

Generic Name Etizolam 0.5mg + Escitalopram 10mg

Trade Name Suprabenz plus 10 mg



1. **NAME OF THE MEDICINAL PRODUCT:** Etizolam 0.5mg + Escitalopram 10mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

Each film coated tablet contains:

Etizolam JP.....0.5 mg

Escitalopram Oxalate IP 10 mg

3. **PHARMACEUTICAL FORM:** Tablet

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications:** Combination indicated for Co-morbid Anxiety and Depression

4.2 **Posology and Method of Administration:**

Combination can be given once or twice a day orally

4.3 **Contraindications**

Cases of serious reactions have been reported in patients receiving an SSRI. Escitalopram in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an SSRI and have been started on an MAOI. Escitalopram should not be used in combination with an MAOI. Escitalopram may be started 14 days after discontinuing treatment with an MAOI. At least 7 days should elapse after discontinuing Escitalopram treatment before starting an MAOI.

Disease conditions like myasthenia gravis, acute angle-closure glaucoma, severe respiratory failure or hepatic Impairment and in patients with hypersensitivity to benzodiazepine.

Suprabenz plus is contraindicated in pregnancy and breast feeding.

4.4 **Special Warnings and Special Precautions for Use**

Escitalopram

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

Use in children and adolescents under 18 years of age

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

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.

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, 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.

Etizolam

Caution should be exercised in patients with history of lung insufficiency, muscle weakness, impaired liver or kidney function, alcoholism or drug addiction, elderly, during pregnancy and breastfeeding.

Etizolam is contraindicated in patients with increased eye pressure, coma, sleep disorder, porphyria, severe lung disease and hypersensitivity.

It may cause dizziness or drowsiness, lack of attentiveness, concentration or ability of reflexive motion. Avoid driving a car or operating machinery requiring alertness.

Do not drink alcoholic beverage because it may cause this medicine to work excessively.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Pharmacodynamic interactions

Escitalopram

Contraindicated combinations:

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients receiving an 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 contraindicated 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-malarial 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), mefloquin, 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, 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.

Etizolam

Drug interactions have been reported with CNS depressants phenothiazines, barbiturates and alcohol; MAO inhibitors and Fluvoxamine maleate

4.6 Fertility, Pregnancy and Lactation

Escitalopram

Pregnancy

For escitalopram, only limited clinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity. Escitalopram 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, particularly 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.

Breast-feeding

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

Consequently, breast-feeding is not recommended during treatment.

Fertility

Animal data have shown that citalopram 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.

Etizolam

Pregnancy

Pregnancy Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Breast-feeding

It should most certainly not be used during pregnancy due to the risk of the drug passing into the breast milk. For similar reasons it should not be used during pregnancy or when attempting to become pregnant without medical supervision from a doctor.

4.7 Effects on Ability to Drive and Use Machines

Escitalopram

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.

Etizolam

Patient should avoid driving a car or operating machinery requiring alertness. Patient should not drink alcoholic beverage because it may cause this medicine to work excessively.

4.8 Undesirable Effects

Escitalopram

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), 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	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 ¹
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams libido decreased Female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalisation, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour ²
Nervous system disorders	Very common	Headache
	Common	Insomnia, somnolence, dizziness, paraesthesia, tremor
	Uncommon	Taste disturbance, sleep disorder, syncope
	Rare	Serotonin syndrome
	Not known	Dyskinesia, movement disorder, convulsion, psychomotor

System organ class	Frequency	Undesirable Effect
		restlessness/akathisia ¹
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes
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 Male: priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

¹ These events have been reported for the therapeutic class of SSRIs.

² Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation.

QT interval prolongation

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.

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

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 escitalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

Etizolam

Benzodiazepines such as Etizolam which are more rapidly eliminated from the body are less likely to accumulate, and there is evidence to suggest that Etizolam is less likely to induce tolerance and dependence compared with classical benzodiazepines. However, dependence may develop with regular use of benzodiazepines, even in therapeutic doses for short periods. If benzodiazepines are discontinued abruptly after regular use, withdrawal symptoms may develop. Administration of regular doses of benzodiazepines can result in physical dependence, characterized by a withdrawal syndrome when the drug is discontinued. With larger doses, the physical dependence develops more rapidly. Withdrawal symptoms include: anxiety, insomnia, headache, dizziness, tinnitus, anorexia, vomiting, nausea, tremor, weakness, perspiration, irritability, hypersensitivity to visual and auditory stimuli, palpitations, tachycardia (fast heart rate) and postural hypotension (drop in blood pressure on standing). In severe and rare cases of withdrawal from high doses, patients may develop affective disorders or motor dysfunction: seizures, psychosis, agitation, confusion, and hallucinations. There is also evidence that links benzodiazepine use (in conjunction with alcohol) as a factor in offending.

4.9 Overdose

Escitalopram

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 800 mg 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.

Etizolam

Overdose using Etizolam have been reported. Although Etizolam has a lower LD50 than certain benzodiazepines, the LD50 is still far beyond the prescribed or recommended dose. Many lethal Etizolam overdoses were due to drug interactions.

In case of overdose do not stop your medication without the instructions of your doctor.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Escitalopram

Pharmacotherapeutic group: antidepressants, selective serotonin reuptake inhibitors

ATC-code: N 06 AB 10

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.

Pharmacodynamic effects

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 4.3 ms (90% CI: 2.2, 6.4) at the 10 mg/day dose and 10.7 ms (90% CI: 8.6, 12.8) at the supratherapeutic dose 30 mg/day

Etizolam

Mainly acts on Limbic system and ascending reticular formation in the CNS and binds to BZD receptor. The binding will facilitate GABA mediated chloride channel opening and produce hyperpolarisation. This will produce an increase in the concentration of the inhibitory neurotransmitter GABA and chloride ions and decrease firing rate of neuron. These in turn alters normal function of the body.

5.2 Pharmacokinetic Properties

Escitalopram

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 bioavailability of escitalopram is expected to be about 80%.

Distribution

The apparent volume of distribution ($V_{d,\beta}/F$) 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 ($t_{1/2\beta}$) 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.

Linearity

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)

Escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients. Systemic exposure (AUC) is about 50 % higher in elderly compared to young healthy volunteers.

Reduced hepatic function

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function.

Reduced renal function

With racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (CL_{cr} 10-53 ml/min). Plasma concentrations of the metabolites have not been studied, but they may be elevated.

Polymorphism

It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6.

Etizolam

Absorption and Distribution

Etizolam, a thienodiazepine derivative, is absorbed fairly rapidly. Oral doses have an onset of 30-60 minutes and peak at 3-4 hours. The duration is generally 6-8 hours although higher doses can last longer. Usual after effects are between 1-5 hours although many users report little after effects, especially if they have had a 7-8 hour period of uninterrupted sleep after use. It is distributed widely in the body in protein bound form.

Metabolism and Elimination

Etizolam is purportedly metabolized by the hydroxylation of the methyl group and that of the ethyl group by the cytochrome P450 (CYP) enzymes. It is excreted mainly in the urine, elimination half life of about 3 and a half hour. However, Etizolam has an active main metabolite, alphahydroxyetizolam with an elimination half-life of about 8.2 hours.

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 haemodynamic 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, do 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 implantation number and abnormal sperm at exposure well in excess of human exposure. No animal data related to this aspect are available for escitalopram.

Etizolam:

Few studies on fertility, development and teratogenicity in laboratory animals have been published in Japanese language. When given orally to male rats for 63 days and to female rats for 14 days, etizolam (1, 5, and 25 mg/kg/day) had no significant effects on fertility, fetal mortality, and development. When given to dams from day 17 of gestation to day 21 after delivery, etizolam (5, 25, and 100 mg/kg/day) inhibited body weight gain and spontaneous movements but had no significant effect on duration of pregnancy and delivery. The development of offspring was normal when the dose was < 1 mg/kg.⁵⁵ When given to rabbits (5 and 25 mg/kg) and mice (100 mg/kg), etizolam inhibited growth; and when given to mice at 500 mg/kg/day, etizolam induced teratogenic effects.⁵⁶ The maximal safe dose of etizolam in pregnant mice, rats, and rabbits was 50, 25, and 0.25 mg/kg body weight/day, respectively. No data are available on genotoxic and carcinogenic effects of etizolam.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life
24 months

6.2 Special Precautions for Storage
Store in a cool, dry place below 25 Degree C, Protected from light

6.3 Nature and Contents of Container
10X10 Tablets Blister Packs

Marketed By:

Alkem Laboratories Limited,
Alkem House, S.B. Road,
Lower Parel (West)
Mumbai 400013