APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Cipralex 5 mg Tablets
Cipralex 10 mg Tablets
Cipralex 15 mg Tablets
Cipralex 20 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains escitalopram oxalate corresponding to 5 mg escitalopram, 10 mg escitalopram, 15 mg escitalopram or 20 mg escitalopram.
Sugar free
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cipralex 5 mg Round, white, film-coated tablets, marked “EK” on one side.
Cipralex 10 mg Oval, white, scored, film-coated tablets, marked “EL” on one side.
Cipralex 15 mg Oval, white, scored, film-coated tablets, marked “EM” on one side.
Cipralex 20 mg Oval, white, scored, film-coated tablets, marked “EN” on one side.

The 10, 15 and 20 mg tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.
Treatment of panic disorder with or without agoraphobia.
Treatment of social anxiety disorder (social phobia).
Treatment of generalised anxiety disorder.
Treatment of obsessive-compulsive disorder.

4.2 Posology and method of administration

Posology

Adults

Major depressive episodes:

Cipralex should be administered as a single oral dose of 10 mg daily in otherwise healthy adults. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.
Usually 2- 4 weeks are necessary for an antidepressant response.

Panic disorder with or without agoraphobia:

A single oral dose of 5 mg is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response.
Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

Social anxiety disorder:
Usual dosage is 10 mg once daily. The dose may be increased to a maximum of 20 mg daily depending on individual patient response.
Usually 2- 4 weeks are necessary to obtain symptom relief. Treatment for 3 months is recommended to consolidate response. Long-term treatment of responders for 6 months has been shown to prevent relapse and can be considered on an individual basis. Treatment benefits should be re-evaluated at regular intervals.

Generalised anxiety disorder:
Recommended dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.
Long term treatment of responders has been studied for at least 6 months and can be considered on an individual basis to prevent relapse.

Obsessive-compulsive disorder:
Usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to 20 mg daily.
Long-term treatment of patients responding to a 16-week open treatment phase has been studied for at least 24 weeks in patients receiving 10 or 20 mg/day.
As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Elderly patients (> 65 years of age)
A longer half-life and a decreased clearance have been demonstrated in the elderly, therefore a lower initial and maximum dose should be considered.

Children and adolescents (< 18 years)
Safety and efficacy have not been investigated in this population (see section 4.3).

Reduced renal function
Dosage adjustment is not necessary in patients with mild or moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min).

Reduced hepatic function
Dosages should be halved to the lower end of the dose range in patients with hepatic insufficiency.

Withdrawal reactions

When stopping treatment with Cipralex the dose should be gradually reduced over a period of one or two weeks in order to avoid possible withdrawal reactions (see section 4.4).

Method of administration
Cipralex is administered as a single daily dose. Cipralex may be taken without regard to food intake.

4.3 Contraindications
Hypersensitivity to escitalopram, the active ingredient of Cipralex, or to any of the excipients as listed in section 6.1.
Children and adolescents under the age of 18 years.

Monoamine Oxidase Inhibitors - Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on an MAOI (see section 4.5). Some cases presented with features resembling serotonin syndrome (see section 4.8).
Cipralex should not be used in combination with an MAOI.
Cipralex may be started 14 days after discontinuing treatment with an MAOI. At least 7 days should elapse after discontinuing Cipralex treatment before starting an MAOI.
Concomitant treatment with linezolid.
Concomitant treatment with pimozide as the combination may lead to clinically significant QT_C prolongation.
Cipralex is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.

4.4 Special warnings and precautions for use
Safety and efficacy in children and adolescents under the age of 18 years have not been established (see section 4.3).
Cipralex should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt, suicidal thoughts as well as suicidal ideation and self-harm), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants including SSRIs such as Cipralex.

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

Paradoxical anxiety - Some patients with panic disorder may experience increased anxiety symptoms at the start of treatment with antidepressants including Cipralex. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Seizures - Cipralex should be discontinued if a patient develops seizures for the first time, or if there is an increase in seizure frequency (in patients with a previous diagnosis of epilepsy). Cipralex should be avoided in patients with unstable epilepsy and patients with controlled

epilepsy should be carefully monitored.

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

Suicide/thoughts or clinical worsening - Patients with depression, may experience worsening of their depression and or the emergence of suicidal thoughts, ideation, self-harm and suicide (suicide-related events) whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. As improvement may not occur during the first weeks or more of treatment, patients being treated with Cipralex 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 Cipralex 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 medicines 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 Cipralex 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.

The following symptoms have been reported in patients being treated with antidepressants such as Cipralex for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing Cipralex, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision is made to discontinue treatment, Cipralex should be tapered (see section 4.2 and section 4.4).

Akathisia/psychomotor restlessness - The use of SSRIs/SNRIs has been associated with the development of 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 Cipralex.

Hyponatraemia - Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as the elderly, or patients with cirrhosis or if Cipralex is used in combination with other medications which may cause hyponatraemia.

Haemorrhage - There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with Cipralex. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Caution is advised in patients taking Cipralex, particularly in concomitant use with medicines known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory medicines (NSAIDs), as well as in patients with a history of bleeding disorders.

ECT (electroconvulsive therapy) – There is limited published clinical experience of concurrent administration of Cipralex and ECT, therefore caution is advisable.

Monoamine oxidase inhibitor (MAOI) – Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on a MAOI. In some cases the patient developed serotonin syndrome (see section 4.8). Cipralex should not be used in combination with a MAOI (see section 4.3). Cipralex may be started 14 days after discontinuing treatment with an MAOI. At least 7 days should elapse after discontinuing Cipralex treatment before starting a MAOI.
The combination of escitalopram with MAO-A inhibitors is contraindicated.

Serotonin syndrome - Caution is advisable if Cipralex is used concomitantly with medicinal products with serotonergic effects such as triptans (including sumatriptan), opioids (including tramadol), and tryptophan.
Serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the Cipralex and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

St. John´s Wort - Concomitant use of SSRIs such as Cipralex and herbal remedies containing St. John´s Wort (Hypericum perforatum) may result in an increased incidence of adverse reactions.

Discontinuation symptoms seen when stopping treatment
Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (see section 4.8).

The risk of discontinuation 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 and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances 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 Cipralex should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see section 4.2).

Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Coronary heart disease
Due to limited clinical experience, caution is advised in patients with coronary heart disease.

QT Prolongation - In a double –blind, placebo-controlled ECG study in healthy subjects, there was a dose related QTc prolongation: the change from baseline in QTc (Fridericia-correction) was 4.3 msec at the 10 mg/day dose and 10.7 msec at the 30 mg/day dose.
Escitalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8 and 4.9).

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant dysrhythmias and should be corrected before treatment with escitalopram is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.
If signs of cardiac arrhythmia occur during treatment with escitalopram, the treatment should be withdrawn and an ECG should be performed.

Angle-Closure Glaucoma
SSRIs including escitalopram may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular

pressure and angle-closure glaucoma, especially in patients pre-disposed. Cipralex should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

4.5 Interaction with other medicines and other forms of interactions

Escitalopram, the active ingredient of Cipralex, has a low potential for clinically significant medicine interactions. In vitro studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2 C19, 3A4 and 2D6). Escitalopram is a very weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A, and weak inhibitor of 2D6.

Effects of other medicinal products on Cipralex in vivo

The pharmacokinetics of single doses of Cipralex was not changed by co-administration with a single dose of ritonavir (CYP3A4 inhibitor). Furthermore, co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of racemic citalopram. Co-administration of racemic citalopram with cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) resulted in increased plasma concentrations of the racemate (43 % increase in AUC, 39 % increase in Cmax). Thus, caution should be exercised at the upper end of the dose range of Cipralex when used concomitantly with high doses of cimetidine.

Monoamine Oxidase (MAO) Inhibitors

Co-administration with MAO inhibitors may cause serotonin syndrome (see section 4.3 and section 4.4).

Co-administration with other serotonergic medicines e.g. opioids (including tramadol), and triptans (including sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome.
There have been reports of enhanced effects when Cipralex has been given with lithium or tryptophan and therefore concomitant use of Cipralex with these medicines should be undertaken with caution.

Effects of Cipralex on other medicinal products in vivo

Co-administration with a single dose of desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when Cipralex and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Co-administration with a single dose of metoprolol 100 mg (a CYP2D6 substrate) resulted in a twofold increase in the C_{max} and a 52 % increase of the AUC of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.
The pharmacokinetics of ritonavir (CYP3A4 inhibitor) was not changed by co-administration with Cipralex.

Selegiline

The combination with selegiline (irreversible MAO-B inhibitor), is contraindicated due to the risk

of developing serotonin syndrome. Racemic citalopram increased the AUC of selegiline by 29 %.

Pimozide
Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide. The co-administration of pimozide and citalopram resulted in a mean increase in the QT_C interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Furthermore, pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate) (single dose), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin. However, prothrombin time was slightly increased after a single dose of 25 mg warfarin. The International Normalised Ratio (INR) needs to be carefully monitored in patients on the combination of warfarin and Cipralex.

When using Cipralex with the following medicines, caution should be exercised:

- ***Medicinal products lowering the seizure threshold***
  SSRIs such as Cipralex can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs) neuroleptics (phenothiazines, thioxanthenes, butyrophenones) mefloquine, bupropion, and tramadol).
- Flecainide, propafenone, metoprolol, desipramine, clomipramine, nortriptyline, risperidone, thioridazine, and haloperidol. The dosage of Cipralex may need to be adjusted.
- St John's wort: Concomitant use of SSRIs and herbal remedies containing St. John's Wort (*Hypericum perforatum)* may result in an increased incidence of adverse reactions (see section 4.4)
- Concomitant use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) may increase bleeding tendency (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Cipralex should not be used during pregnancy.
Limited clinical data are available regarding exposure to Cipralex during pregnancy.
In reproductive toxicity studies performed in rats, embryo-fetotoxic effects (reduced foetal weight and minor delay in ossification) were observed with exposure to escitalopram, the active ingredient of Cipralex, but there was no effect on foetal viability and no increased incidence of malformations.
If Cipralex is used until or shortly before birth, discontinuation effects in the newborn are possible.
Using Cipralex in the third trimester may result in effects, including neurobehavioral disturbances, in the newborn infant.
The following symptoms may occur in the newborn after maternal SSRI/SNRI use such as

Cipralex in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In a majority of instances, such complications begin immediately or soon (<24 hours) after delivery.
Epidemiological data have suggested that the use of SSRIs such as Cipralex in pregnancy, particularly in late pregnancy may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).
Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Lactation
Escitalopram is excreted in breastmilk and breastfeeding is not recommended during the treatment.

Fertility
Animal data have shown that some SSRIs may affect sperm quality.
Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.
Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines
Cipralex does not impair intellectual function or psychomotor performance. Nevertheless, patients who are depressed and require treatment may have an impaired ability to drive or operate machinery. They should be warned of the possibility and advised to avoid such tasks if so affected.

4.8 Undesirable effects
Adverse reactions observed with Cipralex are most frequent during the first one or two weeks of treatment and may decrease in intensity and frequency with continued treatment.
Adverse reactions known for SSRIs and also reported for Cipralex in either placebo-controlled clinical studies or as spontaneous post-marketing events are listed below by system organ class and frequency.
Frequencies are taken from clinical studies; they are not placebo-corrected. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to ≤1/100), rare (≥1/10000 to ≤1/1000), very rare (≤1/10000), or not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Rare	Angiodema, anaphylactic reaction
Endocrine disorders	Not known	Inappropriate ADH secretion[1], Hyperprolactineamia[3]
Metabolism and nutrition	Common	Decreased appetite, increased

disorders		appetite, weight increased
	Uncommon	Weight decreased
	Not known	Hyponatraemia, anorexia
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams Female and male: libido decreased female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalisation, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour [1]
Nervous system disorders	Common	Insomnia, somnolence, dizziness, paraesthesia, tremor
	Uncommon	Taste disturbance, sleep disorder, syncope
	Rare	Serotonin syndrome
	Not known	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged
Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, constipation, vomiting, dry mouth
	Uncommon	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepatobiliary disorders	Not known	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Sweating increased
	Uncommon	Urticaria, alopecia, rash, pruritus
	Not known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia
Renal and urinary disorders	Not known	Urinary retention

Reproductive system and breast disorders	Common	Male: ejaculation disorder, impotence
	Uncommon	Female: metrorrhagia, menorrhagia
	Not known	Galactorrhoea, Female: postpartum haemorrhage[2] Male: priapism
General disorders and administrative site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

[1]Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4).
[2]This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).
[3]This event has been reported for the therapeutic class of SSRIs/SNRIs.
Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease.
QT-prolongation may lead to ventricular dysrhythmia and torsade de pointes.
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs. The mechanism leading to this risk is unknown.

The following symptoms, hostility, suicidal ideation and self-harm, have been reported in children being treated with antidepressants.
After prolonged administration abrupt cessation of Cipralex may produce withdrawal reactions in some patients.

Discontinuation symptoms seen when stopping treatment
Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances 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 Cipralex treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose
Symptoms and signs as described in the side effects section may occur.
Treatment
There is no specific antidote. Treatment is supportive and symptomatic. The use of activated

charcoal should be considered. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.
ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradydysrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 1.2 Psychoanaleptics (antidepressants)
Biochemical and behavioural studies have shown that escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake.
Escitalopram has minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.
Escitalopram 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-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors.
Escitalopram has high affinity for the primary binding site, and an allosteric modulating effect on the serotonin transporter.
Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.

5.2 Pharmacokinetic properties

Absorption

Absorption is independent of food intake (mean T_{max} is 4 hours after multiple dosing).

Distribution

The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 L/kg. The plasma protein binding of escitalopram is approximately 55 %.

Biotransformation

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31 % and <5 % of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Elimination

The elimination half-life ($t_{½\,\beta}$) after multiple dosing is about 30 hours and the plasma clearance ($Cl_{oral)}$ is about 0.6 L/min. Escitalopram and major metabolites are - like racemic citalopram - assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. Hepatic clearance is mainly by the P450 enzyme system. CYP2C19 is the primary isoenzyme involved in the demethylation of escitalopram, followed by CYP3A4 and CYP2D6.

There is linear pharmacokinetics. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Elderly patients (> 65 years of age)

A longer half-life (about 50%) and decreased clearance values, due to a reduced rate of metabolism, have been demonstrated in the elderly.

Reduced hepatic function

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

Reduced renal function

Escitalopram is eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 30 mL/min).

Polymorphism

Based on in vitro results with escitalopram and in vivo results with the racemic citalopram, genetic polymorphism with respect to CYP2D6 is not known, with respect to CYP2C19, it may be of clinical relevance, as shown in limited numbers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients are microcrystalline cellulose, silicified, talc, croscarmellose sodium, magnesium stearate.
Coating: hypromellose, macrogol 400
Colour: titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30°C.
Keep out of reach of children.

6.5 Nature and contents of container

PVC / Aluminium blister packs containing 28 tablets.

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

H. Lundbeck (Pty) Ltd

Office A1002, 1st Floor, Knightsbridge,
33 Sloane Street,
Bryanston, 2190
South Africa

8 REGISTRATION NUMBERS

Cipralex 5 mg: 36/1.2/0318
Cipralex 10 mg: 36/1.2/0319
Cipralex 15 mg: 36/1.2/0320
Cipralex 20 mg: 36/1.2/0321

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 March 2004

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13 August 2024