

CITALOPRAM 10MG TABLETS (PL 20438/0005)
CITALOPRAM 20MG TABLETS (PL 20438/0006)
CITALOPRAM 40MG TABLETS (PL 20438/0007)

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TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 12
Steps taken after authorisation – summary	Page 13
Summary of Product Characteristics	
Product Information Leaflet	
Labelling	

CITALOPRAM 10MG TABLETS (PL 20438/0005)
CITALOPRAM 20MG TABLETS (PL 20438/0006)
CITALOPRAM 40MG TABLETS (PL 20438/0007)

LAY SUMMARY

The MHRA today granted Norpharm Limited Marketing Authorisations (licences) for the medicinal products Citalopram 10mg Tablets (PL 20438/0005), Citalopram 20mg Tablets (PL 20438/0006) and Citalopram 40mg Tablets (PL 20438/0007). These are prescription only medicines (POM) for the prevention and treatment of depression, and to relieve the symptoms in patients prone to panic attacks.

Citalopram Tablets contain the active ingredient citalopram hydrobromide, which acts by increasing the amount of a chemical called serotonin in the brain to relieve symptoms of depression.

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

CITALOPRAM 10MG TABLETS (PL 20438/0005)
CITALOPRAM 20MG TABLETS (PL 20438/0006)
CITALOPRAM 40MG TABLETS (PL 20438/0007)

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment (including statistical assessment)	Page 9
Overall conclusions and risk benefit assessment	Page 10

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Citalopram 10mg, 20mg and 40mg Tablets to Norpharm Limited (PL 20438/0005-7) on 18th October 2006. The products are prescription only medicines.

These are three strengths of Citalopram Tablets, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Cipramil 10mg, 20mg and 40mg Film-Coated Tablets (H Lundbeck AS).

The products contain the active ingredient citalopram hydrobromide, a selective serotonin reuptake inhibitor, and are indicated for the 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.

The MAA form, SPC, PIL and labelling are satisfactory. The pharmaceutical, preclinical and clinical expert reports have been written by appropriately qualified professionals.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Citalopram Hydrobromide

rINNM: Citalopram hydrobromide

Chemical names: 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide

General properties: White to off-white powder, freely soluble in methanol, soluble in acetonitrile, ethanol, chloroform and 0.1N hydrochloric acid. Sparingly soluble in water and insoluble in 1N sodium hydroxide. There is no evidence of polymorphism.

Citalopram hydrobromide is not the subject of a BP or Ph Eur monograph, although a draft monograph was published for consultation in Pharmeuropa Volume 17, Number 2 (April 2005).

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 specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

A signed declaration has been provided confirming that no materials used in the manufacture of the active citalopram hydrobromide are of animal origin.

An appropriate specification is provided for the active substance citalopram hydrobromide.

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.

Appropriate stability data have been generated supporting a retest period of 1 year.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely mannitol, cellulose microcrystalline, silica (colloidal anhydrous), magnesium stearate, hypromellose, titanium dioxide, macrogol and purified water. The function of each excipient has been described. No results from excipient-active compatibility studies have been provided, however, given the stability of the product, this is not a major deficiency.

All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

Dissolution

Satisfactory comparative dissolution profiles for the proposed products and reference products have been provided. The data demonstrate that the dissolution specification is acceptable.

Manufacture

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on full-scale batches of each strength. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. 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

Tablets are presented in transparent colourless PVC/PVdC/Al blisters in packs of 10, 14, 20, 28, 30, 50, 56, 98 and 100 tablets, in blisters of 100 x1 unit dose blisters and in sample blister packs of 10, 14 and 20 tablets. Tablets are also packaged in HDPE tablet containers with LDPE tamper evident caps in packs of 100 tablets for all strengths. A heat-seal lacquer is applied to the aluminium foil.

Satisfactory specifications and certificates of analysis have been provided for the packaging components. The applicant has confirmed that the packaging requirements comply with EU requirements for contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 4 years has been set, which is satisfactory. There are no specific storage conditions for these applications.

Bioequivalence/Bioavailability

Citalopram is rapidly and completely absorbed following oral administration with peak plasma concentrations achieved after 2-4 hours for immediate release oral products. Bioavailability is unaffected by food. Kinetics are linear over the proposed dose range. Terminal elimination half life is 23-75 hours. Two bioequivalence studies have been performed comparing the test and reference products.

Study 1

Satisfactory Certificates of Analysis have been provided for the test (Citalopram 40mg Film-Coated Tablets) and reference (Cipramil 40mg Tablets, Lundbeck GmbH and Co, Germany) batches. More than 90% of citalopram is released from each test and reference tablet within 20 minutes in the dissolution test.

The test product is identical in composition and manufacturing procedure to the product intended for marketing.

Table 7: Pharmacokinetic results for citalopram and demethylcitalopram from a randomised single dose two-period crossover study between the test and reference product. Log transformed. ANOVA. n=20 healthy male subjects, dosed fasted; t=120 hours. Wash out period: at least 21 days

Test parameter	Test product (geometric mean)	Reference product (geometric mean)	Ratio Test/reference x 100	90% Confidence intervals
Citalopram				
AUC _{0-t} (ng.h/ml)	1336	1358	0.98	95.3-101.5
AUC _{0-∞} (ng.h/ml)	1514	1551	0.98	93.9-101.4
C _{max} (ng/ml)	34.32	34.88	0.98	94.2-102.8
T _{max} (h)*	3.63	3.63	-	-
Demethylcitalopram				
AUC _{0-t} (ng.h/ml)	346.7	356.7	0.97	94.2-99.9
AUC _{0-∞} (ng.h/ml)	587	580	0.99	92.6-106.4
C _{max} (ng/ml)	4.02	4.05	0.99	95.4-102.9
T _{max} (h)*	27.85	30.00	-	-

* non parametric test (MANN/WHITNEY/WILCOXON)

The 90% confidence intervals for citalopram and for demethylcitalopram for the log-transformed parameters C_{max}, AUC_{0-∞} and AUC_{0-t} lie within the range 80-125%, such that the test and reference products may be considered bioequivalent after a single dose under fasted conditions in male subjects.

Plasma samples were analysed using a HPLC method using UV detection. Limit of quantitation was 0.4 ng/ml for citalopram and for demethylcitalopram. The method has been validated.

Study 2

Satisfactory Certificates of Analysis have been provided for the test (Citalopram 20mg Film-Coated Tablets) and reference (Seropram 20mg Tablets, Lundbeck SA, France) batches.

Table 8: Pharmacokinetic results for a randomised single dose 2-way crossover study between the test and reference product. Log transformed. ANOVA. n=18 healthy male subjects, dosed fasted; t=168 hours. Wash out period: at least 3 weeks

Test parameter	Test product (geometric mean)	Reference product (geometric mean)	Ratio Test/reference x 100	90% Confidence intervals
Citalopram				
AUC _{0-t} (ng.h/ml)	647.9	694.2	93.3	90.7-96.0
AUC _{0-∞} (ng.h/ml)	701.8	746.0	94.1	91.1-97.1
C _{max} (ng/ml)	15.97	16.82	95.0	89.3-100.9
T _{max} (h)*	3.50	3.75	-	-
Demethylcitalopram				
AUC _{0-t} (ng.h/ml)	217.3	233.6	93.0	86.9-99.5
AUC _{0-∞} (ng.h/ml)	310.0	327.3	94.7	89.0-100.8
C _{max} (ng/ml)	2.20	2.26	97.2	93.7-100.9
T _{max} (h)*	35.39	35.43	-	-

* non parametric test (median)

The 90% confidence intervals for the log-transformed parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ lie within the range 80-125%, such that the test and reference products may be considered bioequivalent after a single dose under fasted conditions in male subjects.

Plasma samples were analysed using a HPLC method using UV detection. Limit of quantitation was 0.4 ng/ml for citalopram and for demethylcitalopram. The method has been validated.

Bioequivalence studies have been conducted with the 20mg and 40mg strengths. Given that the three strengths are based on a proportional formulation, that similar dissolution profiles occur for the three strengths and as linear kinetics apply over the proposed dose range, it is acceptable that a bioequivalence study has not been performed on the 10mg tablets.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Cipramil Tablets (H Lundbeck AS, Denmark), 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 an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

These national abridged applications are submitted claiming essential similarity to Cipramil, Lundbeck.

2. INDICATIONS

Satisfactory. Consistent with current UK cross-reference SPC.

3. DOSE & DOSE SCHEDULE

Satisfactory. Consistent with current UK cross-reference SPC.

4. TOXICOLOGY

No new data

5. EFFICACY

No new data.

6. SAFETY

No new data.

7. EXPERT REPORTS

These are satisfactory.

8. PATIENT INFORMATION LEAFLET (PIL)

Satisfactory.

9. LABELLING

Satisfactory.

10. APPLICATION FORM (MAA)

Medically satisfactory.

11. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory. Consistent with current cross-reference SPC

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

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 20mg and 40mg Tablets and the reference product Cipramil 20mg and 40mg Tablets (Lundbeck). Given that linear kinetics apply between the three tablet strengths, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 10mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Cipramil Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with citalopram hydrobromide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 27 th June 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 7 th July 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 8 th October 2003 and 15 th June 2005, and further information relating to the quality dossiers on 13 th February 2004, 22 nd December 2004, 11 th March 2005, 18 th April 2005 and 18 th May 2005.
4	The applicant responded to the MHRA's requests, providing further information on 18 th November 2003 and 20 th January 2006 for the clinical sections, and again on 22 nd December 2004, 19 th January 2005, 11 th March 2005, 4 th April 2005, 19 th April 2005 and 25 th May 2005 for the quality sections.
5	The applications were determined on 18 th October 2006

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg citalopram, as citalopram hydrobromide
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Round, white tablets with a diameter of 6 mm.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

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

4.2 Posology and method of administration

Posology – Treating depression:

Adults: 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.

Duration of treatment: A treatment period of at least six 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 the 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.

Withdrawal symptoms seen on discontinuation of SSRI: 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.

4.3 Contraindications

Hypersensitivity to citalopram or to any of the excipients.

Monoamine Oxidase Inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

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

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

4.4 Special warning 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/suicidal thoughts: 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 self harm is highest shortly after presentation and the risk of suicide may increase in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura 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.

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

Psychomotor restlessness: The use of citalopram 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.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 0.06% to 0.9% of patients treated with citalopram.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including somnia and intense dream), 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 need (see "Withdrawal Symptoms Seen on Discontinuation of Citalopram", Section 4.2 Posology and Method of Administration).

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.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see 4.2 Posology and method of administration) reduces the likelihood of this effect.

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 4.3 Contraindications).

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2 D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this

important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80 %). These properties give citalopram a low potential for clinically significant drug interactions.

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

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

Lithium and tryptophan: There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic 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.

Imipramine: In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased.

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

Dynamic interactions between citalopram and the 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):

	Very Common (> 10%)	Common (> 1%)	Uncommon (< 1 %)	Post-marketing events
Psychiatric Disorders	somnolence, insomnia, agitation, nervousness	sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, suicide attempt, confusion	euphoria, increased libido	hallucinations, mania, depersonalisation, panic attack (these symptoms may be due to the underlying disease)
Nervous System Disorders	headache, tremor, dizziness	migraine, paraesthesia	extrapyramidal disorder, convulsions	
Cardiac Disorders	palpitations	tachycardia	bradycardia	
Vascular Disorders		postural hypotension		
Gastrointestinal disorders	nausea, dry mouth, constipation, diarrhoea	dyspepsia, vomiting, abdominal pain, flatulence, increased salivation		
Renal and urinary disorders		micturition disorder, polyuria		urinary retention
Metabolism and nutrition Disorders		weight decrease, weight increase		
Respiratory Disorders		rhinitis, sinusitis	coughing	
Reproductive system Disorders		ejaculation failure, female anorgasmia, dysmenorrhoea, impotence		galactorrhoea
Skin disorders	increased sweating	rash, pruritus	photosensitivity	angiodema,
Eye disorders	abnormal accommodation	abnormalities of vision		
Special senses disorders		taste abnormalities		
Ear and Labyrinth Disorders			tinnitus	
Musculoskeletal disorders			myalgia	arthralgia
Hepato-biliary disorders			increased liver enzyme values	
Neurological				

	Very Common (> 10%)	Common (> 1%)	Uncommon (< 1 %)	Post-marketing events
disorders				
General Disorders	asthenia	fatigue, yawning	allergic reactions, syncope, malaise	anaphylactoid reactions

Rare (<0.1%): psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use); haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucous membranes) can occur on rare occasions.

In rare cases a serotonin syndrome has been reported in patients using SSRIs. Hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) have been reported rarely, predominantly in the elderly (see Section 4.4 Special warning and precautions for use).

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

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

ATC code: N 06 AB 04

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT₂, dopamine D₁ and D₂ receptors, α ₁-, α ₂- and β -adrenoceptors, histamine H₁, muscarinic cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

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 metabolised 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

Core:

Mannitol

Microcrystalline cellulose

Colloidal silica, anhydrous

Magnesium stearate

Coating:

Hypromellose

Macrogol 6000

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/PVDC/Al blister

Pack size: 10, 14, 20, 28, 30, 50, 56, 98, 100 tablets.

100 x 1 unit dose blister

HDPE tablet container with LDPE tamper evident cap

Pack size: 100 tablets

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norpharm Ltd.

26, Laurence St

Drogheda, Co. Louth

Ireland

- 8 MARKETING AUTHORISATION NUMBER**
PL 20438/0005
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/10/2006
- 10 DATE OF REVISION OF THE TEXT**
18/10/2006

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg citalopram, as citalopram hydrobromide
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Round, white tablets with a break-line and diameter of 8 mm.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

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

4.2 Posology and method of administration

Posology – Treating depression:

Adults: 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.

Duration of treatment: A treatment period of at least six 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 (from a lower strength tablet) 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 the 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.

Withdrawal symptoms seen on discontinuation of SSRI: 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.

4.3 Contraindications

Hypersensitivity to citalopram or to any of the excipients.

Monoamine Oxidase Inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

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

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

4.4 Special warning 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/suicidal thoughts: 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 self harm is highest shortly after presentation and the risk of suicide may increase in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura 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.

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

Psychomotor restlessness: The use of citalopram 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.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 0.06% to 0.9% of patients treated with citalopram.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including somnia and intense dream), 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 need (see "Withdrawal Symptoms Seen on Discontinuation of Citalopram", Section 4.2 Posology and Method of Administration).

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.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see 4.2 Posology and method of administration) reduces the likelihood of this effect.

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 4.3 Contraindications).

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2 D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this

important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, TCAs and some SSRIs). Protein binding is relatively low (<80 %). These properties give citalopram a low potential for clinically significant drug interactions.

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

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

Lithium and tryptophan: There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic 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.

Imipramine: In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased.

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

Dynamic interactions between citalopram and the 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):

	Very Common (> 10%)	Common (> 1%)	Uncommon (< 1%)	Post-marketing events
Psychiatric disorders	somnolence, insomnia, agitation, nervousness	sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, suicide attempt, confusion	euphoria, increased libido	hallucinations, mania, depersonalisation, panic attack (these symptoms may be due to the underlying disease)
Nervous system disorders	headache, tremor, dizziness	migraine, paraesthesia	extrapyramidal disorder, convulsions	
Cardiac disorders	palpitations	tachycardia	bradycardia	
Vascular disorders		postural hypotension		
Gastrointestinal disorders	nausea, dry mouth, constipation, diarrhoea	dyspepsia, vomiting, abdominal pain, flatulence, increased salivation		
Renal and urinary disorders		micturition disorder, polyuria		urinary retention
Metabolism and nutrition disorders		weight decrease, weight increase		
Respiratory disorders		rhinitis, sinusitis	coughing	
Reproductive system disorders		ejaculation failure, female anorgasmia, dysmenorrhoea, impotence		galactorrhoea
Skin disorders	increased sweating	rash, pruritus	photosensitivity	angiodema
Eye disorders	abnormal accommodation	abnormalities of vision		
Special senses disorders		taste abnormalities		
Ear and labyrinth disorders			tinnitus	
Musculoskeletal disorders			myalgia	arthralgia
Hepato-biliary disorders			increased liver enzyme values	

	Very Common (> 10%)	Common (> 1%)	Uncommon (< 1%)	Post-marketing events
Neurological disorders				
General disorders	asthenia	fatigue, yawning	allergic reactions, syncope, malaise	anaphylactoid reactions

Rare (< 0.1%): psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use); haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucous membranes) can occur on rare occasions.

In rare cases a serotonin syndrome has been reported in patients using SSRIs. Hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) have been reported rarely, predominantly in the elderly (see Section 4.4 Special warning and precautions for use).

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

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

ATC code: N 06 AB 04

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT₂, dopamine D₁ and D₂ receptors, α ₁-, α ₂- and β -adrenoceptors, histamine H₁, muscarinic cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

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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 metabolised 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} β) 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

Core:

Mannitol
Microcrystalline cellulose
Colloidal silica, anhydrous
Magnesium stearate

Coating:

Hypromellose
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/PVDC/Al blister
Pack size: 10, 14, 20, 28, 30, 50, 56, 98, 100 tablets.
100 x 1 unit dose blister
HDPE tablet container with LDPE tamper evident cap
pack size: 100 tablets
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norpharm Ltd.
26, Laurence St
Drogheda, Co. Louth
Ireland

- 8 MARKETING AUTHORISATION NUMBER**
PL 20438/0006
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/10/2006
- 10 DATE OF REVISION OF THE TEXT**
18/10/2006

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 40mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg citalopram, as citalopram hydrobromide
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Round, white tablets with a break-line and diameter of 10 mm.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

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

4.2 Posology and method of administration

Posology – Treating depression:

Adults: Citalopram should be administered as a single oral dose of 20 mg (from a lower strength tablet) 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.

Duration of treatment: A treatment period of at least six 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 (from a lower strength tablet) 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 (from a lower strength tablet). Dependent on the 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.

Withdrawal symptoms seen on discontinuation of SSRI: 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.

4.3 Contraindications

Hypersensitivity to citalopram or to any of the excipients.

Monoamine Oxidase Inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

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

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

4.4 Special warning 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/suicidal thoughts: 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 self harm is highest shortly after presentation and the risk of suicide may increase in the early stages of recovery. Furthermore, there is evidence that in a small group of people, antidepressants may increase the risk of suicidal thoughts and self-harm.

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, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients, (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal thoughts and to seek medical advice immediately if these symptoms present.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura 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.

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

Psychomotor restlessness: The use of citalopram 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.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 0.06% to 0.9% of patients treated with citalopram.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including somnia and intense dream), 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 need (see "Withdrawal Symptoms Seen on Discontinuation of Citalopram", Section 4.2 Posology and Method of Administration).

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.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see 4.2 Posology and method of administration) reduces the likelihood of this effect.

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 4.3 Contraindications).

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

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

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

Lithium and tryptophan: There is no pharmacokinetic interaction between lithium and citalopram. However, there have been reports of enhanced serotonergic 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 to be adjusted.

Imipramine: In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine, was increased.

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

Dynamic interactions between citalopram and the 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):

	Very common (> 10%)	Common (> 1%)	Uncommon (< 1%)	Post-marketing events
Psychiatric Disorders	somnolence, insomnia, agitation, nervousness	sleep disorders, impaired concentration, abnormal dreaming, amnesia, anxiety, decreased libido, increased appetite, anorexia, apathy, suicide attempt, confusion	euphoria, increased libido	hallucinations, mania, depersonalisation, panic attack (these symptoms may be due to the underlying disease)
Nervous system disorders	headache, tremor, dizziness	migraine, paraesthesia	extrapyramidal disorder, convulsions	
Cardiac Disorders	palpitations	Tachycardia	bradycardia	
Vascular Disorders		postural hypotension		
Gastrointestinal disorders	nausea, dry mouth, constipation, diarrhoea	dyspepsia, vomiting, abdominal pain, flatulence, increased salivation		
Renal and urinary disorders		micturition disorder, polyuria		urinary retention
Metabolism and nutrition Disorders		weight decrease, weight increase		
Respiratory disorders		rhinitis, sinusitis	coughing	
Reproductive system Disorders		ejaculation failure, female anorgasmia, dysmenorrhoea, impotence		Galactorrhoea
Skin disorders	increased sweating	rash, pruritus	photosensitivity	angiodema,
Eye disorders	abnormal accommodation	abnormalities of vision		
Special senses disorders		taste abnormalities		
Ear and labyrinth disorders			tinnitus	
Musculoskeletal disorders			myalgia	arthralgia
Hepato-biliary disorders			increased liver enzyme values	
Neurological disorders				

	Very common (> 10%)	Common (> 1%)	Uncommon (< 1%)	Post-marketing events
General disorders	asthenia	fatigue, yawning	allergic reactions, syncope, malaise	anaphylactoid reactions

Rare (<0.1%): psychomotor restlessness/akathisia (see section 4.4 Special Warnings and Special Precautions for Use); haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucous membranes) can occur on rare occasions.

In rare cases a serotonin syndrome has been reported in patients using SSRIs. Hyponatraemia and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH) have been reported rarely, predominantly in the elderly (see Section 4.4 Special warning and precautions for use).

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

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

ATC code: N 06 AB 04

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

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

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT₂, dopamine D₁ and D₂ receptors, α ₁-, α ₂- and β -adrenoceptors, histamine H₁, muscarinic cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

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 metabolised 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} β) 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

Core:

Mannitol

Microcrystalline cellulose

Colloidal silica, anhydrous

Magnesium stearate

Coating:

Hypromellose

Macrogol 6000

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/PVDC/Al blister

Pack size: 10, 14, 20, 28, 30, 50, 56, 98, 100 tablets.

100 x 1 unit dose blister

HDPE tablet container with LDPE tamper evident cap

Pack size: 100 tablets

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norpharm Ltd.

26, Laurence St

Drogheda, Co. Louth

Ireland

- 8 MARKETING AUTHORISATION NUMBER**
PL 20438/0007
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/10/2006
- 10 DATE OF REVISION OF THE TEXT**
18/10/2006

PATIENT INFORMATION LEAFLET

Citalopram 10mg, 20mg and 40mg Tablets

Please read this entire leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor or your 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.

What is in your medicine?

The name of your medicine is Citalopram Tablets. The tablets are available in 3 strengths.

Each film-coated tablet contains citalopram hydrobromide equivalent to 10, 20 or 40 mg of citalopram base.

The other ingredients are mannitol, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate. The film coating of the tablet contains hypromellose, macrogol 6000 and titanium dioxide (E171).

A box of citalopram tablets contains two press-through strips each containing 14 tablets (28 tablets in total).

Marketing Authorisation Holder: Norpharm Ltd., 26, Laurence St, Drogheda, Co. Louth, Ireland

Manufacturer: Dragenopharm Apotheker Püschl GmbH & Co. KG Göllstrasse 1 D-84529 Tittmonong, Germany and Cardinal Health Germany GmbH, Steinbeißstraße 2, 73614 Schorndorf, Germany

What are Citalopram Tablets and what are they used for?

Citalopram belongs to a group of medicines known as selective serotonin re-uptake inhibitors. These are antidepressants which work by increasing

the amount of a chemical called serotonin in the brain. This helps relieve the symptoms of depression.

Citalopram Tablets are used to treat depression and when you are feeling better to help prevent the symptoms recurring.

Citalopram Tablets are also used to relieve symptoms in patients prone to panic attacks.

Before you take Citalopram Tablets

Use in children and adolescents under 18 years of age

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

You should not take these tablets if:

- You are allergic to citalopram or any other ingredients in the tablets.
- You are taking any medicines known as monoamine oxidase inhibitors (MAOIs) for example phenelzine or moclobemide (also known as a reversible MAOI or RIMA), which are also used to treat depression, or selegiline used to treat Parkinson's disease.

If Citalopram Tablets are taken with a MAOI or if a MAOI is started very soon after stopping Citalopram Tablets serious reactions, which on occasion have been fatal, may occur. Symptoms such as agitation, tremor, stiffness, muscle spasm, rigidity, confusion, irritability, fever, delirium and coma have been seen.

If you are taking a MAOI you should not start taking Citalopram Tablets for two weeks after finishing your irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide.

A MAOI or RIMA should not be taken for at least seven days after you have stopped taking Citalopram Tablets.

- You are taking medicines containing sumatriptan or other similar medicines (such as oxitriptan), or ergotamine, to relieve the symptoms of migraine.
- You are taking tramadol for the treatment of pain.
- You are taking tryptophan (sometimes used to treat depression).
- You are taking herbal remedies containing St John's wort (*Hypericum perforatum*). Citalopram Tablets and St John's wort should not be taken together as this may cause an increase in unwanted side effects.
- You are pregnant, think you might be pregnant or are planning to become pregnant.
- You are breast-feeding.

None of the above medicines should be taken at the same time as citalopram.

If you think that any of the above applies to you DO NOT take Citalopram Tablets. Talk to your doctor for advice.

Do not take these tablets before talking to your doctor if you can answer yes to any of the following questions:

- Have you ever thought about suicide or tried to take your own life?
- Do you have a history of mental illness, in particular schizophrenia?
- Do you suffer from mania (hallucinations, great excitement, difficulty concentrating, difficulty in staying still)?
- Are you diabetic? If you are, the treatment for your diabetes (insulin or tablets) may need to be adjusted.
- Do you have epilepsy? You may develop seizures/fits or these may occur more often when taking Citalopram Tablets. For this reason your doctor will carry out regular check-ups to ensure that your epilepsy remains well controlled. Citalopram Tablets should be stopped if you start having more fits than usual or if you have a fit for the first time. You should then see your doctor immediately.
- Do you have kidney or liver disease? If you have liver disease your doctor will need to monitor your liver function and may take blood tests.
- Do you have any problem with your heart or an abnormal heart rhythm?
- Do you have a history of bleeding disorders/abnormal bleeding?
- Are you taking any drugs to thin your blood such as warfarin? Are you taking any other medicines which can cause bleeding such as non-steroidal anti-inflammatory drugs (also known as NSAIDs) such as ibuprofen or diclofenac, aspirin, dipyridamol or ticlopidine or any medicines used to treat mental illness, such as chlorpromazine, clozapine, amisulpride, risperidone, or other medicines used to treat depression such as amitriptyline, clomipramine, doxepin? Taking any of these medicines at the same time as citalopram can increase the risk of bleeding.
- Are you currently having electro-convulsive therapy (ECT)?
- Are you taking lithium? Your doctor will need to monitor the lithium levels in your blood.
- Are you taking imipramine? Your doctor may need to change your imipramine dose.
- Are you taking metoprolol? Your doctor will monitor your blood pressure and heart rate.
- Are you taking a medicine called cimetidine?

1.1.1 Pregnancy

Ask your doctor or pharmacist for advice before taking these tablets.

1.1.2 Breast-feeding

Ask your doctor or pharmacist for advice before taking these tablets.

Driving and using machines

Citalopram Tablets may cause unwanted side effects that include dizziness, drowsiness, changes in vision and an inability to concentrate, make judgements or react to emergencies. If you suffer from any of these side effects, do NOT drive, operate machinery or perform tasks that require you to be alert.

Taking other medicines

If taken with some other medicines the effects of these tablets or the effects of the other medicine may be changed. Before taking Citalopram Tablets, you should tell your doctor of all the medicines and tablets you are taking, including those you have bought without a prescription from the pharmacist.

If you need to see another doctor or go into hospital you should take all your medicines and tablets, including Citalopram Tablets with you so that the doctors will know exactly what you are taking.

Taking Citalopram Tablets with alcohol

As with all antidepressants, you should avoid taking alcohol whilst receiving treatment.

How to take Citalopram Tablets

Citalopram Tablets should be taken regularly according to your doctor's instructions.

The dispensing label on the pack will tell you how many tablets to take and when to take them. If you are not sure how or when to take your tablets, you should talk to your doctor or pharmacist.

Swallow the tablets whole with a drink of water with or without food. Do not chew them.

Depression:

The usual starting dose is 20mg per day, taken as a single dose either in the morning or in the evening. Your doctor may increase this to a maximum of 60mg per day if necessary. Treatment will usually continue for at least 6 months.

Panic attacks:

Patients being treated to alleviate symptoms of panic attacks will probably be prescribed only 10 mg daily for the first week, before increasing the dose to 20mg per day. This low dose is recommended to reduce the chances of you experiencing anxiety when starting therapy. Your doctor may increase this to a maximum of 60mg per day if necessary. The maximum effect is seen after about 3 months. Treatment may continue for several months.

It may take at least 2 weeks 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 your doctor. Never change the dose of your medicine without talking to your doctor first.

Elderly patients will usually be prescribed a dose of 20mg per day. Your doctor may increase this to a maximum of 40 mg per day if necessary.

Patients with liver problems will usually be prescribed a low dose.

Patients with mild to moderate kidney disease will normally be prescribed the usual adult dose. There is no information available on treatment of patients with severe kidney disease.

Citalopram Tablets are not recommended for children and adolescents below 18 years of age.

Symptoms such as dizziness, tingling, headache, anxiety and nausea (feeling sick) may occur when citalopram treatment is stopped. Stopping the tablets too abruptly should be avoided – your doctor will reduce your dose gradually over 1-2 week periods, in order to reduce these effects. These symptoms are generally non-serious and disappear within a few days. If you experience symptoms on stopping treatment, contact your doctor.

If you take more Citalopram Tablets than you should:

If you take too many of these tablets you may experience some of the following symptoms – drowsiness, coma, feeling sick and being sick, fits, cyanosis (blue discoloration of the skin, lips and nails), hyperventilation (over breathing) sweating and palpitations/ rapid, irregular heart beat. If you, or someone else, have accidentally taken too many Citalopram Tablets contact your doctor or nearest hospital casualty department immediately. If you go to the doctor/hospital take any remaining Citalopram Tablets and the container with you.

If you forget to take Citalopram Tablets:

If you forget to take a dose take it as soon as you remember, but do not take two doses at the same time.

Possible side effects

Like all medicines, Citalopram Tablets can cause side effects. Side effects are usually mild and do not last long. Most will occur during the first few weeks of treatment and usually lessen as your condition improves.

Difficulty in sleeping and agitation often occur at the start of treatment. Starting treatment at a low dose and increasing the dose slowly as necessary can reduce these effects.

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 of Citalopram Tablets becomes apparent. Tell your doctor immediately if you have any distressing thoughts or experiences.

Side effects include:

Very common:

- sleepiness or not being able to sleep,
- agitation, nervousness, tremor, dizziness,
- headache,
- palpitations,
- feeling sick, dry mouth,
- constipation or diarrhoea,
- increased sweating,
- not being able to focus your eyes properly,
- feeling weak.

Common:

- not being able to concentrate properly, anxiety, feelings of listlessness, confusion, memory loss, sleep disorders, abnormal dreaming, tiredness, yawning,
- decreased libido/reduced sex drive, impotence and problems with erection and ejaculation, failure to reach orgasm and painful periods in women,
- increased or decreased appetite, aversion to food, weight gain or weight loss,
- migraine, pins and needles,
- a rapid heart beat, or feeling faint or light headed when you stand up,
- indigestion, sickness, stomach pains, suffering from wind, increased salivation (dribbling),
- difficulty in passing urine, or producing large amounts of urine,
- a runny nose or inflammation of the sinuses,
- rash or itching,
- visual disturbances and abnormal taste sensations.

Uncommon:

- an exaggerated sense of well-being,
- increased libido,
- problems with posture or co-ordination, jerky movements, fits,
- a slow heartbeat,
- coughing,
- sensitivity to light,
- ringing in the ears,
- muscle pain,
- allergic reactions
- fainting, feeling generally unwell,
- increased levels of liver enzymes.

Rarely:

In rare cases psychomotor restlessness may occur, characterized 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. Rare reports of bleeding problems which have included heavy periods, vomiting blood or passing blood in the stools or passing black tarry stools, unusual bruising of the skin or bleeding in the mouth and an increased bleeding time.

Another rare side effect is known as the serotonin syndrome, which is a serious condition that causes agitation, tremor and shaking, muscle spasm and abnormal jerky movements, confusion and fever. The condition may progress to seizures/fits and coma or loss of consciousness. If these symptoms occur treatment with Citalopram Tablets should be stopped straight away and advice sought from your doctor immediately.

Changes in the salt balance in your body may also occur; this is more likely in the elderly.

You should avoid abrupt discontinuation because withdrawal symptoms are common. 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.

Citalopram Tablets may also cause:

- hallucinations, great excitement, difficulty in concentrating and staying still, or changes of mood and thinking or feelings of unreality, but these symptoms may be due to the conditions for which you are being treated. Patients who have panic attacks may actually experience a temporary period of increased anxiety after starting treatment and therefore a low starting dose may be prescribed,
- urinary retention (difficulty in passing urine),
- milk leaking from the breasts (in both women and men),
- swelling of the face, hands or other areas,
- bruising,
- joint pain.

Severe allergic (anaphylactoid) reactions have been reported (uncommonly). These reactions may include skin rash, itching, swelling of the face, mouth or lips, difficulty swallowing, difficulty breathing or shortness of breath or collapse.

Any side effects that do occur will usually disappear soon after starting therapy. If they are troublesome or persistent, or if you develop any other unusual side effects while taking Citalopram Tablets, please tell your doctor. If you experience any of the serious or rare side effects mentioned above, you should stop taking Citalopram Tablets straight away and tell your doctor immediately.

1.1.2.1 Storing Citalopram Tablets

Do not use this medicine after the expiry date shown on the pack.


This medicinal product does not require any special storage conditions.


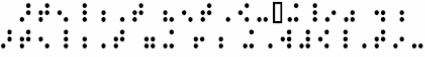


Any unused tablets should be returned to your pharmacist, unless your doctor has advised you otherwise.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

Date of last revision of leaflet May 2005.

This leaflet does not contain all the information about your medicine. If you have any questions, or you are not sure about anything, ask your doctor or pharmacist.

CITALOPRAM 10 mg TABLETS	 Norpharm Ltd.	BN: EXP:
	 28 film-coated tablets CITALOPRAM 10 mg TABLETS	
	CITALOPRAM 10 mg TABLETS	
	<p>Each tablet contains 10 mg citalopram as citalopram hydrobromide. Take by mouth as directed by your doctor. Please read the enclosed leaflet carefully.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p style="text-align: center;">POM</p> <p style="text-align: center;">PL 20438 / 0005 Norpharm Ltd. 26, Laurence St Drogheda, Co. Louth</p> 	

CITALOPRAM 20 mg TABLETS	 Norpharm Ltd.	BN: EXP:
	 28 film-coated tablets CITALOPRAM 20 mg TABLETS	
CITALOPRAM 20 mg TABLETS		
<p>Each tablet contains 20 mg citalopram as citalopram hydrobromide. Take by mouth as directed by your doctor. Please read the enclosed leaflet carefully.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p> PL 20438 / 0006 Norpharm Ltd. 26, Laurence St Drogheda, Co. Louth</p> 		

<p>CITALOPRAM 40 mg TABLETS</p>	<p> Norpharm Ltd. 28 film-coated tablets CITALOPRAM 40 mg TABLETS</p>	<p>BN: EXP:</p>
	<p>CITALOPRAM 40 mg TABLETS</p> <p>Each tablet contains 40 mg citalopram as citalopram hydrobromide. Take by mouth as directed by your doctor. Please read the enclosed leaflet carefully.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>POM PL 20438 / 0007 Norpharm Ltd. 26, Laurence St Drogheda, Co. Louth</p> <p></p>	