IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/027/003
Case No: 2065994

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Cipralam 40 mg Film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/06/2009** until **09/03/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cipralam 40mg Film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40mg Citalopram as Citalopram hydrobromide

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, circular, coated, biconvex, scored on both sides with side scores.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

4.2 Posology and method of administration

Posology:
Treating Depression: Cipralam 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 given in the morning or evening.

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

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

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

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

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

Reduced hepatic function: Dosage should be restricted to the lower end of the dose range.

Reduced renal function: Dosage adjustment is not necessary in cases of mild or moderate renal impairment. No information is available in cases of severe renal impairment (creatinine clearance <20 mL / min).

Method of administration:
Cipralam tablets are administered as a single daily dose and can be taken any time of the day without regard to food intake.

4.3 Contraindications

Hypersensitivity to citalopram.

Sumatriptan's serotonergic effects are suspected to be enhanced by SSRIs. Until further evidence is available it is advised not to use citalopram simultaneously with 5-HT agonists e.g. sumatriptan.

4.4 Special warnings and precautions for use

As with other SSRIs, citalopram should not be given to patients receiving Monoamine Oxidase Inhibitors (MAOIs) or for 14 days after their discontinuation. MAOIs should not be introduced for seven days after discontinuation of citalopram. Rarely, the occurrence of 'serotonin syndrome' has been reported in patients receiving SSRIs. A combination of symptoms, possibly including agitation, tremor, myoclonus and hyperthermia, may indicate the development of this condition.

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.

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymosis, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucus bleeding with SSRIs (see Section 4.8 Undesirable Effects). Caution is advised in patients taking SSRIs, particularly in concomitant use with active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage as well as in patients with a history of bleeding disorders (see Section 4.5 Interactions).

Citalopram 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.

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

Other psychiatric conditions for which citalopram is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions

observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age:
Citalopram tablets should not be used in the treatment of children and adolescents under the age of 18 years, except for patients with OCD. 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 with 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.

Some patients with panic disorder experience an initial anxiogenic effect when starting pharmacotherapy. A low starting dose (see section 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 section 4.4, Special warnings and precautions for use).

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 (Tricyclic Antidepressants) and some SSRIs). Protein binding is relatively low (<80%). These properties give citalopram a low potential for clinically significant drug interactions.

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

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

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

No pharmacodynamic or pharmacokinetic interactions have been demonstrated between Citalopram and alcohol. However, the combination of Citalopram and alcohol is not advisable.

Caution is essential for patients who are being treated simultaneously with anticoagulants, medicines that affect the function of thrombocytes, such as NSAIDs, acetylsalicylic acid, dipyridamol, and ticlopidine or other medicines (e.g. atypical antipsychotics, Phenothiazines, tricylic antidepressants) that can increase risk of haemorrhage (see Section 4.4 Special warnings and precautions for use).

4.6 Pregnancy and lactation

Category B1.
Animal studies did not provide any evidence of teratogenic potential and citalopram does not affect reproduction or perinatal conditions. Citalopram appears in milk in very low concentrations.

Due to limited human data citalopram should only be used in pregnancy if considered necessary and under the close supervision of a physician. In nursing mothers, caution is recommended as it is not known whether citalopram excreted in milk may affect the infant.

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.

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.
Gastro-Intestinal 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%)
Musclo-skeletal system disorder: Myalgia.
Central and Peripheral nervous system disorders: Extrapyramidal disorder, convulsions.
Hearing and vestibular disorders: Tinnitus.
Psychiatric disorders: Euphoria, libido increased, Hallucinations.
Respiratory system disorders: Coughing.
Body as a whole: Malaise.
Skin Disorders: Angioedema

Hyponatraemia, sometimes associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of SSRIs and other antidepressants.

Treatment with SSRIs has occasionally been associated with symptoms suggestive of postural hypotension, hypotension, hypertension and tachycardia. There have also been rare reports of supraventricular and ventricular arrhythmias. To date causality has not been established.

Side effect in Discontinuation: 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.

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

Haemorrhage (for example, gynaecological haemorrhage, gastrointestinal haemorrhage, ecchymosis and other forms of skin haemorrhage or bleeding in the mucus membranes) can occur on rare occasions.

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, and 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: N06A B04

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-HT_2, DA D_1 and D_2 receptors, α_1-, α_2-, ß-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests in isolated organs as well as functional in vivo tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side-effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

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

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

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

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

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

5.2 Pharmacokinetic properties

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

Distribution
The apparent volume of distribution $(V_d)_ß$ 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 ($T_{½ß}$) 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 <20mL/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

Mannitol
Cellulose, microcrystalline
Silica, colloidal anhydrous
Magnesium stearate

Film Coat

Hypromellose
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

PVC/PVDC/Al Strip or HDPE Tablet Container with LDPE Cap
Pack sizes: 7, 14, 21, 28, 30, 50, 56, 60, 84, 98, 100 or 500 tablets

Not all pack size may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/27/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 10 March 2006

10 DATE OF REVISION OF THE TEXT

April 2009