SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

Cipralex 5 mg Tablets

Cipralex 10 mg Tablets

Cipralex 15 mg Tablets

Cipralex 20 mg Tablets

COMPOSITION:

Each tablet contains escitalopram oxalate corresponding to 5 mg escitalopram, 10 mg escitalopram, 15 mg escitalopram or 20 mg escitalopram.

The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, talc, croscarmellose sodium, magnesium stearate

Coating: hypromellose, macrogol 400

Colour: titanium dioxide (E 171)

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

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 H_1, 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.

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.

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.

CONTRA-INDICATIONS:

Hypersensitivity to escitalopram, the active ingredient of Cipralex, or to any of the excipients.

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 Interactions**). Some cases presented with features resembling serotonin syndrome (see Side-Effects and Special Precautions: Class reactions).

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.

WARNINGS AND SPECIAL PRECAUTIONS:

Safety and efficacy in children and adolescents under the age of 18 years have not been established (see Contraindications).

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 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.

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 Precautions and Dosage and directions for use).

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. 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 Side-Effects and Special Precautions). Cipralex should not be used in combination with a MAOI (see Contra-indications). 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 sumatriptan or other triptans, 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.

Withdrawal reactions - When stopping therapy with Cipralex, the dose should be gradually reduced over a period of one or two weeks in order to avoid possible withdrawal reactions (see Dosage and directions for use).

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.

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.

INTERACTIONS:

Escitalopram, the active ingredient of Cipralex, has a low potential for clinically significant medicine interactions. I*n vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways (cytochrome P450 (CYP) 2C19, 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 C_{max}). 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 e MAO inhibitors may cause serotonin syndrome (see Contraindications and Warnings).

Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan and other triptans) 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 QTc 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.
- Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding tendency (see Warnings).

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).

Lactation

Escitalopram is excreted in breastmilk and breast-feeding is not recommended during the treatment.

DOSAGE AND DIRECTIONS FOR USE:

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 Contraindications).

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 Warnings – Withdrawal reactions).

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

SIDE 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 di orders	Not known	Thrombocytopenia
Immune system disorders	Rare	Angiodema, anaphylactic reaction
Endocrine disorders	Not known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Decreased appetite, increased 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	No 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 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 Warnings).

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.

After prolonged administration abrupt cessation of Cipralex may produce withdrawal reactions in some patients.

The following symptoms, hostility, suicidal ideation and self-harm, have been reported in children being treated with antidepressants.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms and signs as described in the side effects section may occur.

Treatment

There is no specific antidote. Treatment is supportive and symptomatic. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

IDENTIFICATION:

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.

PRESENTATION:

PVC / Aluminium blister packs containing 28 tablets.

STORAGE INSTRUCTIONS:

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

REGISTRATION NUMBER:

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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