

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal Product

ECINIL-20 Tablet

2. Quality and Quantitative Composition

Each film coated tablet contains

Escitalopram Oxalate USP

Equivalent to Escitalopram 20mg

Colours: Lake of Quinoline Yellow & Titanium Dioxide BP

3. Pharmaceutical form

Film-Coated Tablets

Yellow coloured, elongated, biconvex, scored on one side & plain on other side film coated tablets.

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

The safety of daily doses above 20 mg has not been demonstrated.

Major depressive episodes

Usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Usually, 2-4 weeks are necessary to obtain antidepressant response. After the symptoms resolve, treatment for at least 6 months is required for consolidation of the response.

Panic disorder with or without agoraphobia

An initial 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. Usually, 2-4 weeks are necessary to obtain symptom relief. The dose may subsequently, depending on individual patient response, be

decreased to 5 mg or increased to a maximum of 20 mg daily.

Social anxiety disorder is a disease with a chronic course, and treatment for 12 weeks is recommended to consolidate response. Long-term treatment of responders has been studied for 6 months and can be considered on an individual basis to prevent relapse; treatment benefits should be re-evaluated at regular intervals.

Social anxiety disorder is a well-defined diagnostic terminology of a specific disorder, which should not be confounded with excessive shyness. Pharmacotherapy is only indicated if the disorder interferes significantly with professional and social activities.

The place of this treatment compared to cognitive behavioural therapy has not been assessed. Pharmacotherapy is part of an overall therapeutic strategy.

Generalised anxiety disorder

Initial dosage is 10 mg once daily. Depending on the 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 in patients receiving 20 mg daily. Treatment benefits and dose should be re-evaluated at regular intervals.

Obsessive-compulsive disorder (OCD)

Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily.

As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free.

Treatment benefits and dose should be re-evaluated at regular intervals.

Elderly patients (> 65 years of age)

Initial dosage is 5 mg once daily. Depending on individual patient response the dose may be increased to 10 mg daily.

The efficacy of escitalopram in social anxiety disorder has not been studied in elderly patients.

Paediatric Population

Escitalopram film-coated tablets should not be used in the treatment of children and adolescents under the age of 18 years.

Reduced renal function

Dosage adjustment is not necessary in patients with mild or moderate renal impairment. Caution is advised in patients with severely reduced renal function (CL_{CR} less than 30 ml/min.)

Reduced hepatic function

An initial dose of 5 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to 10 mg daily. Caution and extra careful dose

titration is advised in patients with severely reduced hepatic function.

Poor metabolisers of CYP2C19

For patients who are known to be poor metabolisers with respect to CYP2C19, an initial dose of 5 mg daily during the first two weeks of treatment is recommended. Depending on individual patient response, the dose may be increased to 10 mg daily.

Discontinuation symptoms seen when stopping treatment

Abrupt discontinuation should be avoided. When stopping treatment with escitalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of discontinuation symptoms. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

Escitalopram is administered as a single daily dose and may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc.

The combination of escitalopram with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome.

Escitalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.

Escitalopram is contraindicated together with medicinal products that are known to prolong the QT- interval.

4.4 Special warnings and precautions for use

The following special warnings and precautions apply to the therapeutic class of SSRIs (Selective Serotonin Re-uptake Inhibitors).

Paediatric Population

Escitalopram should not be used in the treatment of paediatric population. 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 paediatric population concerning growth, maturation and cognitive and behavioural development are lacking.

Paradoxical anxiety

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

Seizures

Escitalopram 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). SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be closely monitored.

Mania

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

Diabetes

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

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 escitalopram 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.

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.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely 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 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 SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

SSRIs/SNRIs may increase the risk of postpartum haemorrhage.

ECT (electroconvulsive therapy)

There is limited clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

Serotonin syndrome

Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan.

In rare cases, 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 SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

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.

Discontinuation symptoms seen when stopping treatment

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt. In clinical trials adverse events seen on treatment

discontinuation occurred in approximately 25% of patients treated with escitalopram and 15% of patients taking placebo.

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 escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Coronary heart disease

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

QT interval prolongation

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, in patients with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases.

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 arrhythmias 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. Escitalopram should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

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.

4.5 Interaction with other FPPs and other forms of interaction Pharmacodynamic interactions

Contra-indicated combinations:

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients receiving a SSRI in combination with a non-selective, irreversible monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment. In some cases, the patient developed serotonin syndrome.

Escitalopram is contra-indicated in combination with non-selective, irreversible MAOIs. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective, irreversible MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO-A inhibitor such as moclobemide is contraindicated. If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.

Reversible, non-selective MAO-inhibitor (linezolid)

The antibiotic linezolid is a reversible non-selective MAO-inhibitor and should not be given to patients treated with escitalopram. If the combination proves necessary, it should be given with minimum dosages and under close clinical monitoring.

Irreversible, selective MAO-B inhibitor (selegiline)

In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome. Selegiline doses up to 10 mg/day have been safely co-administered with racemic citalopram.

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of escitalopram and these medicinal products cannot be excluded. Therefore, co-administration of escitalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarian treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine), is contraindicated.

Combinations requiring precautions for use:

Serotonergic medicinal products

Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan and other triptans) may lead to serotonin syndrome.

Medicinal products lowering the seizure threshold

SSRIs 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 and butyrophenones), mefloquine, bupropion and tramadol).

Lithium, tryptophan

There have been reports of enhanced effects when SSRIs have been given together with lithium or tryptophan, therefore concomitant use of SSRIs with these medicinal products should be undertaken with caution.

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.

Haemorrhage

Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency.

Alcohol

No pharmacodynamic or pharmacokinetic interactions are expected between escitalopram and alcohol. However, as with other psychotropic medicinal products, the combination with alcohol is not advisable.

Medicinal products inducing hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of hypokalaemia/hypomagnesaemia inducing medicinal products as these conditions increase the risk of malignant arrhythmias.

Pharmacokinetic interactions

Influence of other medicinal products on the pharmacokinetics of escitalopram.

The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram.

Co-administration of escitalopram with cimetidine 400 mg twice daily (moderately

potent general enzyme-inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram. Caution is advised when administering escitalopram in combination with cimetidine. Dose adjustment may be warranted.

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment.

Effect of escitalopram on the pharmacokinetics of other medicinal products

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Co-administration with desipramine or metoprolol resulted in both cases in a twofold increase in the plasma levels of these two CYP2D6 substrates.

In vitro studies have demonstrated that escitalopram may also cause weak inhibition of CYP2C19. Caution is recommended with concomitant use of medicinal products that are metabolised by CYP2C19.

4.6 Pregnancy and lactation

Pregnancy

For escitalopram only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity. Escitalopram film-coated tablets should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

Neonates should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonate after maternal SSRI/SNRI use 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 serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery. Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

Breast-feeding

It is expected that escitalopram will be excreted into human milk.

Consequently, breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

Although escitalopram has been shown not to affect intellectual function or psychomotor performance, any psychoactive medicinal product may impair judgement or skills. Patients should be cautioned about the potential risk of an influence on their ability to drive a car and operate machinery.

4.8 Undesirable effects

Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment.

Tabulated list of adverse reactions

Adverse reactions known for SSRIs and also reported for escitalopram 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 ($\geq 1/10$), $\geq$ common ($1/100$ to $\geq <1/10$), uncommon ($\geq 1/1,000$ to $\geq <1/100$), rare ($1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), or Frequency not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders					Thrombocytopenia
Immune system disorders				Anaphylactic reaction	
Endocrine disorders					Inappropriate ADH secretion
Metabolism and nutrition disorders		Decreased appetite, increased appetite			Hyponatraemia, anorexia ¹
Psychiatric disorders		Anxiety, restlessness, abnormal dreams Female and male: libido decreased	Bruxism, agitation, nervousness, panic attack, confusional state	Aggression, depersonalisation, hallucination	Mania, suicidal ideation, suicidal behaviour ²

		Female: anorgasmia			
Nervous system disorders	Headache	Insomnia, somnolence, dizziness, paraesthesia, tremor	Taste disturbance, sleep disorder, syncope	Serotonin syndrome	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/a kathisia ¹
Eye disorders			Mydriasis, visual disturbance		
Ear and labyrinth disorders			Tinnitus		
Cardiac disorders			Tachycardia	Bradycardia	Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes
Vascular disorders					Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Sinusitis, yawning	Epistaxis		
Gastrointestinal disorders	Nausea	Diarrhoea, constipation, vomiting, dry mouth	Gastrointestinal haemorrhages (including rectal haemorrhage)		
Hepatobiliary disorders					Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders		Sweating increased	Urticaria, alopecia, rash, pruritus		Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia			
Renal and urinary disorders					Urinary retention

Reproductive system and breast disorders		Male: ejaculation disorder, impotence	Female: metrorrhagia, menorrhagia		Galactorrhoea, postpartum haemorrhage * Male: priapism
General disorders and administration site conditions		Fatigue, pyrexia	Oedema		
Investigations		Weight increased	Weight decreased		

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Toxicity

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Fatal cases of escitalopram overdose have rarely been reported with escitalopram alone; the majority of cases have involved overdose with concomitant medications. Doses between 400 and 800mg of escitalopram alone have been taken without any severe symptoms.

Symptoms

Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor, and agitation to rare cases of serotonin syndrome, convulsion, and coma), the gastrointestinal system (nausea/vomiting), and the cardiovascular system (hypotension, tachycardia, QT interval prolongation, and arrhythmia) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia).

Management

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. 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.

ECG monitoring is advised in case of overdose, in patients with congestive heart failure/bradyarrhythmias, 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

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

ATC code: N06AB10

Mechanism of action

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity.

Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT₂, DA D₁ and D₂ receptors, α_1 -, α_2 -, β -adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors.

The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

5.2 Pharmacokinetic

Properties Absorption

Absorption is almost complete and independent of food intake. (Mean time to maximum concentration (mean T_{max}) is 4 hours after multiple dosing). As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%.

Distribution

The apparent volume of distribution (V_{d,β}/F) after oral administration is about 12 to 26 L/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites.

Biotransformation

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N- oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.

Elimination

The elimination half-life (t_{1/2 β}) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min. The major metabolites have a significantly longer half-life. Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

5.3 Preclinical Safety Data

No complete conventional battery of preclinical studies was performed with escitalopram since the bridging toxicokinetic and toxicological studies conducted in rats with escitalopram and citalopram showed a similar profile. Therefore, all the citalopram information can be extrapolated to escitalopram.

In comparative toxicological studies in rats, escitalopram and citalopram caused cardiac toxicity, including congestive heart failure, after treatment for some weeks, when using dosages that caused general toxicity. The cardiotoxicity seemed to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at no-effect-level were in excess (8-fold) of those achieved in clinical use, while AUC for escitalopram was only 3- to 4-fold higher than the exposure achieved in clinical use. For citalopram AUC values for the S-enantiomer were 6- to 7-fold higher than exposure achieved in clinical use. The findings are probably related to an exaggerated influence on biogenic amines i.e. secondary to the primary pharmacological effects, resulting in hemodynamic effects (reduction in coronary flow) and ischaemia. However, the exact mechanism of cardiotoxicity in rats is not clear. Clinical experience with citalopram, and the clinical trial experience with escitalopram, does not indicate that these findings have a clinical correlate.

Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment cessation. Accumulation of phospholipids (phospholipidosis) in animals has been observed in connection with many cationic amphiphilic medicines. It is not known if this phenomenon has any significant relevance for man.

In the developmental toxicity study in the rat embryotoxic effects (reduced foetal weight and reversible delay of ossification) were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. A pre- and postnatal study showed reduced survival during the lactation period at exposures in terms of AUC in excess of the exposure achieved during clinical use. Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess of human exposure.

No animal data related to this aspect are available for escitalopram

6 Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch

Lactose monohydrate

Micro Crystalline Cellulose

Povidone (K-30)

Croscarmellose Sodium

Colloidal Anhydrous Silica

Purified Talc

Magnesium Stearate

Isopropyl alcohol
Hypromellose (15 CPS)
Polyethylene Glycol 6000
Methylene chloride
Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and Contents of Container

10 tablets packed in an Alu- Alu blister, further 3 blisters of each 10 tablets packed in a carton with product leaflet.

6.6 Special precautions for disposal

No special requirements

7. Marketing Authorization Holder

Psychotropics India Limited Plot No. 46 & 49, Sector 6A,
IIE, Siidcul, Haridwar-249403, (Uttarakhand) India.

8. Marketing Authorization Number (s)

H2022/CTD6742/3837ER

9. Date of First Authorization/Renewal of the Authorization

15/08/2022

10. Date of revision of text

15/08/2022