITALOPRAM 10 MG FILM-COATED TABLETS
PL 17907/0089

CITALOPRAM 20 MG FILM-COATED TABLETS
PL 17907/0090

CITALOPRAM 40 MG FILM-COATED TABLETS
PL 17907/0091

(CITALOPRAM HYDROBROMIDE)

UK Public Assessment Report

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CITALOPRAM 10MG, 20MG & 40MG FILM-COATED TABLETS (CITALOPRAM HYDROBROMIDE) PL 17907/0089, 0090 & 0091

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Citalopram 10mg film-coated Tablets (PL 17907/0089), Citalopram 20mg film-coated Tablets (PL 17907/0090), and Citalopram 40mg film-coated Tablets (PL 17907/0091) on 22nd August 2006. These are prescription-only medicines (POM) used for the prevention and treatment of depression, and to relieve the symptoms in patients prone to panic attacks.

Citalopram film-coated tablets contain the active ingredient citalopram hydrobromide, which belongs to a group of medicines called Selective Serotonin Reuptake Inhibitors (SSRIs), and acts by increasing the amount of a chemical called serotonin in the brain to relieve symptoms of depression.

The test products were considered the same as the reference products Cipramil Tablets 10mg, 20mg and 40mg (PL 00458/0057, 0058 & 0059, Lundbeck Limited) based on data submitted by Bristol Laboratories Limited.

These applications are based on reference products with valid UK licences. 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 film-coated Tablets outweigh the risk; hence Marketing Authorisations (MAs) have been granted.

CITALOPRAM 10MG, 20MG & 40MG FILM-COATED TABLETS (CITALOPRAM HYDROBROMIDE) PL 17907/0089, 0090 & 0091

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Citalopram 10mg film-coated Tablets (PL 17907/0089), Citalopram 20mg film-coated Tablets (PL 17907/0090), and Citalopram 40mg film-coated Tablets (PL 17907/0091) on 22nd August 2006. The products are prescription-only medicines.

These are standard, abridged, national applications for Citalopram 10mg, 20mg and 40mg film-coated Tablets, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products, Cipramil Tablets 10mg, 20mg and 40mg (PL 00458/0057, 0058 & 0059), granted to Lundbeck Limited on 17th March 1995. The reference products have been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired.

Citalopram tablets contain the active ingredient, citalopram hydrobromide, a Selective Serotonin Reuptake Inhibitor (SSRI), and are indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse or recurrence. They are also indicated in the treatment of panic disorder with or without agoraphobia.

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT)-uptake 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 treatment with citalopram.

These applications for Citalopram 10mg, 20mg and 40mg film-coated Tablets were submitted at the same time and they all depend on the single bioequivalence study presented comparing the applicant's 40mg product with the reference product Cipramil Tablets 40mg (PL 00458/0057, Lundbeck Limited). Consequently, all sections of the Scientific Discussion refer to all three products.

PHARMACEUTICAL ASSESSMENT

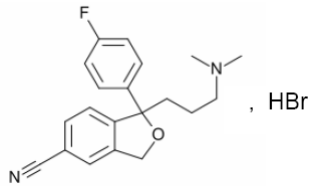
ACTIVE SUBSTANCE

Citalopram Hydrobromide

Nomenclature:

INN:	Citalopram hydrobromide
Chemical name:	1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile hydrobromide

Structure:



Molecular formula:	$C_{20}H_{21}FN_2O,HBr$
Molecular weight:	405.35
Physical form:	White or almost white crystalline powder, odourless or almost odourless
Solubility:	Freely soluble in methanol and sparingly soluble in water

The active substance, citalopram hydrobromide, is not the subject of a European Pharmacopeia (EP) or British Pharmacopeia (BP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Active citalopram hydrobromide is stored in appropriate packaging. It is packed in polyethylene bags, which are packed into HDPE (high density polyethylene) drums. Specifications and Certificates of Analysis have been provided for the packaging material. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed packaging. These data demonstrate the stability of the active substance and support a retest period of 3 years.

DRUG PRODUCT

Composition

The drug product is presented as film-coated tablets containing 10mg, 20mg or 40mg of the active ingredient citalopram, as citalopram hydrobromide.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, maize starch, croscarmellose sodium, and magnesium stearate making up the tablet core; and hypromellose, titanium dioxide (E171), purified talc, and macrogol 400 making up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

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

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as milk collected for human consumption.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications covering the 3 strengths are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The tablets are packed in PVC (polyvinyl chloride) / PVDC (polyvinylidene chloride) / aluminium foil blister strips of 14, which are placed with the PIL into cardboard outer cartons, in pack sizes of 14, 28, 56 or 84 tablets. The tablets are also available as a pack size of 1000, packaged in HDPE containers with screw cap closures.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. Storage directions are 'Do not store above 25°C', and additionally 'Store in the original package' for the blister packs and 'Keep the container tightly closed' for the HDPE containers.

Bioequivalence Study

A single bioequivalence study was submitted comparing the test product, Citalopram 40mg film-coated Tablets, to the innovator product, Cipramil Tablets 40mg (PL 00458/0057, Lundbeck Limited). An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory.

Conclusion

The test products are pharmaceutically equivalent to the reference products, which have been licensed in the UK for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Citalopram 40mg film-coated Tablets is a generic medicinal product of Cipramil Tablets 40mg appears justified. As the test products, Citalopram 10mg, 20mg and 40mg film-coated Tablets, meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength were extrapolated to the 10mg and 20mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted.

PRECLINICAL ASSESSMENT

These abridged applications, submitted under Article 10.1 of Directive 2001/83/EC, as amended, are for Citalopram 10mg, 20mg and 40mg film-coated Tablets, claiming to be generic medicinal products of Cipramil Tablets 10mg, 20mg and 40mg (Lundbeck Limited) respectively, which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory

CLINICAL ASSESSMENT

INDICATIONS

Citalopram 10mg, 20mg and 40mg film-coated Tablets are indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence. They are also indicated in the treatment of panic disorder with or without agoraphobia.

The indications are consistent with those for the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator product and is satisfactory.

TOXICOLOGY

No new data has been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

Pharmacodynamics

No new pharmacodynamic data are presented and none are required.

Pharmacokinetics - Bioequivalence study

Only one bioequivalence study, using 40 mg tablets, has been submitted to cover all three tablet strengths. According to the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), this may be acceptable if the following conditions are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturer and process;
- The drug input has been shown to be linear over the therapeutic dose range;
- The qualititative composition of the different strengths is the same;
- The ratio between amounts of active substance and excipients is the same or, in the case of preparations containing a low concentration of active substance (less than 5%) the ratio between the amounts of excipients is similar
- The dissolution profile is similar under identical conditions for all strengths. Dissolution profiles should cover at least 3 time points and 3 different pHs in the range 1 - 6.8.

As the test products were deemed to meet the criteria specified in the Note for Guidance, the results and conclusions of the bioequivalence study on the 40mg strength were extrapolated to the 10mg and 20mg tablet strengths.

The applicant presented a single bioequivalence study comparing the test product, Citalopram 40mg film-coated Tablets, to the reference product, Cipramil Tablets 40mg (Lundbeck Limited).The design was a single dose, randomised, balanced, two-period, 2-treatment, crossover study in healthy male volunteers.

25 volunteers were recruited to the study. Blood samples were taken as per protocol (24 samples including pre-dose and post-dose samples over 24 hours). Samples were analysed by HPLC with fluorescence detector. The method has been validated.

Pharmacokinetic parameters of area under the curve (AUC_{0-t}), from zero to infinity ($AUC_{0-\infty}$), and the observed maximum plasma drug concentration (Cmax), and time to maximum plasma drug concentration (Tmax), were determined. Analysis was by ANOVA for statistical treatment for ratio of test/reference and 90% confidence intervals for the 25 subjects in the study as per protocol.

The mean ratio of test/reference is 95.4% and 96.5% for AUC and Cmax respectively. 90% confidence intervals of 91.90% – 99.00% and 93.33% - 99.69% for AUC and Cmax respectively. The mean plasma profiles are almost identical. These values are within the accepted regulatory range of 80 – 125% indicating that test is equivalent to the reference in this bioequivalent study for citalopram 40mg film-coated tablets.

Overall conclusions on pharmacokinetics

The 90% confidence intervals for the ratio of the geometric means of the log-transformed values for $AUC_{(0-inf)}$, C_{max} and $AUC_{(0-t)}$ were within the accepted 80-125% bioequivalence range. Bioequivalence was thus demonstrated for the 40mg tablet strength.

EFFICACY

No new data are submitted and none are required for this type of application.

Efficacy is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

SAFETY

No new data are submitted and none are required for this type of application.

Safety is reviewed in the Clinical Expert Report. The reference products are established and the main basis of the application depends upon the bioequivalence study. No new safety issues have been detected.

EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

SUMMARY OF PRODUCT CHARACTERISTICS

The approved SmPCs are consistent with those for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with the approved SmPCs and is satisfactory.

LABELLING

Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 40mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of this bioequivalence study were extrapolated to the 10mg and 20mg strength tablets. We can say, therefore, that the 10mg and 20mg strength formulations are bioequivalent to their corresponding marketed brand formulations, despite bioequivalence not being assessed explicitly.

Sufficient clinical information has been submitted to support these applications. When used as indicated, citalopram hydrobromide has a favourable benefit-to-risk ratio. Marketing authorisations may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Citalopram 10mg, 20mg and 40mg film-coated 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Citalopram 40mg film-coated Tablets, and the reference product Cipramil Tablets 40mg (Lundbeck Limited). As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 40mg strength were extrapolated to the 10mg and 20mg tablet strengths. Thus, no separate bioequivalence studies were necessary for these strengths.

No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with that for Cipramil Tablets 10mg, 20mg and 40mg.

The Marketing Authorisation Holder has provided a commitment to update the Marketing Authorisations with package leaflets in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflets shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, supports the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with citalopram hydrobromide is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

CITALOPRAM 10MG, 20MG & 40MG FILM-COATED TABLETS (CITALOPRAM HYDROBROMIDE) PL 17907/0089, 0090 & 0091

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 18th May 2004

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 15th June 2004

3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 22nd November 2004

4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 20th February 2006

5 Following assessment of the response the MHRA requested further information relating to the quality sections on 21st February 2006 and 13th June 2006

6 The applicant responded to the MHRA's requests, providing further information for the quality sections on 12th June 2006 and 2nd August 2006 respectively

7 The applications were determined on 22nd August 2006

CITALOPRAM 10MG, 20MG & 40MG FILM-COATED TABLETS (CITALOPRAM HYDROBROMIDE) PL 17907/0089, 0090 & 0091

STEPS TAKEN AFTER AUTHORISATION

Date submitted	Application type	Scope	Outcome
12/02/2008	Variation Medical Type II National	To update sections 4.4 and 4.8 of the SPC. *This variation was submitted for all 3 PLs.*	Application granted 15/02/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Citalopram 10mg film-coated Tablets is as follows:

1. NAME OF THE MEDICINAL PRODUCT

Citalopram 10mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains citalopram hydrobromide equivalent to citalopram 10mg
Also contains lactose monohydrate 23.635mg.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated Tablets.

White to off white , round, plain, film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

4.2.1 Posology

Treating Depression
Citalopram should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response this may be increased to a maximum of 60 mg daily. The dose may be taken in the morning or evening without regard for food.

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

Treating Panic Disorder
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. A single oral dose of 10 mg daily is recommended for the first week before increasing the dose to 20 mg daily. The dose may be further increased, up to a maximum of 60 mg daily dependent on individual patient response, however an optimum dose of 20-30 mg daily was indicated in a clinical study.

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

Elderly patients
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children
Not recommended, as safety and efficacy have not been established in this population.

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 CitalopramTablets

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.

4.2.2 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.

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

4.4. Special warnings and precautions for use

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.

Suicide – As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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.

Psychomotor restlessness

The use of Sertraline has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of Citalopram.

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.

Withdrawal symptoms seen on discontinuation of Citalopram

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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).

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 (except for patients with depressive illness and panic disorder with or without agoraphobia). Suicide – related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequent observed tot hose treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long –term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

4.5. Interactions 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.

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.

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.

Treatment emergent adverse events reported in clinical trials (N=2985):

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.

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-billiary 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.

Psychmotor restleness/akathisia (see section 4.4 special warnings and Special Precautions for Use)

Withdrawal symptoms seen on discontinuation of Citalopram 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 Citaolpram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

4.9. Overdose

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

Symptoms

Experience from 8 cases considered due to citalopram alone has recorded the following symptoms/signs: somnolence, coma, stiffened expression, episode of grand mal convulsion, sinus tachycardia, occasional nodal rhythm, sweating, nausea, vomiting, cyanosis, hyperventilation. No case was fatal. The clinical picture was inconsistent, no observation being made in more than two individuals.

Six fatalities have been reported. In one overdose was suspected; high post mortem plasma levels were seen although it is not technically possible to interpret these with confidence. In the remaining five a combination with other drugs had been taken. The clinical syndrome observed prior to death in three of these cases where citalopram was taken with moclobemide was interpreted as that of serotonin syndrome. No clinical details are available on the other two.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Gastric lavage should be carried out as soon as possible after oral ingestion. Medical surveillance is advisable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC-code: N 06 AB 04

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRI's, citalopram has not or very low affinity for a series of receptors including 5-HT $_{1A,}$ 5-HT$_2$, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the 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.

5.2. Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

Elimination

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

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

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

Elderly patients (≥ 65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

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

Reduced renal function

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

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Cellulose, microcrystalline
Crosscarmellose sodium
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Purified talc
Macrogol 400

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Blisters Do not store above 25ºC. Store in the original package

Bulk Do not store above 25ºC. Keep the container tightly closed.

6.5. Nature and contents of container

Al / PVDC/PVC blister, pack sizes of 14, 28, 56 or 84 tablets.

HDPE tablet containers, pack sizes of 1000 tablets

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted, Herts
HP4 1EG

8. MARKETING AUTHORISATION NUMBER

PL 17907/0089

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/08/2006

10 DATE OF REVISION OF THE TEXT

15/02/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Citalopram 20mg film-coated Tablets is as follows:

1. NAME OF THE MEDICINAL PRODUCT

Citalopram 20mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains citalopram hydrobromide equivalent to citalopram 20mg
Also contains lactose monohydrate 47.270mg.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated Tablets.

White to off white , oval, biconvex, film-coated tablets with BL embossed on one side and 20 on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

4.2.1 Posology

Treating Depression
Citalopram should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response this may be increased to a maximum of 60 mg daily. The dose may be taken in the morning or evening without regard for food.

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

Treating Panic Disorder
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. A single oral dose of 10 mg daily is recommended for the first week before increasing the dose to 20 mg daily. The dose may be further increased, up to a maximum of 60 mg daily dependent on individual patient response, however an optimum dose of 20-30 mg daily was indicated in a clinical study.

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

Elderly patients
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children
Not recommended, as safety and efficacy have not been established in this population.

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 CitalopramTablets

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.

4.2.2 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.

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

4.4. Special warnings and precautions for use

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.

Suicide – As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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.

Psychomotor restlessness

The use of Sertraline has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of Citalopram.

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.

Withdrawal symptoms seen on discontinuation of Citalopram

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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).

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 (except for patients with depressive illness and panic disorder with or without agoraphobia). Suicide – related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequent observed tot hose treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long –term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

4.5. Interactions 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.

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.

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.

Treatment emergent adverse events reported in clinical trials (N=2985):

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.

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-billiary 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.

Psychmotor restleness/akathisia (see section 4.4 special warnings and Special Precautions for Use)

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

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Experience from 8 cases considered due to citalopram alone has recorded the following symptoms/signs: somnolence, coma, stiffened expression, episode of grand mal convulsion, sinus tachycardia, occasional nodal rhythm, sweating, nausea, vomiting, cyanosis, hyperventilation. No case was fatal. The clinical picture was inconsistent, no observation being made in more than two individuals.

Six fatalities have been reported. In one overdose was suspected; high post mortem plasma levels were seen although it is not technically possible to interpret these with confidence. In the remaining five a combination with other drugs had been taken. The clinical syndrome observed prior to death in three of these cases where citalopram was taken with moclobemide was interpreted as that of serotonin syndrome. No clinical details are available on the other two.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Gastric lavage should be carried out as soon as possible after oral ingestion. Medical surveillance is advisable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC-code: N 06 AB 04

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRI's, citalopram has not or very low affinity for a series of receptors including 5-HT $_{1A,}$ 5-HT$_2$, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the 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.

5.2. Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

Elimination

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

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

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

Elderly patients (≥ 65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

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

Reduced renal function

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

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Cellulose, microcrystalline
Crosscarmellose sodium
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Purified talc
Macrogol 400

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Blisters Do not store above 25ºC. Store in the original package

Bulk Do not store above 25ºC. Keep the container tightly closed.

6.5. Nature and contents of container

Al / PVDC/PVC blister, pack sizes of 14, 28, 56 or 84 tablets.

HDPE tablet containers, pack sizes of 1000 tablets

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 17907/0090

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/08/2006

10 DATE OF REVISION OF THE TEXT

15/02/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Citalopram 40mg film-coated Tablets is as follows:

1. NAME OF THE MEDICINAL PRODUCT

Citalopram 40mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains citalopram hydrobromide equivalent to citalopram 40mg
Also contains lactose monohydrate 94.540mg.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated Tablets.

White to off white , oval, biconvex, film-coated tablets with BL embossed on one side and 40 on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

4.2.1 Posology

Treating Depression
Citalopram should be administered as a single oral dose of 20 mg daily. Dependent on individual patient response this may be increased to a maximum of 60 mg daily. The dose may be taken in the morning or evening without regard for food.

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

Treating Panic Disorder
In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. A single oral dose of 10 mg daily is recommended for the first week before increasing the dose to 20 mg daily. The dose may be further increased, up to a maximum of 60 mg daily dependent on individual patient response, however an optimum dose of 20-30 mg daily was indicated in a clinical study.

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

Elderly patients
The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children
Not recommended, as safety and efficacy have not been established in this population.

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 CitalopramTablets

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.

4.2.2 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.

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

4.4. Special warnings and precautions for use

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.

Suicide – As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored during this period. The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved and it is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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.

Psychomotor restlessness

The use of Sertraline has been associated with the development of psychomotor restlessness, which clinically may be very similar to akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental and it may be necessary to review the use of Citalopram.

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.

Withdrawal symptoms seen on discontinuation of Citalopram

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). 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).

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 (except for patients with depressive illness and panic disorder with or without agoraphobia). Suicide – related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequent observed tot hose treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long –term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

4.5. Interactions 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.

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.

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.

Treatment emergent adverse events reported in clinical trials (N=2985):

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.

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-billiary 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.

Psychmotor restleness/akathisia (see section 4.4 special warnings and Special Precautions for Use)

Withdrawal symptoms seen on discontinuation of Citalopram 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 Citaolpram treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 Posology and Method of Administration and section 4.4 Special Warnings and Special Precautions for use).

4.9. Overdose

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

Symptoms

Experience from 8 cases considered due to citalopram alone has recorded the following symptoms/signs: somnolence, coma, stiffened expression, episode of grand mal convulsion, sinus tachycardia, occasional nodal rhythm, sweating, nausea, vomiting, cyanosis, hyperventilation. No case was fatal. The clinical picture was inconsistent, no observation being made in more than two individuals.

Six fatalities have been reported. In one overdose was suspected; high post mortem plasma levels were seen although it is not technically possible to interpret these with confidence. In the remaining five a combination with other drugs had been taken. The clinical syndrome observed prior to death in three of these cases where citalopram was taken with moclobemide was interpreted as that of serotonin syndrome. No clinical details are available on the other two.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Gastric lavage should be carried out as soon as possible after oral ingestion. Medical surveillance is advisable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC-code: N 06 AB 04

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRI's, citalopram has not or very low affinity for a series of receptors including 5-HT $_{1A,}$ 5-HT$_2$, DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the 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.

5.2. Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

Elimination

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

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

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

Elderly patients (≥ 65 years)

Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function

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

Reduced renal function

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

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Cellulose, microcrystalline
Crosscarmellose sodium
Magnesium stearate

Tablet coating:
Hypromellose
Titanium dioxide (E171)
Purified talc
Macrogol 400

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Blisters Do not store above 25ºC. Store in the original package

Bulk Do not store above 25ºC. Keep the container tightly closed.

6.5. Nature and contents of container

Al / PVDC/PVC blister, pack sizes of 14, 28, 56 or 84 tablets.

HDPE tablet containers, pack sizes of 1000 tablets

6.6. Instruction for use and handling (, and disposal)

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
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22/08/2006

10 DATE OF REVISION OF THE TEXT

15/02/2008

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Citalopram 10 mg Film-coated Tablets
Citalopram 20 mg Film-coated Tablets
Citalopram 40 mg Film-coated Tablets

- The active substance is citalopram hydrobromide calculated as citalopram base 10 mg or 20 mg or 40 mg.
- The other ingredients are lactose, maize starch, cellulose microcrystalline , crosscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide (E171), purified talc and macrogol 400.

Marketing Authorisation Holder and Manufacturer: Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG.

WHAT CITALOPRAM FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Citalopram 10 mg are white to off white, round, plain, film coated tablets.

Citalopram 20 mg are white to off white, oval, biconvex, film-coated tablets with BL embossed on one side, & '20' on the other.
Citalopram 40 mg are white to off white, oval, biconvex, film-coated tablets with BL embossed on one side, & '40' on the other.

Citalopram Film-coated Tablets are available in a box containing blister strips of 14 tablets (14, 28, 56 or 84 tablets in total). These tablets are also available in tablet containers containing 100, 250, 500 or 1000 tablets, which your pharmacist will dispense to you. Not all pack sizes may be marketed.
Citalopram belongs to a group of medicines known as antidepressants, which work by relieving the symptoms of depressed mood.

Citalopram film-coated tablets are used to treat the symptoms of depression and, when you are feeling better, to help prevent these symptoms recurring. Citalopram is also beneficial in relieving the symptoms in patients prone to panic attacks.
Treatment for depression is usually continued for at least six months and for panic disorder for at least three months.

BEFORE YOU TAKE CITALOPRAM FILM-COATED TABLETS

Do not take this medicine if you are allergic to it, or to any of the other ingredients mentioned above. Consult your doctor if you think you might be.
Citalopram film-coated tablets contain lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

Do not take Citalopram tablets if you are taking an antidepressant medicine of the type called monoamine oxidase inhibitors (MAOIs) like phenelzine, isocarcoxazid and tranylcypromine. Even if you have finished taking the MAOI medicine you will need to wait 2 weeks before starting your Citalopram tablets. You must wait at least one day between stopping the reversible monoamine oxidase inhibitor (RIMA) moclobemide and starting Citalopram.
If your doctor asks you to take an MAOI you will be asked to stop taking Citalopram at least seven days before starting the MAOI.
The herbal remedy St.John's Wort (Hypericum perforatum) should not be taken at the same time as this medicine. If you already take a St.John's Wort preparation stop taking the St.John's Wort and mention it to your doctor at your next visit.
Please tell your doctor if you are taking drugs to control fits (anticonvulsants) or if you fits have increased whilst taking Citalopram, if you are taking insulin or medicines for diabetes (you might need to change your dose of diabetes medicine). Also talk to your doctor if you are taking medicines to thin your blood (anticoagulants), aspirin, and pain relief medicines called non-steroidal anti-inflammatory drugs such as ibuprofen or if you have a bleeding disorder.
Also talk to your doctor if you are taking lithium or tryptophan preparations.
Drugs such as a medicine used to relieve pain, called tramadol and a migraine medicine called sumatriptan can be taken with Citalopram. However, if you feel unwell after taking tramadol or sumatriptan do not take these again. Continue to take your Citalopram and tell your doctor.

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Unless you have recently discussed this with your doctor, please tell him or her if you have a medical condition (such as heart problem or liver complaint), if you are pregnant (or think you may be), or if you are breast-feeding.
Most people do not find their ability to carry out normal daily activity is affected. However, you should be careful when driving, operating machinery or performing jobs that needs you to be alert. Also as with all antidepressants, it is sensible to avoid taking alcohol whilst receiving treatment.

HOW TO TAKE CITALOPRAM FILM-COATED TABLETS

Always take Citalopram Film-coated tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
Swallow the tablets with a drink of water. Do not chew them.

Usually your doctor will prescribe between 20 and 60mg per day, taken as a single dose either in the morning or in the evening. Patients being treated to alleviate symptoms of panic attack will probably be prescribed only 10mg daily for about the first week, before increasing the dose to 20-60 mg per day.
It may take several days before you feel any benefit from these tablets. This is normal for this type of medicine. Continue to take your tablets for as long as your doctor recommends. Do not stop taking them even if you begin to feel better, unless you are told to do so by you doctor. Never change the dose of your medicine without taking to your doctor first.
Elderly patients or patients with liver problems will usually be prescribed a dose between 20 and 40mg per day. Citalopram is not recommended for children.

If you miss a dose, do not take the missed tablets, just take the next dose when it is due.

If you take an overdose of Citalopram film-coated tablets, contact a doctor immediately or go to your nearest hospital casualty department. Take the pack with you to show to the doctor.

Effects when treatment with Citalopram is stopped too quickly include symptoms such as dizziness, tingling, headache, anxiety and nausea. These symptoms are generally non-serious and disappear within a few days. If you experience symptoms on stopping treatment, contact your doctor.

Special information
Occasionally, thoughts of suicide or self-harm may occur or may increase in the first few weeks of treatment for depression, until the antidepressant effect becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences.

Patients who are prone to panic attacks may actually experience a temporary period of heightened anxiety after starting treatment. This generally resolves during the first 1-2 weeks.

POSSIBLE SIDE EFFECTS

Citalopram may cause unwanted effects (side-effects) in some patients. These may include vomiting (sickness), nausea (feeling sick), lack of appetite, diarrhoea, dry mouth, sweating and drowsiness.

Other side effects associated with Selective Serotonin Reuptake Inhibitors (SSRI's) such as Citalopram and other drugs in this class include: difficulty sleeping, agitation, nervousness, dizziness, feeling faint or light-headed on standing up, migraine, disturbed vision, tremor, movement disorders, fits, palpitations, difficulty passing urine, constipation, polyuria, low blood sodium, taste perversion, increased appetite, abdominal pain, flatulence, increased salivation, weight decrease, weight increase, rhinitis, allergic reactions i.e. rash, itching or inflammation of the mouth or tongue, muscle and joint ache, mild liver disorder, impaired concentration, amnesia, reduced sexual performance, impotence, ejaculation failure, female anorgasmia, fatigue and suicide attempt. Also let your doctor know if you continue to have other symptoms associated with your depression. This might include hallucinations, anxiety, mania or confusion.

Any side effects that do occur will usually disappear after a few days. If they are troublesome or persistent or if you develop any other unusual side effects while taking Citalopram, please tell your doctor.

Stopping Citalopram
Do not stop taking Citalopram until your doctor tells you to. Abrupt discontinuation should be avoided. When stopping Citalopram your doctor will help you to reduce your dose over a period of weeks in order to reduce the risk of withdrawal reactions. If intolerable symptoms occur following a decrease in dose or upon discontinuation of treatment, please see your doctor. They may ask you to start taking your tablets again and come of them more slowly.

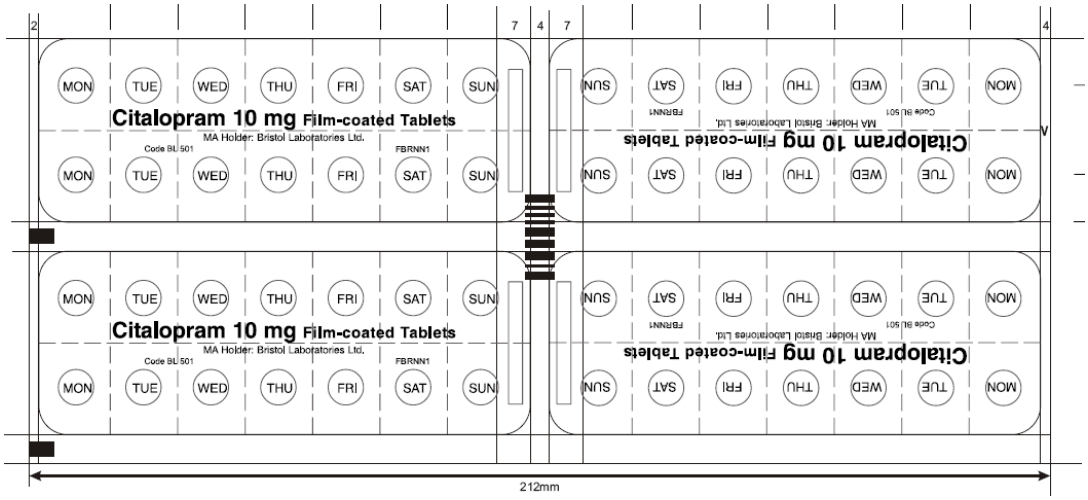
STORING CITALOPRAM FILM-COATED TABLETS

Keep out of the reach and sight of children.
Blisters: Store below 25°C. Store in the original package (Blister carton).
Tablet containers: Store below 25°C. Keep the container tightly closed.
Do not use the tablets after the expiry date as shown on the carton or label.
Unless your doctor tells you to, do not keep any tablets that you no longer need. Give them back to your pharmacist.
Date of preparation of leaflet: November 2005.

IXXXXX

LABELLING
Citalopram 10mg film-coated Tablets
Carton for blisters, with braille

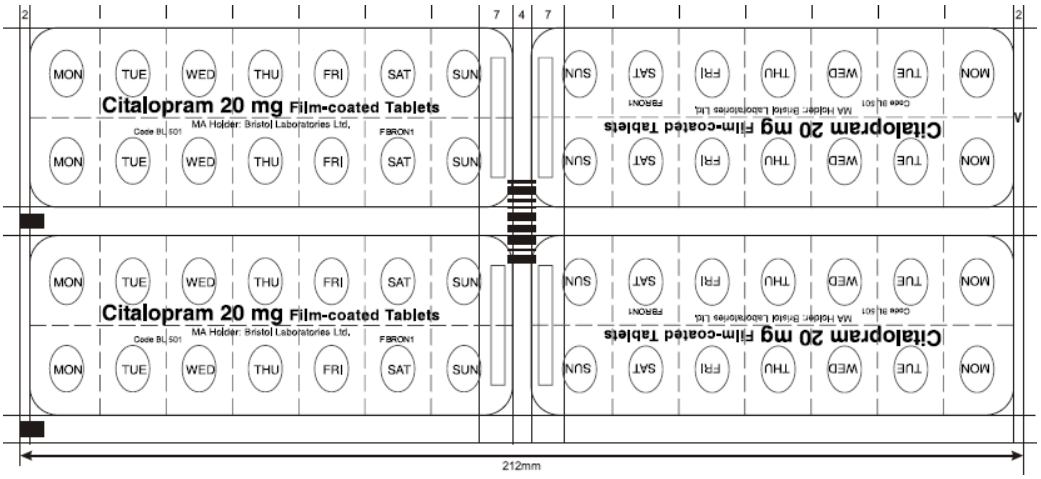
Blister foil



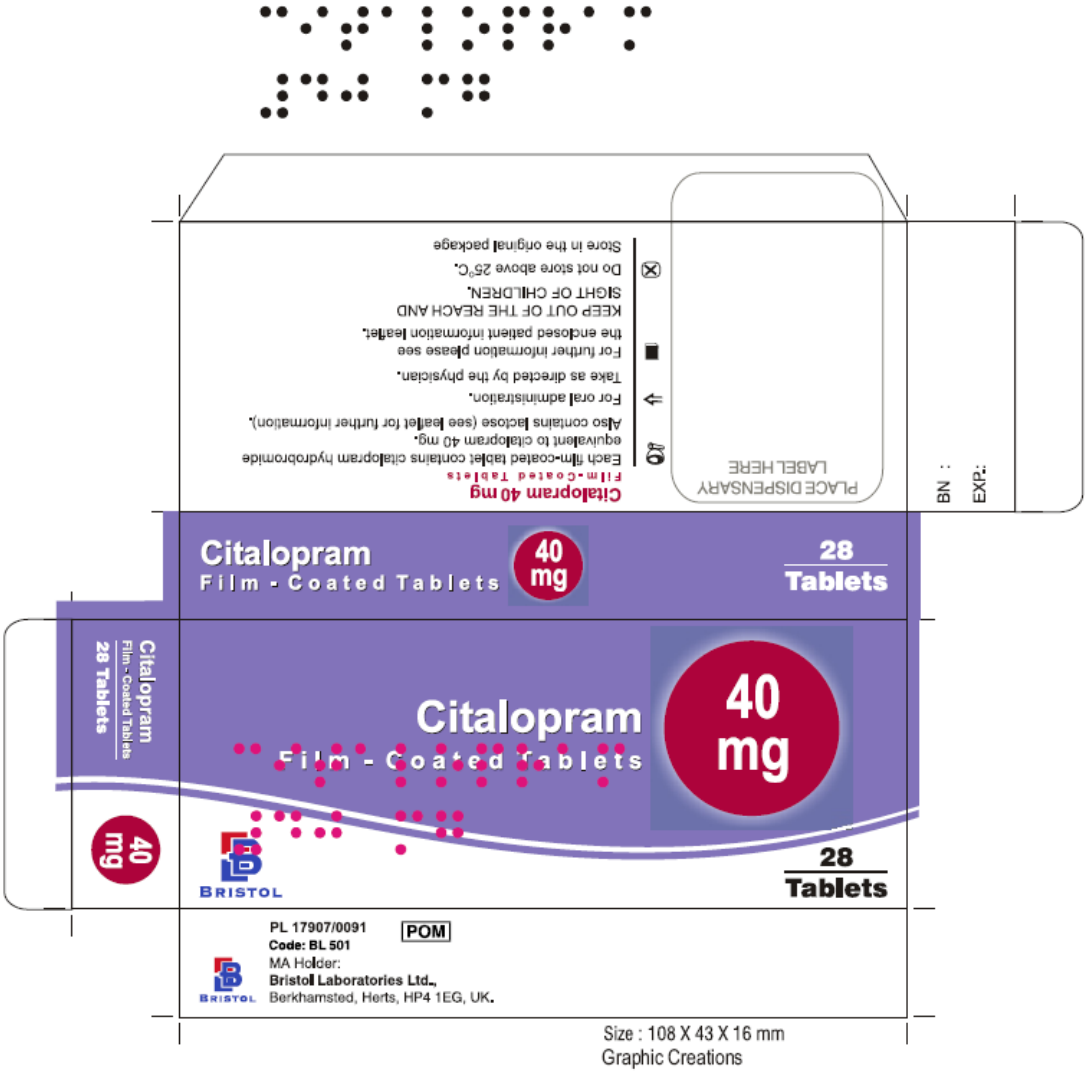
Citalopram 20mg film-coated Tablets

Carton for blisters, with braille

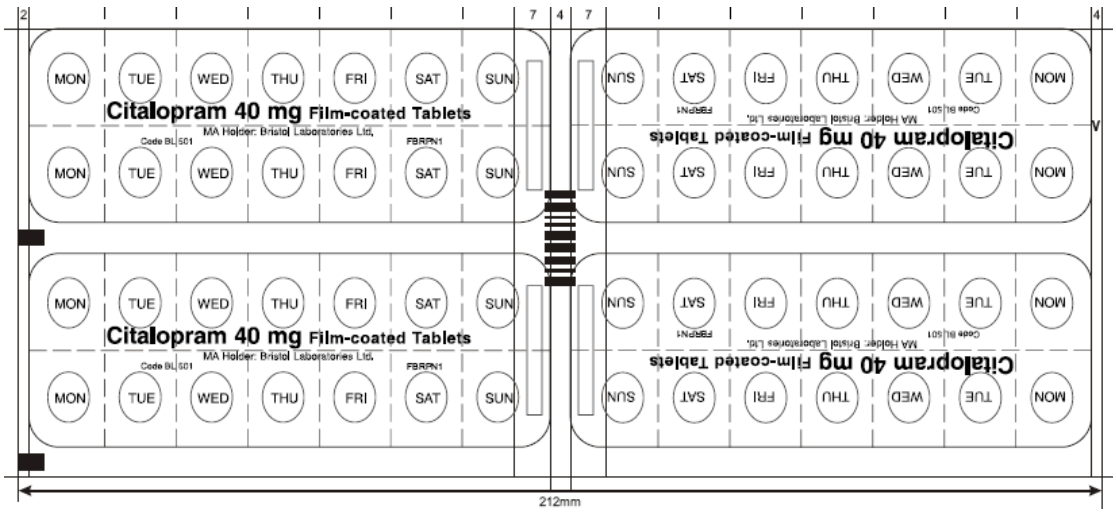
Blister foil



Citalopram 40mg film-coated Tablets
Carton for blisters, with braille



Blister foil



HDPE container labels