CITALOPRAM 40MG/ML ORAL DROPS, SOLUTION

PL 20176/0029

UKPAR

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CITALOPRAM 40MG/ML ORAL DROPS, SOLUTION

PL 20176/0029

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Citalopram 40mg/ml Oral drops, solution (Product Licence number: 20176/0029).

Citalopram is a type of antidepressant known as a selective serotonin re-uptake inhibitor (SSRI). It increases the effects of the body's naturally occurring hormone, serotonin, by inhibiting its re-uptake in the nerve cells. Citalopram 40mg/ml Oral drops, solution is used to treat depression, to prevent depression from coming back, and to treat panic attacks which may or may not be associated with a severe fear of leaving the house (agoraphobia).

Citalopram 40mg/ml Oral drops, solution raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Citalopram 40mg/ml Oral drops, solution to Technopharm Limited on 28 November 2008. This medicine is only available on prescription.

This is an abridged, complex application for Citalopram 40mg/mL Oral drops, solution, which contains the active substance citalopram hydrochloride. This application was submitted under Article 10(1) of EC Directive 2001/83, last paragraph, claiming that this medicinal product is a generic version of the originator product, Cipramil 10mg Tablets, which was first authorised in Denmark to Lundberk Limited on 30 January 1989. The ten year rule is, therefore, met. In the United Kingdom, the reference product is Cipramil Drops 40mg/mL (PL 00458/0071), which was authorised on 4 August 1998. Citalopram oral drops are in a different pharmaceutical form to the tablet reference product and have approximately 25% increased bioavailability compared to the tablets. The oral drops are, therefore, 'suprabioavailable'.

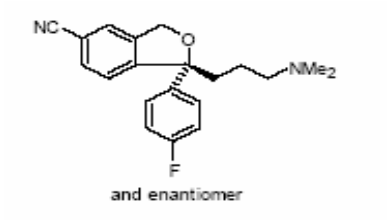
Citalopram 40mg/mL Oral drops, solution is indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence and for the treatment of panic disorder, with or without agoraphobia. Citalopram is a bicyclic phthalane derivative. It is an SSRI with actions and uses similar to those of fluoxetine.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Citalopram hydrochloride

Ph. Eur. / rINN: Citalopram hydrochloride
Chemical names: 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile hydrochloride
CAS registration no: 85118-27-0



Molecular formula: $C_{20}H_{21}FN_{2O}.HCl$
Molecular weight: 360.5
Melting point: 174-179 °C

Citalopram hydrochloride is a white or almost white crystalline powder, very soluble in water and freely soluble in methanol. It has a chiral centre and exhibits stereo isomerism.

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

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

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

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

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

Appropriate stability data have been generated supporting a retest period of 12 months, with no specific storage instructions.

DRUG PRODUCT

Description and Composition of the Drug Product

The clear, colourless solution contains 44.48mg / mL of citalopram hydrochloride, which is equivalent to 40mg / mL of citalopram.

Other ingredients are methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), hydroxyethyl cellulose, ethanol 96% v/v and purified water. Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their

respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for the excipients.

There were no novel excipients used and no overages.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory.

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

Container Closure System
The product is packaged in amber, Type III, glass vials. The closure is a polyethylene screw cap with polyethylene dropper. One bottle is included in each carton. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. Each vial contains 15 ml of solution.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years for unopened product has been set, which is satisfactory. Once the bottle is opened, it has a shelf life of 16 weeks. There are no storage conditions for the unopened product; however, once the container is opened the product should not be stored above 25°C.

Bioavailability and bioequivalence
No bioequivalence study has been performed to support this application and none is needed.

Conclusion
It is recommended that a Marketing Authorisation is granted for this product.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

Overview
An appropriate clinical overview has been included in the dossier. The clinical overview contains a sufficient outline of the published literature concerning the clinical pharmacology, efficacy and safety of citalopram.

Bioavailability and bioequivalence
No bioequivalence study has been performed to support this application and none is needed.

Product literature
All product literature (SPCs, PILs and labelling) are satisfactory. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Assessor's overall conclusions
It is recommended that a marketing authorisation can be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Citalopram 40mg/ml Oral drops, solution 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

The efficacy of citalopram is well established.
The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Citalopram 40mg/ml Oral drops, solution. The risk benefit is therefore considered to be positive.

CITALOPRAM 40MG/ML ORAL DROPS, SOLUTION

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 3 December 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 6 August 2005
4	Following assessment of the application the MHRA requested further information relating to the quality dossier on 8 November 2005
5	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 6 January 2007
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 26 September 2007
7	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 27 June 2008
10	The application was determined on 28 November 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Citalopram 40mg/ml Oral drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of oral drops, solution (= 20 drops) contains 40mg citalopram (equivalent to 44.48mg citalopram hydrochloride). Contains small amounts of ethanol (alcohol), less than 100 mg per dose.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Oral drops, solution.
Citalopram 40mg/ml Oral drops, solution is a clear liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of panic disorder with or without agoraphobia

4.2 Posology and method of administration

Posology

Treating Depression

Citalopram drops should be administered as a single oral dose of 16 mg (8 drops) daily. Dependent on individual patient response this may be increased to a maximum of 48 mg (24 drops) daily. The dose may be taken in the morning or evening without regard for food. It should be drunk straight away following mixing.
A treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse.

Treating Panic Disorder

In common with other pharmacotherapy used in this patient group, a low starting dose is advised to reduce the likelihood of a paradoxical initial anxiogenic effect. A single oral dose of 8 mg (4 drops) daily is recommended for the first week before increasing the dose to 16 mg (8 drops) daily. The dose may be further increased, up to a maximum of 48 mg (24 drops) daily dependent on individual patient response, however an optimum dose of 20-30 mg tablets (drops equivalent - 16 to 24 mg/8 to 12 drops) 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 16 mg (8 drops). Dependent on individual patient response this may be increased to a maximum of 32 mg (16 drops) 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
For oral administration after mixing with water, orange juice or apple juice.
Citalopram drops can be taken as a single daily dose, at any time without regard to food intake.
Citalopram drops have approximately 25% increased biovailability compared to tablets. The tablet dosage corresponds to the number of drops as follows:

Tablets	Drops
10 mg	8 mg (4 drops)
20 mg	16 mg (8 drops)
30 mg	24 mg (12 drops)
40mg	32 mg (16 drops)
60 mg	48 mg (24 drops)

4.3 Contraindications
Hypersensitivity to citalopram.

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

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

Citalopram should not be used in combination with a MAOI. Citalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least

one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI or RIMA.

4.4 Special warnings and precautions for use

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

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

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

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

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

Diabetes - In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and or oral hypoglycaemic dosage may need to be adjusted.

Seizures — Seizures are a potential risk with antidepressant drugs. The drug should be discontinued in any patient who develops seizures. Citalopram should be avoided

in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

ECT — There is little clinical experience of concurrent administration of citalopram and ECT, therefore caution is advisable.

Mania — Citalopram should be used with caution in patients with a history of mania/hypomania. Citalopram should be discontinued in any patient entering a manic phase.

Haemorrhage – There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as haemorrhagic manifestations e.g. gastrointestinal haemorrhage with SSRIs. The risk of gastrointestinal haemorrhage may be increased in elderly people during treatment with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.

Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

Consideration should be given to factors which may affect the disposition of a minor metabolite of citalopram (didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in susceptible individuals. However, in ECG monitoring of 2500 patients in clinical trials, including 277 patients with pre-existing cardiac conditions, no clinically significant changes were noted.

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

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

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

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

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

Lithium & tryptophan-There is no pharmacokinetic interaction between lithium and citalopram. However, there 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.

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

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

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

4.6 Pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea,

somnolence, dry mouth, increased sweating and tremor. The incidence of each in excess over placebo is low (<10%).

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

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

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

Frequent: (≥ 5 - 20%)

Skin and appendages disorders: Sweating increased (13%).
Central and peripheral nervous system disorders: Headache (19%), tremor (12%), dizziness (8%).
Vision disorders: Accommodation abnormal (5%).
Psychiatric disorders: Somnolence (17%), insomnia (12%), agitation (6%), nervousness (6%).
Gastro-intestinal system disorders: Nausea (20%), mouth dry (18%), constipation (10%), diarrhoea (7%).
Heart rate and rhythm disorders: Palpitation (6%).
Body as a whole: Asthenia (11%).

Less frequent: (1 - <5%)

Skin and appendages disorders: Rash, pruritus.
Central and peripheral nervous system disorders: Paraesthesia, migraine.
Vision disorders: Vision abnormal.
Special senses other, disorder: Taste perversion.
Psychiatric disorders: Sleep disorder, libido decreased, concentration impaired, dreaming abnormal, amnesia, anxiety, appetite increased, anorexia, apathy, impotence, suicide attempt, confusion, yawning.
Gastrointestinal system disorders: Dyspepsia, vomiting, abdominal pain, flatulence, saliva increased.
Metabolic and nutritional disorders: Weight decrease, weight increase.
Cardiovascular disorders, general: Hypotension postural.
Heart rate and rhythm disorders: Tachycardia.
Respiratory system disorders: Rhinitis.
Urinary system disorders: Micturition disorder, polyuria.
Reproductive disorders, male: Ejaculation failure.
Reproductive disorders, female: Anorgasmia female.
Body as a whole: Fatigue

Rare: (<1%)

Musculo-skeletal system disorder: Myalgia.

Central and peripheral nervous system disorders: Exrapyramidal disorder, convulsions.
Hearing and vestibular disorders: Tinnitus.
Psychiatric disorders: Euphoria, libido increased.
Respiratory system disorder: Coughing.
Body as a whole: Malaise.

Frequency not known:

Suicidal ideation and suicidal behaviour*
Post Marketing - The following adverse reactions apply to the therapeutic class of SSRIs

Skin Disorders: Angiodema; ecchymoses. Photosensitivity reactions have been reported very rarely.

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

Gastrointestinal disorders : Gastrointestinal bleeding.
.
General disorders: Anaphylactoid reactions.

Hepato-billiary disorders: Abnormal LFT's.

Musculoskeletal disorders: Arthralgia.

Neurological disorders: Serotonin syndrome.

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

Reproductive disorders: Galactorrhoea.

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

4.9 Overdose

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

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

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

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Observe for a minimum of 4 hours due to long half life of citalopram.
Control convulsions with intravenous diazepam if they are frequent or prolonged. An ECG should be taken.

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 the serotonin (5-HT)-uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram.

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

In contrast to many tricyclic antidepressants and some of the newer SSRI's, citalopram has no or very low affinity for a series of receptors including 5-HT 1A, 5-HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional *in vitro* tests in isolated organs as well as functional *in vivo* tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

5.2 Pharmacokinetic properties

Absorption

Absorption is almost complete and independent of food intake (T max mean 2 hours after ingestion of drops and T max mean 3 hours after intake of tablets). Oral bioavailability is about 80% after ingestion of tablets. Relative bioavailability of drops is approximately 25% greater than the tablets.

Distribution

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

Biotransformation

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

Elimination

The elimination half-life (T½β) is about 1.5 days and the systemic citalopram plasma clearance (Cls) is about 0.33 L/min, and oral plasma clearance (Cl oral) is about 0.41 L/min.

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

Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Hydroxyethyl cellulose
Ethanol 96% v/v
Purified water

6.2 Incompatibilities

Citalopram Drops should only be mixed with water, orange juice or apple juice.

6.3 Shelf life

Unopened product: 2 years.
Opened product: 16 weeks.

6.4 Special precautions for storage

Unopened product: The medicinal product does not require any special storage conditions.
Opened product: Do not store above 25°C.

6.5 Nature and contents of container

Amber Type III glass vial containing 15 ml of solution, with polyethylene screw cap and polyethylene dropper. One bottle per carton.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Technopharm Limited
Fannin House, South County Business Park
Dublin 18
Republic of Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20176/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/11/2008

10 DATE OF REVISION OF THE TEXT

28/11/2008

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Citalopram 40mg/ml Oral Drops

Citalopram Oral Drops are not recommended for use in children or adolescents under 18 years of age. See section 2 'Do not take Citalopram Oral Drops:'.

You are at risk of having suicidal thoughts while taking this medicine. Take special care with Citalopram Oral Drops if you have previously had thoughts about killing or harming yourself or you are a young adult. See section 2 'Take special care with Citalopram Oral Drops:'.

When you stop taking this medication you may experience withdrawal symptoms. This is most likely if you stop taking your medicine suddenly. See section 4 'Withdrawal symptoms'.

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

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

In this leaflet:

❶ What Citalopram Oral Drops are and what they are used for

Citalopram is one of a type of antidepressants known as Selective Serotonin Re-uptake Inhibitors (SSRIs). It increases the effects of the body's naturally occurring hormone, serotonin, by inhibiting its re-uptake in the nerve cells.

Citalopram Oral Drops are used:

- To treat depression
- To prevent depression from coming back
- To treat panic attacks, which may or may not be associated with a severe fear of leaving the house (agoraphobia)

❷ Before you take Citalopram Oral Drops

Do not take Citalopram Oral Drops:

- If you are allergic (hypersensitive) to citalopram or any of the other ingredients of this medicine
- If you are taking, or have taken within the last two weeks, any monoamine oxidase inhibitors (MAO inhibitors). These are medicines used to treat depression or Parkinson's disease (e.g. selegiline or moclobemide)
- If you are pregnant or there is a chance you may be pregnant
- If you are breast-feeding
- If you are under 18 years of age

Citalopram Oral Drops are not recommended for use in children or adolescents under 18 years of age. 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 behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe this medicine for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed this product 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. Also, the long-term safety effects of this medication in this age group, concerning growth and development, have not yet been demonstrated.

Take special care with Citalopram Oral Drops:

Thoughts of suicide and worsening of your depression

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

You may be more likely to think like this:

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

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

If any of the following apply to you discuss it with your doctor or pharmacist BEFORE taking Citalopram Oral Drops:

- If you have a history of suicide attempts or suicidal thoughts or feelings
- If you are diabetic
- If you suffer from epilepsy
- If you have a history of bleeding disorders
- If you suffer from liver problems
- If you suffer from manic phases
- If you are having electric shock treatment

Taking other medicines

Do not take Citalopram Oral Drops in combination with:

- Any monoamine oxidase inhibitors (MAO-inhibitors) or if you have taken these in the last two weeks. See Section 2 'Do not take Citalopram Oral Drops'

Tell your doctor or pharmacist if you are taking any of the following:

- Antipsychotics (drugs used to treat mental disorders) e.g. fluphenazine, quetiapine, risperidone or phenothiazines (a type of antipsychotic e.g. chlorpromazine)
- Antidepressants (pimozide, zotepine)
- Aspirin or non-steroidal anti-inflammatory drugs (NSAIDS) e.g. ibuprofen, ketoprofen
- Medicines which increases the level of serotonin (a brain neurotransmitter) e.g. tramadol (a painkiller) or sumatriptan (for migraine)
- Medicine for manic depression (lithium)
- Tryptophan (a dietary supplement)
- Herbal remedy St John's Wort (Hypericum perforatum)

It is important that you consult your doctor or pharmacist if you are taking any other medicine as he/she may need to monitor you or adjust your dose. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Citalopram Oral Drops with food and drink

Citalopram Oral Drops may be taken with or without food.

Do not take alcohol while taking this medicine.

Pregnancy and breast-feeding

Do not breast-feed if you are taking this medicine.

Speak to your doctor before taking this medicine if you are pregnant or may be pregnant.

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

Driving and using machines

Do not drive or use any tools or machines if you feel that your abilities are affected. Medicines for the treatment of mental illnesses may decrease your ability to perform tasks requiring precision or close attention.

Important information about some of the ingredients of Citalopram 40mg/ml Oral Drops

This medicine contains methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per 20 drops.

❸ How to take Citalopram Oral Drops

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

To obtain the drops the vial should be held vertically as shown in the diagram.

- The drops should be added to a glass of either water, apple juice or orange juice, which is taken as a single drink
- Count the required number of drops into the drink and then stir briefly
- All the drink should be drunk immediately following mixing
- You may take your medicine in the morning or the evening, with or without food
- You may need to take Citalopram Oral Drops for more than 6 months to treat depression or for more than 3 months to treat panic attacks

It is very important that you follow your doctor's instructions as to the dosage of Citalopram Oral Drops and for how long you should continue to take them. You may not start feeling better straight away but you should keep taking them for as long as your doctor tells you.

Adults

Treating Depression

The normal starting dose is 16mg (8 drops) once daily, in the morning or evening. This may be increased up to maximum of 48mg (24 drops) once daily.

Treating Panic Attacks

The usual starting dose is 8mg (4 drops) once daily, which may increase to 16mg (8 drops) after the first week. This may be increased up to a maximum of 48mg (24 drops) once daily.

Elderly

The usual dose is 16mg (8 drops) once daily dose, and may be increased to 32mg (16 drops) per day.

Children

Citalopram is not recommended for use in children.

Reduced liver function

Your doctor may choose to keep you on one of the lower doses.

Reduced kidney function

The usual adult doses may be used.

Citalopram is also available in tablet form. Citalopram Oral Drops are absorbed into the body differently to Citalopram Tablets. Therefore if you have taken Citalopram Tablets before you will not require exactly the same dose when you are taking the liquid form to get the same effect. The tablet dosage corresponds to the number of drops as follows:

Tablets	Drops
10mg	8mg (4 drops)
20mg	16mg (8 drops)
30mg	24mg (12 drops)
40mg	32mg (16 drops)
60mg	48mg (24 drops)

Depending on your dose this bottle will last you between 12 and 75 days.

If you take more medicine than you should

If you have taken too large a dose of this medicine, contact your doctor or hospital immediately. Symptoms of overdose may include feeling or being sick, sweating, drowsiness, high fever or heat stroke, coma, fits, faster heart beat and abnormal muscle tone.

If you forget to take your medicine

If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, miss the forgotten dose altogether and continue with the rest of the medication as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking Citalopram Oral Drops

Even when you start to feel better it is important for you to keep on taking your medicine for as long as your doctor tells you. Never change the dose of your medicine without talking to your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, this product can cause side effects, although not everybody gets them.

If you experience any of the following side effects, stop taking your medicine and either tell your doctor immediately or go to your nearest hospital. You may be experiencing an allergic reaction to the oral drops:

- Swelling of the hands, feet, ankles, face, lips, mouth or throat
- Problems with swallowing or breathing

Tell your doctor immediately if you experience:

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

You may experience some of the following side effects. Speak to your doctor or pharmacist if you are concerned about any of these side effects:

Frequent side effects
(more than 5 in 100 but less than 20 in 100 patients):

- Feeling sick
- Dry mouth
- Constipation
- Diarrhoea
- Sleepiness
- Sleeplessness
- Agitation
- Nervousness
- Fast heart rate
- Increased sweating
- Headache
- Tremor (shaking)
- Dizziness
- Changes to the size of your pupils
- General weakness

Less frequent side effects
(more than 1 in 100 but less than 5 in 100 patients):

- Skin rashes
- Itching
- Tingling of the skin
- Migraines
- Blocked nose
- Severe tiredness
- Anxiety
- Confusion
- Yawning
- Lack of interest
- Taste disturbances
- Increase or decrease in appetite
- Increase or decrease in weight
- Indigestion
- Being sick
- Stomach ache
- Wind
- Increased saliva production
- Abnormal heart rate
- Abnormal vision
- Dizziness or light-headedness when standing up or getting out of bed
- Sleep disturbances
- Inability to concentrate
- Strange dreams
- Forgetfulness
- Impotence
- Decreased sex drive
- Failure to ejaculate in men
- Inability to reach orgasm in females
- Difficulty in passing urine or increased need to pass urine

Rare side effects
(less than 1 in 100 patients):

- Pain in the muscles
- Movement disturbances
- Fits
- Ringing in the ears
- Coughing
- Generally feeling unwell

- Extreme happiness (euphoria)
- Increased sex drive

Other side effects which have been reported include:

- Low sodium levels in the blood
- Gastro-intestinal bleeding
- Swelling of the skin
- Blueblack spots on the skin
- Sensitivity to sunlight
- Allergic reactions
- Hallucinations
- Mania
- Panic attacks
- Feelings of detachment
- Serotonin syndrome (fever, stiffness, muscle spasms, difficulty carrying out normal tasks, rapid changes in breathing and heart rate, changes in mental status including confusion, irritability and extreme agitation which may lead to delirium and coma)
- Variation in number of certain types of blood cells
- Abnormal liver function test results
- Joint pain
- Involuntary production of milk

Withdrawal symptoms

When you stop taking this medication you may experience withdrawal symptoms. This is most likely if you stop taking your medicine suddenly. Withdrawal symptoms include dizziness, tingling of the skin, headache, anxiety and feeling sick.

You should not stop taking your oral drops abruptly, and should discuss stopping taking this medication with your doctor.

If you suffer from any of the side effects listed above and they are severe or prolonged or if you experience any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist immediately.

5 How to store Citalopram Oral Drops

Keep out of the reach and sight of children. Once the drops have been opened they should not be stored above 25°C and any remaining solution should be discarded after 16 weeks.

Do not use Citalopram Oral Drops after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

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

6 Further information

What Citalopram Oral Drops contain

The active ingredient is citalopram. One ml contains 40mg of the active ingredient

The other ingredients are methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), hydroxyethyl cellulose, ethanol 96%v/v and purified water.

What Citalopram Oral Drops look like and the contents of the pack

It is a clear liquid.

Citalopram Oral Drops comes in packs of 15ml.
The vial contains 300 drops.

Marketing Authorisation Holder

TechnoPharm Ltd
Fannin House, South County Business Park
Dublin 18, Ireland

Manufacturer

HELP S.A. Pharmaceuticals
Pedini, Ioannina, Greece

Distributor

PLIVA Pharma Ltd
Vision House, Bedford Road, Petersfield
Hampshire GU32 3QB,

United Kingdom

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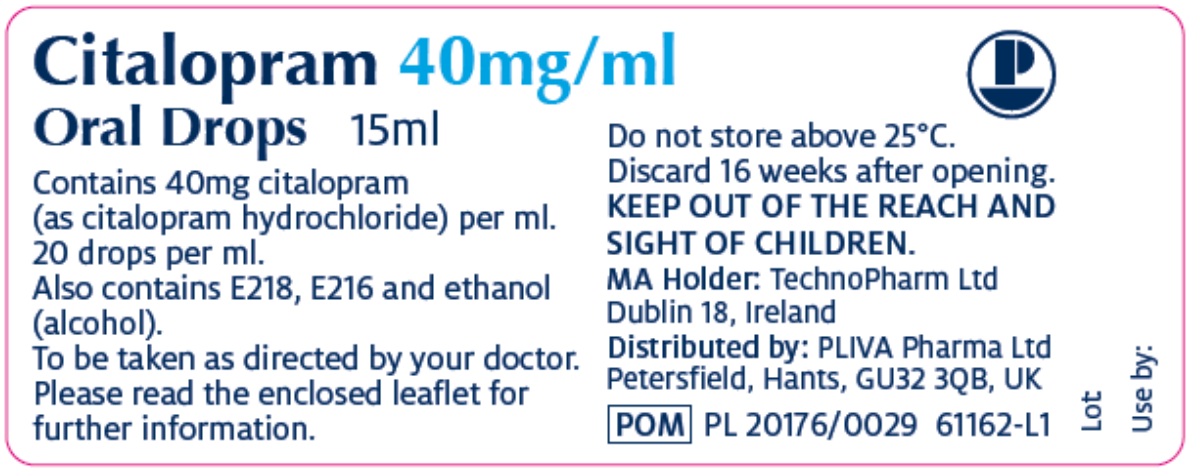
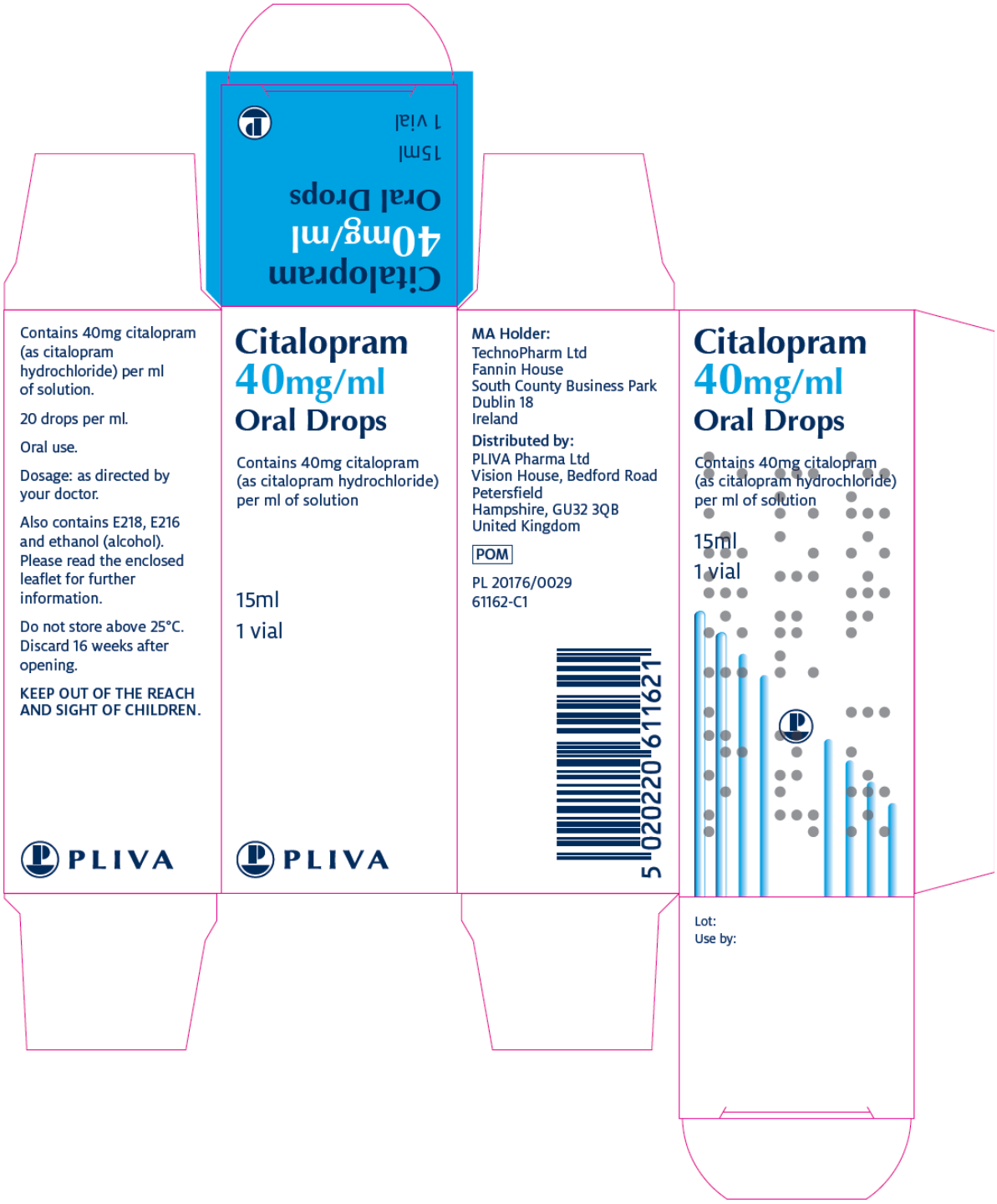
PLIVA

LABELLING

Label:



Carton:


Citalopram
40mg/ml
Oral Drops
15ml
1 vial
Contains 40mg citalopram (as citalopram hydrochloride) per ml of solution.
20 drops per ml.
Oral use.
Dosage: as directed by your doctor.
Also contains E218, E216 and ethanol (alcohol). Please read the enclosed leaflet for further information.
Do not store above 25°C. Discard 16 weeks after opening.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
PLIVA
Citalopram
40mg/ml
Oral Drops
Contains 40mg citalopram (as citalopram hydrochloride) per ml of solution
15ml
1 vial
PLIVA
MA Holder:
TechnoPharm Ltd
Fannin House
South County Business Park
Dublin 18
Ireland
Distributed by:
PLIVA Pharma Ltd
Vision House, Bedford Road
Petersfield
Hampshire, GU32 3QB
United Kingdom
POM
PL 20176/0029
61162-C1
5 020220 611621
Citalopram
40mg/ml
Oral Drops
Contains 40mg citalopram (as citalopram hydrochloride) per ml of solution
15ml
1 vial
Lot:
Use by: