

Citalopram 20MG Tablets

PL 22903/0001

UKPAR

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Citalopram 20MG Tablets

PL 22903/0001

LAY SUMMARY

The MHRA granted RIC Chemicals PLC a Marketing Authorisation (licence) for the medicinal product Citalopram 20mg Tablets (PL 22903/0001). This medicine is available by prescription only.

Citalopram is a selective serotonin reuptake inhibitor (SSRI). Citalopram is used to treat depression and when you are feeling better, to prevent it coming back. It may also be used to treat panic disorder. In some patients these episodes may be associated with agoraphobia (fear of open spaces).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Citalopram Tablets outweigh the risks, hence Marketing Authorisation has been granted.

Citalopram 20MG TABLETS

PL 22903/0001

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisation for the medicinal product Citalopram 20mg Tablets (PL 22903/0001) to RIC Chemicals PLC on 29th August 2008. This is a prescription-only medicine (POM).

This is a national standard abridged application for Citalopram 20mg Tablets submitted under Article 10.1 of Directive 2001/83. The original product is Cipramil 20mg film-coated Tablets authorised to Lundbeck AS in Denmark in December 1989. The reference medicinal products in the UK and France are Cipramil 20mg Film-coated Tablets (PL 00458/0058) (authorised to Lundbeck Limited in 17 March 1995) and Seropram 20 mg Film-coated Tablet (MA No. 338 336-1) respectively.

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

PHARMACEUTICAL ASSESSMENT

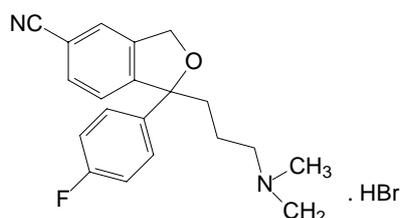
DRUG SUBSTANCE

Nomenclature

INN: Citalopram hydrobromide

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

Structure



Molecular Formula: $C_{20}H_{21}FN_2OF.HBr$

Molecular Weight: 405.31

This is subject to DMF. A letter of access has been provided.

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.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active citalopram hydrobromide is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, hypromellose, lactose anhydrous, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, talc, macrogol 6000, and water purified. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

All the excipients are either of mineral or vegetable origin, apart from the lactose monohydrate that is prepared using calf-rennet.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce a product containing citalopram hydrobromide 20mg Tablets that are tolerable and which could be considered as generic product to the originator product.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

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 has been carried out on batches. The results are satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The finished product specification is 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 product is packaged in a PVC/PVDC and aluminium blister packs. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with a storage condition 'Do not store above 25 degrees C' has been set. This is acceptable.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels

The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

Conclusion

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a standard abridged National Marketing Applications for a generic immediate release 20mg citalopram tablet from RIC Chemicals plc, submitted under EC Article 10.1, first paragraph of Directive 2001/83/EC.

Essential similarity is claimed to the originator product Cipramil 20 mg tablets marketed by Lundbeck Ltd, Denmark authorised more than 10 years ago {Denmark, granted October 1989) along with 10 and 40 mg strengths. The reference product in the UK is Cipramil 20mg Film-coated tablets marketed by Lundbeck Ltd PL 00458/0058 (granted 17/3/95).

Citalopram hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The therapeutic mechanism of action of SSRIs involves the potentiation of serotonin [5-hydroxytryptamine (5-HT)] by the inhibition of its neuronal uptake. Serotonin is a neurotransmitter with neurons located in the raphe nuclei. Serotonergic neurons are known to play a part in sleep-wakefulness cycles, thermoregulation, mood, emotional and food behaviours.

Citalopram is indicated for the treatment of both the initial phase of depressive illness and as maintenance therapy against relapse or recurrence, as well as the treatment of panic disorder with or without agoraphobia. The relatively long half life allows once daily dosing.

The proposed indications and other details in the SPC are broadly in line with those of the reference product but various sections of the SPC will require updating to incorporate the latest warnings on the SSRI class of drugs including those relating to use in children/adolescents, suicidal thoughts, withdrawal reactions and akathisia / psychomotor restlessness.

2. INDICATIONS

Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

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

3 DOSE & DOSE SCHEDULE

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).

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. TOXICOLOGY

No new data

5. CLINICAL PHARMACOLOGY

PHARMACOKINETICS

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

Biotransformation

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

Elimination

The elimination half-life ($T_{1/2\beta}$) 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).

BIOEQUIVALENCE

A study to assess the single dose bioequivalence between the applicant's 20mg Citalopram tablets (manufactured by Cadila Healthcare Ltd, India) and Seropram 20mg tablets (LundbeckSA, France) compare the bioavailability of two 40mg citalopram tablets under fasting conditions.

Centres: Clinical site at Lotus Labs Pvt. Ltd., Brigade Plaza, South Block, 71/1, SC Road, Anand Rao Circule, Bangalore – 560 009, India. The analytical site was at Lotus Labs Pvt. Ltd., No 15, 80 Feet Road, ST Bed, 4th Block, Koramangala, Bangalore – 560 095, India.

Design: a randomised, open label, two treatment, two periods, two sequences, single dose and crossover.

Subjects: healthy adult males

Test: 20mg Citalopram tablets (manufactured by Cadila Healthcare Ltd, India)

Reference: Seropram 20mg tablets of Lundbeck SA France

[Satisfactory three-way *in vitro* comparative dissolution profile of Citalopram 20 mg Tablets against Seropram 20 mg Tablets (France) and Cipramil 20 mg Tablet (UK) have also been demonstrated. Citalopram 20 mg Tablets have been shown to be pharmaceutical equivalent to UK and French innovator products. All tablets tested released more than 85% of label claim within 15 minutes.]

Blood sampling: the sampling frequency was prior to drug administration and then every 0.25 hours from 3 until 4.5 hours post dosing up to 180 hours. NB The terminal half life is approximately 35 hrs.

Parameters: AUC_{0-t} , AUC_{0-inf} , C_{max} with secondary variables T_{max} and $t_{1/2}$. Descriptive safety data were recorded.

Results:

Comparative pharmacokinetics:

	Citalopram test	Cipramil reference	Point Estimate	Test/Ref (90% CI)
AUC_{0-t} (ng/ml h)	1119.67	1146.53	97.65 %	93.83-101.63
AUC_{0-inf} (ng/ml h)	1236.04	1255.41	98.43 %	94.49-102.53
C_{max} (ng/ml)	24.13	24.40	98.83%	93.65-104.30
T_{max} (hrs)	4.96	4.66		

Conclusions: The test product was accepted as bioequivalent in terms of rate and extent of absorption to the reference product.

PHARMACODYNAMICS

ATC-code: N06AB04

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-HT₂, DA D₁ and D₂ receptors, α_1 -, α_2 -, β -adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

6. EFFICACY

No new data

7. SAFETY

No new data

8. EXPERT REPORTS

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)

Satisfactory.

10. LABELLING

Satisfactory.

11. APPLICATION FORM (MAA)

Satisfactory.

12. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory. Consistent with current cross-reference SPC

14. MEDICAL CONCLUSION

Marketing authorisation should be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Citalopram 20mg 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

Based on the submitted bioequivalence study Citalopram 20mg Tablets are considered bioequivalent with Cipramil 20mg Tablets and Seropram 20mg Tablets.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with Citalopram 20mg Tablets is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Citalopram 20mg Tablets**PL 22903/0001****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation application on 28 th February 2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 9 th March 2005
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 22/12/2005 and 21/03/2007
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 28/01/2006 and 30/04/2007
5	The applications were determined on 29 th August 2008

Citalopram 20mg Tablets

PL 22903/0001

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Citalopram 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Citalopram 20 mg as the hydrobromide salt.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet

White, oval shaped, biconvex film-coated tablets having a lip-type breakline on one side and plain on other side.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

Cipramil 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).

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 case presented with features resembling serotonin syndrome. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Citalopram should not be used in combination with a MAOI. Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

‘Patient 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.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors (MAOIs) should not be used in combination with SSRIs (see Contraindications)

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

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

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

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

In a pharmacokinetic study no Effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased. 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 Cipramil. Common symptoms include dizziness, paraesthesia, headache, anxiety and nausea. Abrupt discontinuation of treatment with Cipramil 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: Angioedema; ecchymoses. Photosensitivity reactions have been reported very rarely.

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

Gastrointestinal disorders : Gastrointestinal bleeding.

General disorders: Anaphylactoid reactions.

Hepato-biliary disorders: Abnormal LFT's.

Musculoskeletal disorders: Arthralgia.

Neurological disorders: Serotonin syndrome.

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

Reproductive disorders: Galactorrhoea.

4.9 Overdose

The fatal dose not known. Patients have survived ingestion of up to 2 g citalopram. The effects will be potentiated by alcohol taken at the same time. There is a potential interaction with tricyclic antidepressants and MAOIs.

Symptoms

Nausea, vomiting, sweating, tachycardia, drowsiness, coma, dystonia, convulsions, hyperventilation and hyperpyrexia have been reported. Cardiac features that have been observed include nodal rhythm, prolonged QT intervals and wide QRS complexes. Prolonged bradycardia with severe hypotension and syncope has also been reported.

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

Management

An ECG should be taken. Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: N06AB04

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-HT₂, DA D₁ and D₂ receptors, α_1 -, α_2 -, β -adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

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

Biotransformation

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

Elimination

The elimination half-life ($T_{1/2\beta}$) 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

Microcrystalline cellulose

Hypromellose

Lactose anhydrous

Colloidal anhydrous silica

Magnesium stearate

Tablet Coat

Hypromellose

Talc

Titanium dioxide (E171)

Macrogol 6000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

PVC/PVdC aluminium foil blister packs containing 28 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

RIC Chemicals plc

Unit 1 Conqueror Court

Spilsby Road

Harold Hill

Essex RM3 8SB

England

8 MARKETING AUTHORISATION NUMBER(S)

PL 22903/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/08/2008

10 DATE OF REVISION OF THE TEXT

29/08/2008

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

Information on Citalopram 20mg Tablets

Please read this leaflet carefully before taking your medicine.

- Keep it in a safe place in case you need to read it again
- If you need further information, please ask your doctor or pharmacist (chemist)
- Your doctor has prescribed this medicine only for you. Never give it to anyone else.

Table of contents:

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

Citalopram Tablets

Your medicine is known as Citalopram Tablets. It comes in strength of 20 mg.

The active ingredient is citalopram hydrobromide.

The tablets also contain: Microcrystalline cellulose, lactose anhydrous, colloidal anhydrous silica, magnesium stearate, hypromellose, talc, titanium dioxide (E171) and macrogol.

Marketing authorisation holder:

RIC Chemicals plc

Unit 1, Conqueror Court, Spilsby Road, Harold Hill, Romford, Essex RM3 8SB

Importer

Zydus France

40 rue Lécuyer, 93300 Aubervilliers, France

Manufacturer:

Cadila Healthcare Limited

Sarkhej-Bavla N.H. No.8A, Moraiya, Tal: Sanand, Dist: Ahmedabad 382 210, India

1. What Citalopram Tablets are and what they are used for

Citalopram 20 mg Tablets is a white oval shaped film coated tablet. One side of the tablet is marked with a line. Each box of Citalopram Tablets contains 28 tablets.

Citalopram is a selective serotonin reuptake inhibitor (SSRI). Citalopram Tablets is used to treat depression and when you are feeling better, to prevent it coming back. It may also be used to treat panic disorder. In some patients these episodes may be associated with agoraphobia (fear of open spaces).

Your doctor may have prescribed the drug for another reason. Always follow your doctor's instructions.

2. Before you take Citalopram Tablets

Do not take Citalopram Tablets if:

- You are taking other medicines known as Monoamine Oxidase Inhibitors (MAOIs) such as isocarboxazid, phenelzine and tranylcypromine
- You are allergic to citalopram or any of the other ingredients in Citalopram Tablets
- You are under 18 years old.
- If you are a patient with rare hereditary problems of galactose intolerance, in the Lapp lactase deficiency or glucose-galactose malabsorption .

Special precautions:

Tell your doctor if you suffer from epilepsy or if your fits have increased while taking Citalopram Tablets.

Also tell your doctor if you have diabetes as control of glucose levels may be affected by citalopram. If this is the case, it may be necessary to closely monitor your blood glucose levels and adjust the dose of insulin or hypoglycaemic agent.

You should tell your doctor if you have a history of bleeding disorders, especially if you are taking medicines to thin the blood such as warfarin. You should also tell your doctor if you have kidney or liver problems. If your liver function is impaired, your doctor may decide to keep the citalopram dosage at the lower end of the recommended range. If you have a history of mania tell your doctor as citalopram may cause manic episodes.

Taking Citalopram Tablets with food and drink:

You can take your medicine with or without food at any time of the day or evening.

It is recommended that you should avoid alcohol during treatment with Citalopram Tablets as the combination is more likely to make you feel drowsy.

Pregnancy and breast-feeding:

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

Driving and using machinery:

Citalopram is unlikely to affect your ability to operate machinery or drive a car. However, it is wise to be careful in situations where you need to be alert.

Important information about an ingredients of Citalopram Tablets:

This medicine contains lactose. If you have been told by your doctor that you are intolerant to certain sugars, tell him/her before taking this medicine.

Taking other medicines:

Citalopram Tablets should never be taken at the same time as other antidepressant medicines known as Monoamine Oxidase Inhibitors (MAOIs). Typical examples of MAOIs are tranylcypromine, phenelzine and isocarboxazid. If your doctor decides to switch you from an MAOI to citalopram, you may need to wait two weeks before starting the new treatment. If you are being switched from the reversible MAOI known as moclobemide, you may need to wait just one day before starting Citalopram Tablets.

If your doctor tells you to switch from Citalopram Tablets to an MAOI medicine, you will be told how to stop taking the Citalopram Tablets and to then wait 7 days before starting the new medicine.

You should also tell your doctor about other medicines in the following situations:

- Tricyclic Antidepressants (TCAs), for example amitriptyline, dothiepine and imipramine and other SSRI antidepressant medicines - there is an increased risk of side effects (see section 4). The medicine sibutramine, which may be prescribed for weight loss, may cause a similar type of interaction
- Serotonergic medicines such as tramadol which may be given for pain and antimigraine medicines such as sumatriptan and zolmitriptan may occasionally cause side effects with citalopram (see section 4)

- The herbal medicines known as St John's Wort should not be taken at the same time as Citalopram Tablets. Stop taking the St John's Wort and tell your doctor at your next visit
- Aspirin and NSAID medicines such as ibuprofen, which may be taken for pain and various arthritic conditions should be used with care as there is an increased risk of bleeding
- Lithium which may be prescribed for mania or tryptophan which may be prescribed for some kinds of depression.

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed such as over-the-counter, herbal drugs as well as strong vitamins and minerals.

Other preparations may influence the effect of Citalopram Tablets, and/or Citalopram Tablets may influence the effect of other preparations. Normally, this is of no practical importance. If you need any further information, please ask your doctor or pharmacist.

3. How to take Citalopram Tablets

Always take Citalopram Tablets exactly as your doctor tells you. Each person has different requirements. You should check with your doctor or pharmacist if you are unsure.

It is normal for it to take several days or weeks before you start to feel better. Do not stop taking your medicine or change the dose without discussing it with your doctor, even if you are feeling better. Your doctor will tell you how to stop taking the medicine.

Dosage:

For depression, you should start treatment with one Citalopram tablet each day which may be taken in the morning or evening. Depending on your individual response, your doctor may gradually increase the dose to three tablets a day. Your treatment may last up to six months.

For panic disorder, the dose is normally 10 mg (half a tablet) during the first week, which may be increased to one – three tablets (20 – 60 mg). Your treatment may last up to three months.

Liver problems: your doctor may tell you to take one or two tablets (20 – 40 mg) a day .

Children: Citalopram Tablets should not be used in patients under 18 years old.

Elderly: your doctor may tell you to take one or two tablets (20 – 40 mg) a day .

The total daily dose should be swallowed with some water.

Always take Citalopram Tablets exactly as your doctor tells you. Each person has different requirements.

Stopping your medicine: Your doctor will tell you the best way to stop taking your tablets. You should never stop taking your medicine without first discussing it with your doctor. It is important to reduce the dose slowly over several weeks as you may get side effects such as anxiety, flu-like symptoms, headache, nausea, dizziness, and sensations of 'pins and needles' if treatment ends suddenly.

What happens if you take too many Citalopram Tablets?

Contact your doctor, your nearest hospital casualty department or your pharmacist, if you have taken more Citalopram Tablets than mentioned in this leaflet or more than your doctor has prescribed.

What to do if you forget to take a dose?

If you forget to take a dose, take it as soon as you remember. However, if you do not remember the missed dose until the next day, only take the normal dose. Do not double the dose.

4. Possible side effects

Important information about your medicine

In common with other SSRI medicines, patients taking Citalopram Tablets for depression may occasionally experience thoughts of suicide or self-harm during the first few weeks until the effects of treatment start to be felt. If these thoughts happen to you, tell your doctor immediately.

Patients taking Citalopram Tablets for panic disorder should be aware that their panic attacks may sometimes get worse at the start of treatment. However, your symptoms should get better within 1 – 2 weeks. If your panic attacks do get worse, tell your doctor immediately.

You should also tell your doctor if you experience other symptoms associated with depression such as hallucinations, anxiety, mania or confusion.

Like all medicines, Citalopram Tablets can have side effects. Most side effects will settle after a few days treatment. The most common side effects are vomiting (being sick), nausea (feeling sick), dry mouth, diarrhoea, lack of appetite, sweating and drowsiness.

Other side effects that may occur with SSRI-type medicines such as citalopram include dry mouth, palpitations, tremor, confusion, dizziness, low blood pressure, mania, convulsions, interference with sexual function and movement disorders.

Very rarely, citalopram may cause bleeding in the stomach and intestines. If you vomit blood or experience black or bloody stools, tell your doctor at once.

Tell your doctor immediately if you experience an allergic reaction such as rash, itching or swelling of the face after taking your medicine.

If you notice any other side effects than mentioned in this leaflet, please inform your doctor or pharmacist so that these side effects are reported to the authorities for supplementing the knowledge on side effects.

Please inform your doctor or pharmacist if you experience persisting or disturbing side effects. Some side effects may require treatment.

5. Storing Citalopram Tablets

Always keep medicines out of reach and sight of children.
Do not store above 25°C.

There is an expiry date on the label. Do not use the medicine after this date.

You should return any left over tablets to your pharmacist

6. Further information

Always return any unused tablets to your pharmacy for safe disposal.

This leaflet was prepared on September 2006

LABELLING

93300 France
Aubervilliers
France
Importer : Zyclus

Essex RM3 8SB
Spillsby Road, Harold Hill,
Unit 1, Conqueror Court,
MA Holder : RIC Chemicals Plc

Storage condition - Do not store above 25°C

OF CHILDREN
KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT

See leaflet for further information

Contains Lactose

For oral use

Each tablet contains Citalopram 20 mg (as Citalopram Hydrobromide)

Batch No. : . . .

Expiry : . . .

PL 22903/0001

POM

Citalopram 20 mg Tablets

28 Tablets



Citalopram 20 mg Tablets

28 Tablets

Citalopram						
20 mg						
Tablets						
Citalopram						
RIC Chemicals Plc						
Citalopram						
20 mg						
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RIC Chemicals Plc						