

FELIZ S EZ

Antidepressants increased the risk compared to placebo of suicidal thinking and behaviour (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro (US brand of Escitalopram) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behaviour. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro (US brand of Escitalopram) is not approved for use in paediatric patients less than 12 years of age. [as per Warnings and Precautions: Clinical Worsening and Suicide Risk (4.4), Patient Counselling Information: Information for Patients (9), and Use in Specific Populations: Paediatric Use (4.6)].

1. Generic Name

Escitalopram and Etizolam Tablets

2. Qualitative and quantitative Composition:

Feliz S EZ 5

Each film coated tablet contains:

Escitalopram Oxalate I.P. equivalent to Escitalopram...5 mg

Etizolam J.P..... 0.5 mg

Colour: Titanium Dioxide I.P.

Feliz S EZ 10

Each film coated tablet contains:

Escitalopram Oxalate I.P. equivalent to Escitalopram...10 mg

Etizolam J.P..... 0.5 mg

Colour: Titanium Dioxide I.P.

3. Dosage form and strength

Dosage form: Film coated tablets.

Strength: 5 mg and 10 mg

4. Clinical particulars

4.1 Therapeutic indication

FELIZ S EZ is indicated for depression, obsessive-compulsive disorder, major depressive episodes, panic disorder, anxiety disorder and insomnia.

4.2 Posology and method of administration

Posology

Escitalopram

In the treatment of depression, the usual dose is 10 mg once daily increased, after at least a week, to a maximum of 20 mg once daily if necessary. Escitalopram is also used in the treatment of panic disorder with or without agoraphobia. Initial doses are 5 mg once daily, increased after a week to 10 mg once daily; further increases up to a maximum of 20 mg daily may be necessary in some patients. Doses of escitalopram used in the treatment of generalized anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder are similar to those used in depression.

Etizolam

An initial oral dose of one tablet of 0.5mg twice a day increased depending upon individual response to 1 mg 2 to 3 times daily. Sleep disorder: one to three tab of 1 mg of Etizolam once at bedtime.

Method of administration

As directed by physician

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.

FELIZ S EZ is contraindicated in pregnancy and breast feeding.

4.4 Special warnings and precautions for use

Escitalopram

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a longstanding concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Shortterm studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 shortterm trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebocontrolled trials in adults with MDD or other psychiatric disorders included a total of 295 shortterm trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences

in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in below Table.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, Akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. 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, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Escitalopram should

be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Escitalopram is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Escitalopram, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination) seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Escitalopram with MAOIs intended to treat psychiatric disorders is contraindicated. Escitalopram should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Escitalopram. Escitalopram should be discontinued before initiating treatment with the MAOI.

If concomitant use of Escitalopram with other serotonergic drugs including, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Escitalopram and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Discontinuation of Treatment with Escitalopram

During marketing of Escitalopram and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Escitalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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.

Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Escitalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Escitalopram, cases of convulsion have been reported in association with Escitalopram treatment. Like other drugs effective in the treatment of major depressive disorder, Escitalopram should be introduced with care in patients with a history of seizure disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of Escitalopram in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Escitalopram and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Escitalopram treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Escitalopram should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Escitalopram. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Escitalopram was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volumes depleted may be at greater risk. Discontinuation of Escitalopram should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Abnormal Bleeding

SSRIs and SNRIs, including Escitalopram, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Escitalopram and NSAIDs, aspirin, or other drugs that affect coagulation.

Interference with Cognitive and Motor Performance

In a study in normal volunteers, Escitalopram 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may

impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Escitalopram therapy does not affect their ability to engage in such activities.

Angle Closure Glaucoma

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Escitalopram may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Use in Patients with Concomitant Illness

Clinical experience with Escitalopram in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Escitalopram in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Escitalopram in hepatically impaired patients is 10 mg/day.

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Escitalopram, however, it should be used with caution in such patients.

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 Drugs interactions

Escitalopram

Triptans

There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Escitalopram with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

CNS Drugs

Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol

Although Escitalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Escitalopram is not recommended.

Drugs that interfere with hemostasis (NSAIDs, aspirin, warfarin, etc.)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Escitalopram is initiated or discontinued.

Cimetidine

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg twice a day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium

Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Escitalopram and lithium are coadministered.

Pimozide and Celexa

In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic Citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Sumatriptan

There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised.

Theophylline

Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Warfarin

Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine

Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of

carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.

Triazolam

Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

Ritonavir

Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.

CYP3A4 and -2C19 Inhibitors

In vitro studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Drugs Metabolized by Cytochrome P4502D6

In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic Citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on Escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

Metoprolol

Administration of 20 mg/day Escitalopram for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Escitalopram and metoprolol had no clinically significant effects on blood pressure or heart rate.

Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and Escitalopram.

Etizolam

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

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Escitalopram

Pregnancy: Pregnancy Category C

In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately \geq 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis.

In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses \geq 24 mg/kg/day. A no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects

Neonates exposed to Escitalopram and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly,

a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 - 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including Escitalopram) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with Escitalopram, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

Labor and Delivery

The effect of Escitalopram on labor and delivery in humans is unknown.

Nursing Mothers

Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Escitalopram is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Escitalopram has not been established in pediatric patients (less than

12 years of age) with Major Depressive Disorder. Safety and effectiveness of Escitalopram has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

Safety and effectiveness of Escitalopram has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder.

Decrease appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as Escitalopram.

Geriatric Use

Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Escitalopram in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Escitalopram between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible

differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Escitalopram cannot be ruled out.

SSRIs and SNRIs, including Escitalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged. 10 mg/day is the recommended dose for elderly patients.

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

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.

Nursing Mothers

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

Avoid driving a car or operating machinery requiring alertness.

4.8 Undesirable effects

Summary of the safety profile

Escitalopram

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Trial Data Sources Pediatrics (6 -17 years)

Adverse events were collected in 576 pediatric patients (286 Escitalopram, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Escitalopram in pediatric patients less than 12 years of age has not been established.

Adults

Adverse events information for Escitalopram was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Escitalopram in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials

Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder Pediatrics (6 -17 years)

Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Escitalopram and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Escitalopram and greater than placebo) associated with discontinuation was insomnia (1% Escitalopram, 0% placebo).

Adults

Among the 715 depressed patients who received Escitalopram in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Escitalopram was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Escitalopram was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Escitalopram (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Escitalopram, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder Adults

Among the 429 GAD patients who received Le Escitalopram xapro 10-20 mg/day in placebocontrolled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Escitalopram, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%).

Tabulated list of adverse reactions

Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials Major Depressive Disorder Pediatrics (6 -17 years)

The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in **Table 2**. However, the following adverse reactions (excluding those which appear in **Table 2** and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Escitalopram and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.

Adults

The most commonly observed adverse reactions in Escitalopram patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence.

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Escitalopram at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Escitalopram and for which the incidence in patients treated with Escitalopram was greater than the incidence in placebo-treated patients.

TABLE 2		
Treatment-Emergent Adverse Reactions observed with a frequency of $\geq 2\%$ and greater than placebo for Major Depressive Disorder		
<u>Adverse Reaction</u>	<u>Escitalopram Oxalate</u>	<u>Placebo</u>
	(N=715)	(N=592)

	%	%
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder ^{1,2}	9%	<1%
Impotence ²	3%	<1%
Anorgasmia ³	2%	<1%

¹Primarily ejaculatory delay.

²Denominator used was for males only (N=225 escitalopram oxalate; N=188 placebo).

³Denominator used was for females only (N=490 escitalopram oxalate; N=404 placebo).

Generalized Anxiety Disorder Adults

The most commonly observed adverse reactions in Escitalopram patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia.

Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Escitalopram 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Escitalopram and for which the incidence in patients treated with Escitalopram was greater than the incidence in placebo-treated patients.

TABLE 3		
Treatment-Emergent Adverse Reactions observed with a frequency of $\geq 2\%$ and greater than placebo for Generalized Anxiety Disorder		
<u>Adverse Reaction</u>	<u>Escitalopram Oxalate</u>	<u>Placebo</u>
	(N=429) %	(N=427) %
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%

Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder ^{1,2}	14%	2%
Anorgasmia ³	6%	<1%
Menstrual Disorder	2%	1%

¹Primarily ejaculatory delay.

²Denominator used was for males only (N=182 escitalopram oxalate; N=195 placebo).

³Denominator used was for females only (N=247 escitalopram oxalate; N=232 placebo).

Dose Dependency of Adverse Reactions

The potential dose dependency of common adverse reactions (defined as an incidence rate of $\geq 5\%$ in either the 10 mg or 20 mg Escitalopram groups) was examined on the basis of the combined incidence of adverse reactions in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Escitalopram -treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Escitalopram -treated patients was greater (86%). **Table 4** shows common adverse reactions that occurred in the 20 mg/day Escitalopram group with an incidence that was approximately twice that of the 10 mg/day Escitalopram group and approximately twice that of the placebo group.

TABLE 4			
Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder			
Adverse Reaction	Placebo	10 mg/day	20 mg/day
	(N=311)	Escitalopram	Escitalopram
		(N=310)	(N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

TABLE 5		
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials		
Adverse Event	Escitalopram	Placebo
	In Males Only	
	(N=407)	(N=383)

Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Escitalopram treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Escitalopram indicated that Escitalopram treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with Escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes

Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Escitalopram treatment.

ECG Changes

Electrocardiograms from Escitalopram (N=625) and placebo (N=527) groups were compared with respect to outliers defined as subjects with QTc changes over 60 msec from baseline or absolute values over 500 msec post-dose, and subjects with heart rate increases to over 100 bpm or decreases to less than 50 bpm with a 25% change from baseline (tachycardic or bradycardic outliers, respectively). None of the patients in the Escitalopram group had a QTcF interval >500 msec or a prolongation >60 msec compared to 0.2% of patients in the placebo group. The incidence of tachycardic outliers was 0.2% in the Escitalopram and the placebo group. The incidence of bradycardic outliers was 0.5% in the Escitalopram group and 0.2% in the placebo group.

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg) controlled cross-over, escalating multipledose study in 113 healthy subjects. The maximum

mean (95% upper confidence bound) difference from placebo arm were 4.5 (6.4) and 10.7 (12.7) msec for 10 mg and suprathapeutic 30 mg escitalopram given once daily, respectively. Based on the established exposure-response relationship, the predicted QTcF change from placebo arm (95% confidence interval) under the C_{max} for the dose of 20 mg is 6.6 (7.9) msec. Escitalopram 30 mg given once daily resulted in mean C_{max} of 1.7-fold higher than the mean C_{max} for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under suprathapeutic 30 mg dose is similar to the steady state concentrations expected in CYP2C19 poor metabolizers following a therapeutic dose of 20 mg.

Other Reactions Observed During the Premarketing Evaluation of Escitalopram

Following is a list of treatment-emergent adverse events, as defined in the introduction to the adverse reactions section, reported by the 1428 patients treated with Escitalopram for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in **Tables 2 & 3**, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system.

Cardiovascular - hypertension, palpitation.

Central and Peripheral Nervous System Disorders - light-headed feeling, migraine.

Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis.

General - allergy, chest pain, fever, hot flushes, pain in limb.

Metabolic and Nutritional Disorders - increased weight.

Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness.

Psychiatric Disorders - appetite increased, concentration impaired, irritability.

Reproductive Disorders/Female - menstrual cramps, menstrual disorder.

Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache.

Skin and Appendages Disorders - rash.

Special Senses - vision blurred, tinnitus.

Urinary System Disorders - urinary frequency, urinary tract infection.

Post-Marketing Experience Adverse Reactions Reported Subsequent to the Marketing of Escitalopram

The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia.

Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.

Ear and labyrinth disorders: vertigo

Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.

Eye Disorders: angle closure glaucoma, diplopia, mydriasis, visual disturbance.

Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage. *General Disorders and Administration Site Conditions:* abnormal gait, asthenia, edema, fall, feeling abnormal, malaise.

Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. *Immune System Disorders:* allergic reaction, anaphylaxis.

Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.

Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.

Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis.

Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor.

Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.

Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.

Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.

Reproductive System and Breast Disorders: menorrhagia, priapism.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.

Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.

Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

Etizolam

These are some of the typical effects and side effects experienced by people who use Etizolam. Not everyone will experience all of the effects listed and many can be dose-dependent. Overall, Etizolam is reported to be “well tolerated with little side effects” when prescribed.

Physical	Mental
Decrease in energy	Mood enhancement
Decreased heart rate	Relaxation
Impaired coordination	Reduced anxiety
Sleepiness	Lowered inhibitions
Respiratory depression	Sedative effects

Blurred vision	Mental confusion
Yawning	Short term memory loss
Constricted pupils	
Decreased appetite	
Nausea and vomiting	
Muscle relaxation	
Dry mouth	
Headache	
Involuntary eye closure	
Rebound insomnia (prolonged use)	

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Escitalopram

Human Experience

In clinical trials of Escitalopram, there were reports of Escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the post marketing evaluation of Escitalopram, Escitalopram overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of Escitalopram has been rarely reported.

Symptoms most often accompanying Escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

Management of Overdose

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of Escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Escitalopram.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

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 Mechanism of Action

Escitalopram

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Escitalopram has no or very low affinity for serotonergic (5-HT₁₋₇) or other receptors including alpha- and beta-adrenergic, dopamine (D₁₋₅), histamine (H₁₋₃), muscarinic (M₁₋₅) and benzodiazepine receptors. Escitalopram also does not bind to or has low affinity for various ion channels including Na⁺, K⁺, Cl⁻ and Ca⁺⁺ channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

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. This in turn alters normal function of the body.

5.2 Pharmacodynamic properties

Not Available

5.3 Pharmacokinetic properties

Absorption and Distribution

Escitalopram

The single and multiple-dose pharmacokinetics of escitalopram are linear and dose proportional in a dose range of 10 to 30 mg/day. Following a single oral dose (20mg tablet) of escitalopram, the peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food. The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12L/kg. Data specific on escitalopram are unavailable. The binding of escitalopram to human plasma proteins is approximately 56%.

Etizolam

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

Escitalopram

Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 2732 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose.

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10% respectively. The oral clearance of the escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance. Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Etizolam

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.

6 Nonclinical properties

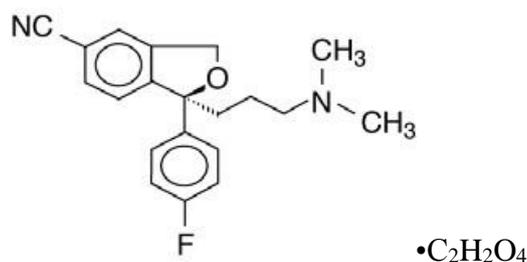
6.1 Animal Toxicology or Pharmacology

Not Available

7 Description

Escitalopram Oxalate

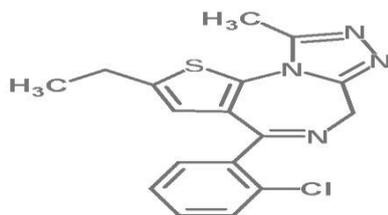
Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3(dimethyl-amino)propyl]-1(p-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



The molecular formula is C₂₀H₂₁FN₂O • C₂H₂O₄ and the molecular weight is 414.40.

Etizolam

Etizolam is a benzodiazepine analog. The etizolam molecule differs from a benzodiazepine in that the benzene ring has been replaced by a thiophene ring, making the drug a thienodiazepine. It possesses amnesic, anxiolytic, anticonvulsant, hypnotic, sedative and skeletal muscle relaxant properties. The molecular formula is [C₁₇H₁₅ClN₄S](#) and Molecular mass is 342.07.



8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

FELIZ S EZ is available in strip pack of 10 tablets

8.4 Storage and handling instructions

Store protected from light and moisture at a temperature not exceeding 30°C.

Keep all tablets out of the reach of children.

9 Patient Counselling Information

Package leaflet: Information for the user

FELIZ S EZ

(Escitalopram and Etizolam Tablets)

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What FELIZ S EZ is and what it is used for

9.2 What you need to know before you take FELIZ S EZ

9.3 How to take FELIZ S EZ

9.4 Possible side effects

9.5 How to store FELIZ S EZ

9.6 Contents of the pack and other information

9.1 What FELIZ S EZ is and what it is used for

FELIZ S EZ is Escitalopram and Etizolam Tablets.

FELIZ S EZ is indicated for depression, obsessive-compulsive disorder, major depressive episodes, panic disorder, anxiety disorder and insomnia.

9.2 What you need to know before you take FELIZ S EZ

Do not take FELIZ S EZ

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.

FELIZ S EZ is contraindicated in pregnancy and breast feeding.

Warnings and precautions

Escitalopram

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a longstanding concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Shortterm studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, Akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. 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, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Escitalopram should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Escitalopram is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Escitalopram, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination) seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Escitalopram with MAOIs intended to treat psychiatric disorders is contraindicated. Escitalopram should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Escitalopram. Escitalopram should be discontinued before initiating treatment with the MAOI.

If concomitant use of Escitalopram with other serotonergic drugs including, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Escitalopram and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Discontinuation of Treatment with Escitalopram

During marketing of Escitalopram and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with Escitalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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.

Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Escitalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Escitalopram, cases of convulsion have been reported in association with Escitalopram treatment. Like other drugs effective in the treatment of major depressive disorder, Escitalopram should be introduced with care in patients with a history of seizure disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of Escitalopram in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Escitalopram and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Escitalopram treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Escitalopram should be used cautiously in patients with a history of mania.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Escitalopram. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Escitalopram was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volumes depleted may be at greater risk. Discontinuation of Escitalopram should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Abnormal Bleeding

SSRIs and SNRIs, including Escitalopram, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to

SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Escitalopram and NSAIDs, aspirin, or other drugs that affect coagulation.

Interference with Cognitive and Motor Performance

In a study in normal volunteers, Escitalopram 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Escitalopram therapy does not affect their ability to engage in such activities.

Angle Closure Glaucoma

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Escitalopram may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Use in Patients with Concomitant Illness

Clinical experience with Escitalopram in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Escitalopram in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Escitalopram in hepatically impaired patients is 10 mg/day.

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Escitalopram, however, it should be used with caution in such patients.

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.

Pregnancy, breast-feeding and fertility

Escitalopram

Pregnancy Pregnancy Category C

In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately \geq 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental

no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m² basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m² basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m² basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m² basis.

In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses \geq 24 mg/kg/day. A no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects

Neonates exposed to Escitalopram and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 - 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use (including Escitalopram) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant

increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy.

When treating a pregnant woman with Escitalopram, the physician should carefully consider both the potential risks of taking an SSRI, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

Labor and Delivery

The effect of Escitalopram on labor and delivery in humans is unknown.

Nursing Mothers

Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Escitalopram is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Escitalopram has not been established in pediatric patients (less than

12 years of age) with Major Depressive Disorder. Safety and effectiveness of Escitalopram has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

Safety and effectiveness of Escitalopram has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder.

Decrease appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as Escitalopram.

Geriatric Use

Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Escitalopram in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Escitalopram between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Escitalopram cannot be ruled out.

SSRIs and SNRIs, including Escitalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged. 10 mg/day is the recommended dose for elderly patients.

Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

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.

Nursing Mothers

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

Driving and using machines

Avoid driving a car or operating machinery requiring alertness.

9.3 How to take FELIZ S EZ

As directed by physician

9.4 Possible side effects

Escitalopram

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Trial Data Sources

Pediatrics (6 -17 years)

Adverse events were collected in 576 pediatric patients (286 Escitalopram, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Escitalopram in pediatric patients less than 12 years of age has not been established.

Adults

Adverse events information for Escitalopram was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Escitalopram in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials

Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder

Pediatrics (6 -17 years)

Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Escitalopram and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Escitalopram and greater than placebo) associated with discontinuation was insomnia (1% Escitalopram, 0% placebo).

Adults

Among the 715 depressed patients who received Escitalopram in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Escitalopram was not significantly different from the rate of

discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Escitalopram was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Escitalopram (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Escitalopram, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder

Adults

Among the 429 GAD patients who received Le Escitalopram xapro 10-20 mg/day in placebo controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Escitalopram, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%).

9.5 How to store FELIZ S EZ

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep all tablets out of the reach of children.

9.6 Contents of the pack and other information

FELIZ S EZ is available in strip pack of 10 tablets.

10 Details of manufacturer

Pure and Cure Healthcare Pvt. Ltd.
Plot No. : 26A-30, Sector – 8A, IIE, SIDCUL,
Ranipur, Haridwar, 249 403 (Uttarakhand)

11 Details of permission or licence number with date

Mfg. Lic. No.: 31/UA/2013

12. Date of revision

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