For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

FELIZ S

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (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 behavior. 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: Package leaflet: Information for the user (9), and Use in Specific Populations: Paediatric Use (4.6)]*.

1. Generic Name

Escitalopram Oxalate Tablets I.P.

2. Qualitative and quantitative composition

FELIZ S 5

Each film coated tablet contains:
Escitalopram Oxalate I.P. equivalent to
Escitalopram …....5 mg
Excipients…….q.s.
Colours: Lake of Quinoline Yellow and Titanium Dioxide I.P.

The excipients used are. Lactose, Starch, Magnesium stearate, Polyvinyl Pyrrolidone, Sodium starch glyollate, Colloidal silicon dioxide, Escitalopram oxalate, Lake of Quinoline Yellow, Propylene glycol, Hydroxy propyl methyl cellulose, Talc, Collodial silicon dioxide(Aerosil), Talc, Titanium dioxide.

FELIZ S 10

Each film coated tablet contains:
Escitalopram Oxalate I.P. equivalent to

Escitalopram …....10 mg

Excipients…….q.s.
Colous: Lake of Quinoline Yellow and Titanium Dioxide I.P.

The excipients used are Lactose monohydrate, Corn Starch, Magnesium stearate, Polyvinyl Pyrrolidone, Sodium starch glyollate, Colloidal silicon dioxide, Escitalopram oxalate, Lake of Quinoline Yellow, Propylene glycol, Hydroxy propyl methyl cellulose, Talc, Collodial silicon dioxide(Aerosil), Talc, Titanium dioxide.

FELIZ S 20

Each film coated tablet contains:
Escitalopram Oxalate I.P. equivalent to
Escitalopram …....20 mg
Excipients…….q.s.
Colours: Lake of Quinoline Yellow and Titanium Dioxide I.P.

The excipients used are Lactose monohydrate, Corn Starch, Magnesium stearate, Polyvinyl Pyrrolidone, Sodium starch glyollate, Colloidal silicon dioxide, Escitalopram oxalate, Lake of Quinoline Yellow, Propylene glycol, Hydroxy propyl methyl cellulose, Talc, Collodial silicon dioxide(Aerosil), Talc, Titanium dioxide.

3. Dosage form and strength Dosage

Dosage Form: Film coated tablets

Strength: 5 mg, 10 mg and 20 mg

4. Clinical particulars

4.1 Therapeutic indication

Feliz S is indicated for treatment of Major depressive disorder & panic disorders with or without agoraphobia.

4.2 Posology and method of administration

Posology

Safety of daily doses above 20 mg has not been demonstrated.

Major depressive episodes

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

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

Panic disorder with or without agoraphobia

An initial dose of 5 mg is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response.

Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

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

Elderly patients (> 65 years of age)

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

Paediatric population

Escitalopram should not be used in the treatment of children and adolescents under the age of 12 years.

Reduced renal function

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

Reduced hepatic function

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

Poor metabolisers of CYP2C19

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

Discontinuation symptoms seen when stopping treatment

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

4.3 Contraindications

Escitalopram is contraindicated in patients with known hypersensitivity to any component of the formulation of escitalopram or citalopram

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

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

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

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

4.4 Special warnings and precautions for use

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

Paediatric population

Escitalopram should not be used in the treatment of paediatric population. Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among the paediatric population 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 the paediatric population concerning growth, maturation and cognitive and behavioural development are lacking.

Paradoxical anxiety

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

Seizures

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

Mania

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

Diabetes

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

Clinical Worsening and Suicide Risk

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 nonsteroidal 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.

Sexual dysfunction

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

Coronary heart disease

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

QT 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.

4.5 Drugs interactions

Pharmacodynamic interactions

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 nonselective, 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 coadministered 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 (e.g. astemizole, hydroxyzine, 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 nonsteriodal 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.

Clonazepam

Using Clonazepam together with Escitalopram may increase side effects such as dizziness, drowsiness, confusion, & difficulty concentrating. Some people, especially elderly, may also experience impairment in thinking, judgment, & motor coordination.

Etizolam

Escitalopram in combination with Etizolam may synergize the propensity of adverse drug reactions like dizziness, drowsiness, confusion, and difficulty concentrating. Some people,

especially the elderly, may also experience impairment in thinking, judgment, and motor coordination etc.

Pharmacokinetic interactions

Influence of other medicinal products on the pharmacokinetics of escitalopram

The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6. Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram.
Co-administration of escitalopram with cimetidine 400 mg twice daily (moderately potent general enzyme-inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram. Caution is advised when administering escitalopram in combination with cimetidine. Dose adjustment may be warranted.
Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment.

Effect of escitalopram on the pharmacokinetics of other medicinal products

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

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

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

4.6 Use in special populations

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.

Paediatric Use

Escitalopram should not be used in the treatment of paediatric population. Suicide related behaviours (suicide attempt and suicidal thoughts), and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among the paediatric population treated with antidepressants compared to those treated with placebo. Escitalopram should not be used in the treatment of children and adolescents under the age of 12 years.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions

Adverse reactions known for SSRIs and also reported for escitalopram in either placebocontrolled clinical studies or as spontaneous post-marketing events are listed below by system organ class and frequency.

Frequencies are taken from clinical studies; they are not placebo-corrected. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to

<1/100), rare (≥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 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.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. 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: http://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

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.

5. Pharmacological properties

5.1 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- HT1A, 5–HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors.

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

5.2 Pharmacodynamic properties

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 ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha-and betaadrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$) 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.

5.3 Pharmacokinetic properties

Absorption and Distribution

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%.

Metabolism and Elimination

Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 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-demethycitalopram (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 (SDDCT). 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 noeffect-level were in excess (8-fold) of those achieved in clinical use, while AUC for escitalopram was only 3- to 4-fold higher than the exposure achieved in clinical use. For citalopram AUC values for the S-enantiomer were 6- to 7-fold higher than exposure achieved in clinical use. The findings are probably related to an exaggerated influence on biogenic amines i.e. secondary to the primary pharmacological effects, resulting in hemodynamic effects (reduction in coronary flow) and ischemia. 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

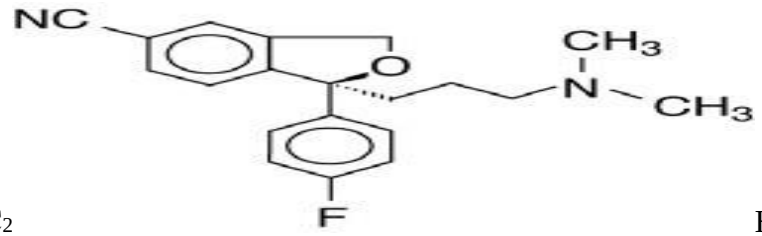
in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment cessation. Accumulation of phospholipids (phospholipidosis) in animals has been observed in connection with many cationic amphiphilic medicines. It is not known if this phenomenon has 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 number in implantation and abnormal sperm at exposure well in excess of human exposure. No animal data related to this aspect are available for escitalopram.

7. Description

Escitalopram oxalate is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure Senantiomer (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:



•C_2 H_2O_4

The molecular formula is $C_{20}H_{21}FN_{2O}$ • $C_2H_2O_4$ and the molecular weight is 414.40.

FELIZ S 5/10/20

Feliz S 20- Yellow coloured, biconvex, round shaped, film coated tablets.

Feliz S 10- Yellow coloured, biconvex, round shaped, film coated tablets with break line on one side.

Feliz S 20- Yellow coloured, biconvex, Oval shaped, film coated tablets with break line on one side.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

Feliz S available in Blister pack of 10 Tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30ºC, protected from light and moisture.

Keep all tablets out of reach of children.

9. Patient counselling information Package leaflet: Information for the user Feliz S

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- Dosage will be as directed by the Physician
- Keep all medicines out of reach of children
- 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 is and what it is used for

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

9.3.How to take FELIZ S

9.4.Possible side effects

9.5.How to store FELIZ S

9.6.Contents of the pack and other information

9.1 What FELIZ S is and what it is used for

FELIZ S is indicated for treatment of Major depressive disorder & panic disorders with or without agoraphobia

9.2 What you need to know before you take FELIZ S

Do not take FELIZ S

- If you are allergic to escitalopram or any of the other ingredients of this medicine

Warnings and precautions

- Talk to your doctor before taking FELIZ S
- When treating a pregnant woman with Escitalopram, the physician should carefully consider both the potential risks of taking an SSRl, along with the established benefits of treating depression with an antidepressant. This decision can only be made on a case by case basis.

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.
- SSRIs and SNRIs, including Escitalopram, may increase the risk of bleeding events.
- Patients should be monitored for withdrawal reactions when discontinuing treatment with Escitalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.
- Using Clonazepam together with Escitalopram may increase side effects such as dizziness, drowsiness, confusion, & difficulty concentrating. Some people, especially elderly, may also experience impairment in thinking, judgment, & motor coordination.
- Escitalopram in combination with Etizolam may synergize the propensity of adverse drug reactions like dizziness, drowsiness, confusion, and difficulty concentrating. Some people, especially the elderly, may also experience impairment in thinking, judgment, and motor coordination etc.

Other medicines and FELIZ S

- Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Pregnancy and breast-feeding

- If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

Paediatric use

- Escitalopram should not be used in the treatment of children and adolescents under the age of 12 years.

Driving and using machines

- Patients should be cautioned about the potential risk of an influence on their ability to drive a car and operate machinery.

9.3 How to take FELIZ S

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

FELIZ S Tablets should be administered orally with food to enhance absorption.

If you take more FELIZ S than you should contact your doctor if you took more tablets than you should. Your doctor will establish the best possible treatment of overdose.

The possible side effects of an overdose of FELIZ S are convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes).

If you forget to take FELIZ S:

Contact your doctor if you have missed one or more doses.

Do not take a double dose to make up for a forgotten tablet.

If you stop taking FELIZ S

Should your doctor decide to stop your FELIZ S treatment, he/she will instruct you about the gradual withdrawal of FELIZ S.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects:

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- gastrointestinal disturbances, nausea, vomiting, or diarrhoea
- muscle Pain
- dizziness, insomnia, somnolence, anxiety, nervousness, paraesthesia, vertigo.
- cough, epistaxis, bronchitis, dyspnoea, sinus congestion, sinus headache, pulmonary embolism
- urticaria, dermatitis, angioedema, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. 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: http://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.

9.5 How to store FELIZ S

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

9.6 Contents of the pack and other information

What FELIZ S contains

The active substance is Escitalopram 5mg/ 10mg /20mg.

FELIZ S 5

The excipients used are Lactose, Starch, Magnesium stearate, Polyvinyl Pyrrolidone, Sodium starch glyollate, Colloidal silicon dioxide, Escitalopram oxalate, Lake of Quinoline Yellow, Propylene glycol, Hydroxy propyl methyl cellulose, Talc, Collodial silicon dioxide(Aerosil), Talc, Titanium dioxide.

FELIZ S 10 and 20

The excipients used are Lactose monohydrate, Corn Starch, Magnesium stearate, Polyvinyl Pyrrolidone, Sodium starch glyollate, Colloidal silicon dioxide, Escitalopram oxalate, Lake of

Quinoline Yellow, Propylene glycol, Hydroxy propyl methyl cellulose, Talc, Collodial silicon dioxide(Aerosil), Talc, Titanium dioxide.

10. Details of manufacturer

Manufactured by:

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
32 No. Middle Camp, NH-10,
East District, Gangtok, Sikkim-737 135.

Or

M/S. Swiss Garnier Genexiaaa Sciences Pvt. Ltd.,

Plot No. 54 & 78

Mamring Bashti, Rangpo Post,

SouthSikkim-737132

11. Details of permission or licence number with date

Mfg lic M/563/2010 Dated 23.12.2016

Or

Mfg Lic. No. M/605/2021 issued on 05 Dec. 2018

12. Date of revision

MAY-2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/FELIZ S 5,10,20 mg/MAY-21/04/PI