

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

FELIZ S PLUS

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 Feliz S Plus 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. Feliz S Plus 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 and Clonazepam Tablets I.P.

2. **Qualitative and quantitative composition**

FELIZ S PLUS

Each film-coated tablet contains:

Escitalopram Oxalate I.P. equivalent to

Escitalopram....10 mg

Clonazepam I.P.0.5 mg

Colour: Yellow Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Lactose, Starch, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Lake of Quinoline Yellow, Propylene Glycol and TRC Coat C.

FELIZ S PLUS 5

Each film-coated tablet contains:

Escitalopram Oxalate I.P. equivalent to

Escitalopram.....5 mg

Clonazepam I.P.0.5 mg

Colour: Titanium dioxide I.P

The excipients used are Lactose, Starch, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, and TRC Coat A.

3. Dosage form and strength

FELIZ S PLUS

Film coated (Escitalopram 10 mg + Clonazepam 0.5 mg) tablets

FELIZ S PLUS 5

Film coated (Escitalopram 5 mg + Clonazepam 0.5 mg) tablets

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for treatment of comorbid depression and anxiety disorders.

4.2 Posology and method of administration

Posology

As directed by the physician

4.3 Contraindications

- Hypersensitivity to the active substance (Clonazepam and Escitalopram)
- History of sensitivity to benzodiazepines. Hypersensitivity to any of the excipients.
- Clinical or biochemical evidence of significant liver disease.
- Acute narrow angle glaucoma (it may be used in patients with open angle glaucoma who are receiving appropriate therapy).
- Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc.
- The combination of Escitalopram Oxalate and Clonazepam tablets with reversible MAO-an 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 Oxalate and Clonazepam tablets is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Escitalopram Oxalate and Clonazepam tablets is contraindicated together with medicinal products that are known to prolong the QT interval.
- Acute pulmonary insufficiency; severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency.
- Escitalopram Oxalate and Clonazepam tablets must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol.

4.4 Special warnings and precautions for use **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. 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 with antidepressants compared to placebo in adults aged 65 and older.

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 non-psychiatric.

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 withdrawal symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non psychiatric, 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.

Clonazepam:

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Risks from Concomitant Use with Opioids:

Concomitant use of benzodiazepines, including Escitalopram Oxalate and Clonazepam tablets, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Reported observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Escitalopram Oxalate and Clonazepam tablets concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Escitalopram Oxalate and Clonazepam tablets is used with opioids.

Interference with Cognitive and Motor Performance: Since Escitalopram Oxalate and Clonazepam tablets produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during Escitalopram Oxalate and Clonazepam tablets therapy.

PRECAUTIONS

Worsening of Seizures: When used in patients in whom several different types of seizure disorders coexist, Escitalopram Oxalate and Clonazepam tablets may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and Escitalopram Oxalate and Clonazepam tablets may produce absence status.

Laboratory Testing During Long-Term Therapy: Periodic blood counts and liver function tests are advisable during long-term therapy with Escitalopram Oxalate and Clonazepam tablets.

Psychiatric and Paradoxical Reactions: Paradoxical reactions, such as agitation, irritability, aggression, anxiety, anger, nightmares, hallucinations, and psychoses are known to occur when using benzodiazepines. Should this occur, the use of the drug should be discontinued gradually? Paradoxical reactions are more likely to occur in children and in the elderly.

Risks of Abrupt Withdrawal: The abrupt withdrawal of Escitalopram Oxalate and Clonazepam tablets, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing Escitalopram Oxalate and Clonazepam tablets,

gradual withdrawal is essential. While Escitalopram Oxalate and Clonazepam tablets is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.

Caution in Renally Impaired Patients: Metabolites of Escitalopram Oxalate and Clonazepam tablets are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Hyper salivation: Escitalopram Oxalate and Clonazepam tablets may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions.

Respiratory Depression: Escitalopram Oxalate and Clonazepam tablets may cause respiratory depression and should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, sleep apnea).

Porphyria: Escitalopram Oxalate and Clonazepam tablets may have a porphyrogenic effect and should be used with care in patients with porphyria.

Paediatric population

Escitalopram Oxalate and Clonazepam tablets 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.

Akathisia/psychomotor restlessness: The use of SSRIs/SNRI has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Hyponatraemia: Hyponatraemia, probably due to inappropriate antidiuretic hormone

secretion (SIADH), has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as the elderly, or patients with cirrhosis, or if used in combination with other medications which may cause hyponatraemia.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

ECT (electroconvulsive therapy): There is limited clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

Serotonin syndrome: Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan. In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

St. John's wort: Concomitant use of SSRIs and herbal remedies containing St. John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

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

Clonazepam

Opioids: The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Clonazepam with opioids increases the risk of sedation, respiratory depression, coma

and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited

Alcohol: Alcohol in combination with clonazepam may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects. Under no circumstances should alcohol be consumed while under treatment with clonazepam.

Antiepileptic drugs: When used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy, and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment. The combination of clonazepam and sodium valproate has, rarely, been associated with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered. The antiepileptic drugs phenytoin, phenobarbital, carbamazepine and valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter during combined treatment.

Escitalopram: 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.

Pharmacokinetic interactions: Clonazepam itself does not induce the enzymes responsible for its own metabolism.

Escitalopram

Pharmacodynamic interactions

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

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

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

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

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

QT interval prolongation: Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of escitalopram and these medicinal products cannot be excluded. Therefore, co-administration of escitalopram with medicinal products that prolong the QT interval, such

as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine), is contraindicated.

Combinations requiring precautions for use:

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

Medicinal products lowering the seizure threshold: SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquin, bupropion and tramadol).

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

St. John's wort: Concomitant use of SSRIs and herbal remedies containing St. John's wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

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

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.

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, 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 Population

Pregnancy: Escitalopram Oxalate and Clonazepam tablets should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

Neonates should be observed if maternal use of Escitalopram Oxalate and Clonazepam tablets 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 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.

Nursing Mothers: The effects of Escitalopram Oxalate and Clonazepam tablets on the breastfed infant and on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Escitalopram Oxalate and Clonazepam tablets and any potential adverse effects on the breastfed infant from Escitalopram Oxalate and Clonazepam tablets or from the underlying maternal condition.

Paediatric Use: Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of Escitalopram Oxalate and Clonazepam tablets is important in pediatric patients being treated for seizure disorder.

Geriatric Use: Because Escitalopram Oxalate and Clonazepam tablets undergoes hepatic metabolism, it is possible that liver disease will impair elimination. Metabolites of Escitalopram Oxalate and Clonazepam tablets are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to assess hepatic and/or renal function at the time of dose selection. Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Clonazepam and observed closely.

4.7 Effects on ability to drive and use machines

Because the medicine containing benzodiazepines have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles.

4.8 Undesirable effects

Clonazepam

| <i>System organ class</i> | <i>Undesirable Effect</i> |
|--|---|
| <i>Blood and the lymphatic system disorders</i> | Isolated cases of blood dyscrasias |
| <i>Immune system disorders</i> | Allergic reaction and a very few cases of anaphylaxis and angioedema |
| <i>Endocrine disorders</i> | Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported |
| <i>Psychiatric disorders and Paradoxical Reactions</i> | <p>Anterograde amnesia (risk increases at higher dosages). Amnestic effects may be associated with inappropriate behaviour. Depression, loss of libido, impotence.</p> <p>Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment and is particularly pronounced in predisposed patients with a history of alcoholism or drug abuse.</p> <p>Paradoxical effects such as aggressiveness, excitability, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams, irritability, agitation, psychotic disorders and activation of new types of seizures may occur. If these occur, the benefit of continuing the drug should be weighed against the adverse effect. It may be necessary to add another suitable drug to the regimen or to discontinue clonazepam therapy.</p> |
| <i>Nervous system disorders</i> | <p>Dizziness, light-headedness, somnolence, fatigue, co-ordination disturbances, poor concentration, restlessness, confusion and disorientation, headache. Dysarthria and ataxia are reversible disorders and occur particularly in long-term or high-dose treatment.</p> <p>These undesirable effects occur relatively frequently and may disappear gradually in the course of the treatment or on reduction of</p> |

| <i>System organ class</i> | <i>Undesirable Effect</i> |
|--|--|
| | <p>the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.</p> <p>Headache was observed in rare cases. Causing of generalised fits was observed very rarely.</p> <p>Particularly in long-term or high-dose treatment, reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. Although Clonazepam has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients. With certain forms of epilepsy, an increase in the frequency of seizures during longterm treatment is possible. Rarely, convulsions may be induced in patients with porphyria.</p> |
| <i>Eye disorders</i> | Double vision and nystagmus are reversible disorders and occur particularly in long term or high-dose treatment. |
| <i>Cardiac Disorders</i> | Cardiac failure including cardiac arrest has been reported |
| <i>Respiratory, thoracic and mediastinal disorders</i> | <p>Rarely respiratory depression may occur with intravenous clonazepam, particularly if other depressant drugs have been administered. This effect may be aggravated by pre-existing airways obstruction or brain damage or if other medications which depress respiration have been given .This effect can usually be avoided by careful adjustment of the dose to individual requirements.</p> <p>In infants and small children, and particularly those with a degree of mental impairment, salivary or bronchial hypersecretion with drooling may occur.</p> <p>Supervision of the airway may be required.</p> |
| <i>Gastrointestinal disorders</i> | nausea, gastrointestinal symptoms |
| <i>Hepato-biliary disorders</i> | Isolated cases of abnormal liver function tests have been reported |
| <i>Skin and subcutaneous tissue disorders</i> | urticaria, pruritus, transient hair loss, pigmentation changes |
| <i>Musculoskeletal, connective tissue and bone disorders</i> | Muscle weakness, occasional muscular hypotonia |

| <i>System organ class</i> | <i>Undesirable Effect</i> |
|---|--|
| <i>Renal and urinary disorders</i> | urinary incontinence |
| <i>Reproductive System and Breast Disorders</i> | In rare cases erectile dysfunction or loss of libido may occur |
| <i>General disorders and administration site conditions</i> | Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop, especially withdrawing from high doses or if the daily dose is reduced rapidly or abruptly discontinued. The symptoms include: tremor, sweating, agitation, sleep disturbances and anxiety, headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and epileptic seizures which may be associated with the underlying disease. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, discontinuation should be carried out by gradually reducing the daily dose. |
| <i>Injury, Poisoning and Procedural Complications</i> | An increased risk for falls and fractures has been reported in elderly benzodiazepine users |
| <i>Investigations</i> | In rare cases decreased platelet count may occur. As with other benzodiazepines, isolated cases of blood dyscrasias. |

Escitalopram

| <i>System organ class</i> | <i>Undesirable Effect</i> |
|---|--|
| <i>Blood and lymphatic system disorders</i> | Thrombocytopenia |
| <i>Immune system disorders</i> | Anaphylactic reaction |
| <i>Endocrine disorders</i> | Inappropriate ADH secretion |
| <i>Metabolism and nutrition disorders</i> | Decreased appetite, increased appetite, weight increased |
| | Weight decreased |
| | Hyponatraemia, anorexia |

| <i>System organ class</i> | <i>Undesirable Effect</i> |
|--|--|
| <i>Psychiatric disorders</i> | Anxiety, restlessness, abnormal dreams libido decreased Female: anorgasmia |
| | Bruxism, agitation, nervousness, panic attack, confusional state |
| | Aggression, depersonalisation, hallucination |
| | Mania, suicidal ideation, suicidal behaviour |
| <i>Nervous system disorders</i> | Headache |
| | Insomnia, somnolence, dizziness, paraesthesia, tremor |
| | Taste disturbance, sleep disorder, syncope |
| | Serotonin syndrome |
| | Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia |
| <i>Eye disorders</i> | Mydriasis, visual disturbance |
| <i>Ear and labyrinth disorders</i> | Tinnitus |
| <i>Cardiac disorders</i> | Tachycardia |
| | Bradycardia |
| | Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes |
| <i>Vascular disorders</i> | Orthostatic hypotension |
| <i>Respiratory, thoracic and mediastinal disorders</i> | Sinusitis, yawning |
| | Epistaxis |
| <i>Gastrointestinal disorders</i> | Nausea |

| <i>System organ class</i> | <i>Undesirable Effect</i> |
|---|--|
| | Diarrhoea, constipation, vomiting, dry mouth |
| | Gastrointestinal haemorrhages (including rectal haemorrhage) |
| <i>Hepatobiliary disorders</i> | Hepatitis, liver function test abnormal |
| <i>Skin and subcutaneous tissue disorders</i> | Sweating increased |
| | Urticaria, alopecia, rash, pruritus |
| | Ecchymosis, angioedemas |
| <i>Musculoskeletal and connective tissue disorders</i> | Arthralgia, myalgia |
| <i>Renal and urinary disorders</i> | Urinary retention |
| <i>Reproductive system and breast disorders</i> | Male: ejaculation disorder, impotence |
| | Female: metrorrhagia, menorrhagia |
| | Galactorrhoea |
| | Male: priapism |
| <i>General disorders and administration site conditions</i> | Fatigue, pyrexia |
| | Oedema |

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, 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: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Clonazepam

Human Experience: Symptoms of clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma, and diminished reflexes.

Overdose Management: Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re sedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

Flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly.

Escitalopram

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

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

Management: There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible

after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures. ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5. Pharmacological properties

5.1 Mechanism of Action

Clonazepam, is believed to act via its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT₂, DA D₁ and D₂ receptors, α ₁-, α ₂-, β -adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors. The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

5.2 Pharmacodynamic properties

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects.

Escitalopram

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

5.3 Pharmacokinetic properties

Clonazepam

Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Escitalopram

Absorption of escitalopram is almost complete and independent of food intake. (Mean time to maximum concentration (mean T_{max}) is 4 hours after multiple dosing). As with racemic citalopram, the absolute bioavailability of escitalopram is expected to be about 80%. The apparent volume of distribution (V_{d,β}/F) after oral administration is about 12 to 26 L/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites. Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and

metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the dimethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible. The elimination half-life ($t_{1/2}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min. The major metabolites have a significantly longer half-life. Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

6. Nonclinical properties

Clonazepam

In preclinical murine studies there was at least a two-fold increase in teratogenic birth defects at dose levels of 3, 9 and 18 times the human therapeutic dose compared to the controls.

Escitalopram

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

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

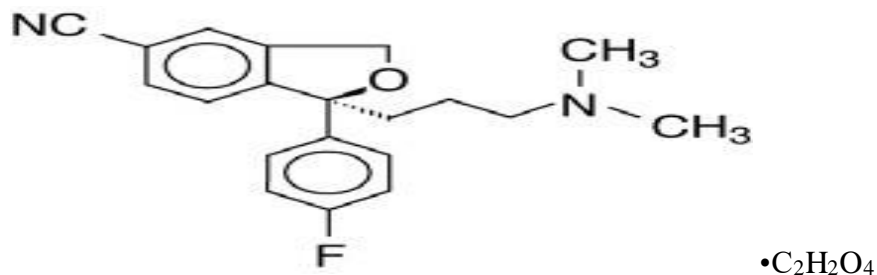
Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment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

In the developmental toxicity study in the rat embryotoxic effects (reduced foetal weight and reversible delay of ossification) were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. A pre- and postnatal study showed reduced survival during the lactation period at exposures in terms of AUC in excess of the exposure achieved during clinical use.

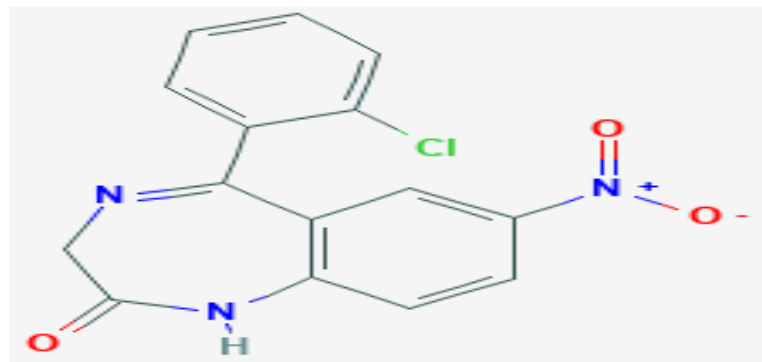
Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in implantation number and abnormal sperm at exposure well in excess of human exposure. No animal data related to this aspect are available for escitalopram.

7. Description

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-phthalanecarbonitrile oxalate with the following structural formula:



Clonazepam is 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one having molecular formula of $\text{C}_{15}\text{H}_{10}\text{ClN}_3\text{O}_3$ and molecular weight is 315.71g/mol. The chemical structure is:



FELIZ S PLUS

Escitalopram Oxalate and Clonazepam Tablets are yellow coloured, round, biconvex, film coated tablets, with breakline on one side and plain on other side. The excipients used are Lactose, Starch, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Lake of Quinoline Yellow, Propylene Glycol and TRC Coat C.

FELIZ S PLUS 5

Escitalopram Oxalate and Clonazepam Tablets are white to off white, round, biconvex, film-coated tablets, plain on both sides. The excipients used are Lactose, Starch, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, and TRC Coat A.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

FELIZ S PLUS IS AVAILABLE 10 BLISTER STRIPS
OF 15 TABLETS EACH

FELIZ S PLUS 5 IS AVAILABLE 10 STRIPS OF
10 TABLETS EACH

8.4 Storage and handling instructions

STORE AT A TEMPERATURE

NOT EXCEEDING 30°C,

PROTECTED FROM MOISTURE

9. Patient counselling information

FELIZ S PLUS

Escitalopram Oxalate and Clonazepam Tablets I.P.

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.
- 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 PLUS is and what it is used for

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

9.3. How to take FELIZ S PLUS 9.4. Possible side effects

9.5. How to store FELIZ S PLUS

9.6. Contents of the pack and other information

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

The name of your medicine is FELIZ S PLUS which is combination of Clonazepam (belongs to a group of medicines called 'benzodiazepine') and escitalopram (belongs to a group of antidepressants called selective serotonin reuptake inhibitors (SSRIs)). It is used to treat patients with comorbid depression & anxiety disorders.

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

Do not take FELIZ S PLUS

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

- If you are allergic to other benzodiazepine medicines and Escitalopram or any of the other ingredients of this medicine.
- Have significant liver disease.
- Have an eye disease called acute narrow angle glaucoma.
- If you take other medicines which belongs to a group called MAO inhibitors, including selegiline (used in the treatment of Parkinson's disease), moclobemide (used in the treatment of depression) and linezolid (an antibiotic).
- If you are born with or have had an episode of abnormal heart rhythm (Seen at ECG; an examination to evaluate how the heart is functioning).
- If you take medicines for heart rhythm problems or that may affect the heart's rhythm.

Warnings and precautions

Tell your healthcare provider if you,

- Have liver or kidney problems.
- Have lung problems (respiratory disease).
- Have or have had depression, mood problems, or suicidal thoughts or behavior.
- Have any other medical problems.
- Are pregnant or plan to become pregnant. It is not known if FELIZ S PLUS can harm your unborn baby.
- if you become pregnant while taking FELIZ S PLUS. You and your healthcare provider will decide if you should take FELIZ S PLUS while you are pregnant.
- Are breastfeeding or plan to breastfeed? FELIZ S PLUS can pass into breast milk. You and your healthcare provider should decide how you will feed your baby while you take FELIZ S PLUS.
- have epilepsy. Treatment with FELIZ S PLUS should be stopped if seizures occur or if there is an increase in the seizure frequency.
- If you have diabetes. Treatment with FELIZ S PLUS may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.
- have a decreased level of sodium in the blood.
- have a tendency to easily develop bleedings or bruises.
- are receiving electroconvulsive treatment.
- have coronary heart disease.
- suffer or have suffered from heart problems or have recently had a heart attack.
- have a low resting heart-rate and/or you know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (Being sick) or usage of diuretics (water tablets).
- experience a fast or irregular heartbeat, fainting, collapse or dizziness on standing up, which may indicate abnormal functioning of the heart rate.
- have or have previously had eye problems, such as certain kinds of glaucoma (increased pressure in the eye).

Please Note,

Some patients with manic-depressive illness may enter into a manic phase. This is characterized by unusual and rapidly changing ideas, inappropriate happiness and excessive physical activity. If you experience this, contact your doctor.

Symptoms such as restlessness or difficulty to in sitting or standing still can also occur during the first weeks of the treatment. Tell your doctor immediately if you experience these symptoms.

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Use in children and adolescents

FELIZ S PLUS should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side effects such as suicide attempts, suicidal thoughts and hostility (predominately aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe FELIZ S PLUS for patients under 18 because he/she decides that this is in their best interest. If your doctor has prescribed FELIZ S PLUS for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any symptoms listed above develop or worsen when patients under 18 are taking Escitalopram Oxalate and Clonazepam tablets. Also, the long term safety effects concerning growth, maturation and cognitive and behavioural development of Escitalopram Oxalate and Clonazepam tablets in this age group have not yet been demonstrated.

Other medicines and FELIZ S PLUS

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking FELIZ S PLUS with certain other medicines can cause side effects or affect how well FELIZ S PLUS or the other medicines work.

Do not start or stop other medicines without talking to your healthcare provider. Tell your doctor if you are taking any of the following medicines:

- Non-selective monoamine oxidase inhibitors (MAOIs)", containing phenelzine, iproniazid, isocarboxazid, nialamide, and tranylcypromine as active ingredients. If you have

taken any of these medicines you will need to wait 14 days before you start taking FELIZ S PLUS. After stopping FELIZ S PLUS you must allow 7 days before taking any of these medicines.

- “Reversible, selective MAO-A inhibitors”, containing moclobemide (used to treat depression).
- “Irreversible MAO-B inhibitors”, containing selegiline (used to treat Parkinson’s disease). These increase the risk of side effects.
- The antibiotic linezolid.
- Lithium (used in the treatment of manic-depressive disorder) and tryptophan.
- Imipramine and desipramine (both used to treat depression).
- Sumatriptan and similar medicines (used to treat migraine) and tramadol (used against severe pain). These increase the risk of side effects.
- Cimetidine and omeprazole (used to treat stomach ulcers), fluvoxamine (antidepressant) and ticlopidine (used to reduce the risk of stroke). These may cause increased blood levels of escitalopram.
- St. John's Wort (*Hypericum perforatum*) - an herbal remedy used for depression.
- Acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory drugs (medicines used for pain relief or to thin the blood, so called anticoagulants). These may increase bleeding-tendency.
- Warfarin, dipyridamole, and phenprocoumon (medicines used to thin the blood, so called anticoagulants). Your doctor will probably check the coagulation time of your blood when starting and discontinuing FELIZ S PLUS in order to verify that your dose of anticoagulant is still adequate.
- Mefloquine (used to treat Malaria), bupropion (used to treat depression) and tramadol (used to treat severe pain) due to a possible risk of a lowered threshold for seizures.
- Neuroleptics (medicines to treat schizophrenia, psychosis) and antidepressants (tricyclic antidepressants and SSRIs) due to a possible risk of a lowered threshold for seizures.
- Flecainide, propafenone, and metoprolol (used in cardiovascular diseases) clomipramine, and nortriptyline (antidepressants) and risperidone, thioridazine, and haloperidol (antipsychotics). The dosage of FELIZ S PLUS may need to be adjusted.
- Medicines that decrease blood levels of potassium or magnesium, as these conditions increase the risk of life-threatening heart rhythm disorders. Do not take FELIZ S PLUS if you take medicines for heart rhythm problems or medicines that may affect the heart’s rhythm, 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, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine). If you have any further questions about this, you should speak to your doctor.
- Do not take FELIZ S PLUS if you take medicines for heart rhythm problems or medicines that may affect the heart’s rhythm, 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, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine). If you have any further questions about this you should speak to your doctor.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not take FELIZ S PLUS if you are pregnant or breast-feeding, unless you and your doctor have discussed the risks and benefits involved.

If you take FELIZ S PLUS during the last 3 months of your pregnancy you should be aware that the following effects may be seen in your newborn baby: trouble with breathing, bluish skin, fits, body temperature changes, feeding difficulties, vomiting, low blood sugar, stiff or floppy muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, constant crying, sleepiness and sleeping difficulties. If your newborn baby has any of these symptoms, please contact your doctor immediately.

Make sure your midwife and/or doctor know you are on FELIZ S PLUS. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like FELIZ S PLUS may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby, you should contact your midwife and/or doctor immediately.

If used during pregnancy FELIZ S PLUS should never be stopped abruptly. It is expected that escitalopram will be excreted into breast milk.

FELIZ S PLUS contains Escitalopram that has been shown to reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.

Driving and using machines

It has not been established that FELIZ S PLUS impairs your ability to drive or operate any tools or machinery. However, you should not drive or use machines until it is established that your ability to perform such activities is not affected.

9.3 How to take FELIZ S PLUS

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you take more FELIZ S PLUS than you should

If you take too many tablets or someone else accidentally takes your medicine, contact your doctor, pharmacist or nearest hospital immediately. Do this even if there are no signs of discomfort. Some of the signs of an overdose could be dizziness, tremor, agitation, convulsion, coma, nausea, vomiting, change in heart rhythm, decreased blood pressure and change in body fluid/salt balance. Take the FELIZ S PLUS box/container with you when you go to the doctor or hospital.

If you forget to take FELIZ S PLUS if you forget to take a dose, simply take the next dose when it is due. Do not take a double dose to make up for a forgotten dose.

Do not suddenly stop taking FELIZ S PLUS. If you need to stop taking the medication, your doctor will tell you how to stop slowly to reduce any side effects as you can get withdrawal symptoms if you stop suddenly. These symptoms may include problems with sleeping, muscle pain, anxiety (sometimes severe), tension, restlessness, confusion, severe mood changes,

irritability, sweating, shakes (tremor), headaches and agitation. In serious cases, withdrawal effects can also include being oversensitive to light, noise and touch, hallucinations, tingling, numbness and a feeling of being unreal. Feeling dizzy (unsteady or off-balance), feelings like pins and needles, burning sensations and (less commonly) electric shock sensations, including in the head, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling anxious, headaches, feeling sick (nausea), sweating (including night sweats), feeling restless or agitated, tremor (shakiness), feeling confused or disorientated, feeling emotional or irritable, diarrhea (loose stools), visual disturbances, fluttering or pounding heartbeat (palpitations).

If you think the effect of Clonazepam is too strong or too weak, talk to your doctor. Do NOT change the dose yourself.

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:

- Changes in behaviour: aggressiveness, excitability, nervousness, hostility, anxiety, problems sleeping, nightmares, vivid dreams, irritability, agitation, extreme mood changes and new types of seizures may occur.
- Allergic reactions can occur (such as itching, swelling of the tongue, eyes, lips and hands).

The following side effects have been reported:

- Memory loss (amnesia) after a traumatic event which may be linked with some strange behaviour (more likely with higher doses).
- Depression.
- Loss of sex drive, impotence.
- Dependence on clonazepam – this is more of a risk when the dose is high or the treatment is for a long time, and is especially likely to occur in patients with a history of alcoholism or drug abuse.
- Dizziness, light-headedness, sleepiness, tiredness, lack of co-ordination, poor concentration, restlessness, confusion, disorientation, floppiness and weakness of the muscles, headache. Particularly at the start of treatment. The side effects are usually short-lived and may disappear by adjusting the dose.
- Breathlessness, swelling of the ankles, cough, tiredness and a racing heart.
- Chest pain which may spread to your neck and shoulders and down your left arm.
- Feeling unsteady when walking.
- Platelet count bruising easily, being short of breath and nose bleeds.
- Slurring of speech, lack of co-ordination of movement, double vision, rapid eye movements are all reversible effects that may occur particularly if on long-term or high- dose treatment.
- Increase in number of fits (epileptic seizures) may occur during long-term treatment or in patients with a rare condition called porphyria.
- Infants and small children may start to dribble or drool because of increased production of saliva and secretions from the airways. Children should therefore be watched carefully as this might cause problems in breathing and/or severe choking and coughing.

- Rarely, nausea and stomach problems can occur.
- Rarely there may be hives, rashes, short-term hair loss or change in skin colouring
- Rarely, urinary incontinence (not being able to control when to pass water) may occur. There have been some isolated reports of:
- Changes to your blood or liver function (seen in test results).
- Early development of puberty in children. This effect is reversible.
- Unusual bleeds, including gastrointestinal bleeds
- Swelling of skin, tongue, lips, pharynx or face, hives or have difficulties breathing or swallowing (serious allergic reaction).
- High fever, agitation, confusion, trembling and abrupt contractions of muscles these may be signs of a rare condition called serotonin syndrome.
- Difficulties urinating
- Seizures (fits)
- Yellowing of the skin and the white in the eyes are signs of liver function impairment/hepatitis
- Fast, irregular heartbeat, fainting which could be symptoms of a life-threatening condition known as torsade de pointes
- Thoughts of harming or killing yourself,
- Sudden swelling of skin or mucosa (angioedemas)
- Feeling sick (nausea)
- Headache
- Blocked or runny nose (sinusitis)
- Decreased or increased appetite
- Anxiety, restlessness, abnormal dreams, difficulties falling asleep, feeling sleepy, dizziness, yawning, tremors, prickling of the skin
- Diarrhoea, constipation, vomiting, dry mouth
- Increased sweating
- Pain in muscle and joints (arthralgia and myalgia)
- Sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties achieving orgasm)
- Fatigue, fever
- Increased weight
- Nettle rash (urticaria), rash, itching (pruritus)
- Grinding one's teeth, agitation, nervousness, panic attack, confusion
- Disturbed sleep, taste disturbance, fainting (syncope)
- Enlarged pupils (mydriasis), visual disturbance, ringing in the ears (tinnitus)

- Loss of hair
- Excessive menstrual bleeding
- Irregular menstrual period
- Decreased weight
- Fast heart beat
- Swelling of the arms or legs
- Nosebleeds Rare
- Aggression, depersonalization, hallucination
- Slow heart beat
- Decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused)
- Dizziness when you stand up due to low blood pressure (orthostatic hypotension)
- Abnormal liver function test (increased amounts of liver enzymes in the blood)
- Movement disorders (involuntary movements of the muscles)
- Painful erections (priapism)
- Signs of abnormal bleeding e.g. from skin and mucous membranes (ecchymosis)
- Increased secretion of a hormone called ADH, causing the body to retain water and dilute the blood, reducing the amount of sodium (inappropriate ADH secretion)
- Flow of milk in men and in women that are not nursing
- Mania
- An increased risk of bone fractures has been observed in patients taking this type of medicines.
- Alternation of the heart rhythm (called “prolongation of QT interval”, seen on ECG, measuring electrical activity of the heart).

Withdrawal symptoms

Stopping Clonazepam suddenly may cause withdrawal symptoms. These include, shakes (tremors), sweating, agitation, problems sleeping, anxiety (sometimes severe), headaches, muscle pain, tension, restlessness, confusion, irritability and fits (epileptic seizures). In severe cases the following effects may happen: a feeling of being unreal, oversensitivity to noise, light and touch, numbness and tingling of the hands and feet or hallucinations. Gradual withdrawal of Clonazepam will help to reduce these effects.

Injury

Patients taking benzodiazepine medicines are at risk of falling and breaking bones. The risk is increased in the elderly and those taking other sedatives (including alcohol).

What is the most important information I should know about FELIZ S PLUS?

- FELIZ S PLUS contains benzodiazepines which can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.

- FELIZ S PLUS can make you sleepy or dizzy and can slow your thinking and motor skills. This may get better over time.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how FELIZ S PLUS affects you.
- FELIZ S PLUS may cause problems with your coordination, especially when you are walking or picking things up.

Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking FELIZ S PLUS until you talk to your healthcare provider.

- When taken with alcohol or drugs that cause sleepiness or dizziness, FELIZ S PLUS may make your sleepiness or dizziness worse.
- FELIZ S PLUS may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.
- Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
 - thoughts about suicide or dying
 - new or worse anxiety
 - trouble sleeping (insomnia)
 - acting on dangerous impulses
 - attempts to commit suicide
 - feeling agitated or restless
 - new or worse irritability
 - an extreme increase in activity and talking (mania)
 - new or worse depression
 - panic attacks or acting aggressive, being angry, or violent
 - other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviours, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms. Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

Do not stop FELIZ S PLUS without first talking to a healthcare provider.

- Stopping FELIZ S PLUS suddenly can cause serious problems. Stopping FELIZ S PLUS suddenly can cause seizures that will not stop (status epilepticus).

FELIZ S PLUS can cause abuse and dependence.

- Do not stop taking FELIZ S PLUS all of a sudden. Stopping FELIZ S PLUS suddenly can cause seizures that do not stop, hearing or seeing things that are not there (hallucinations), shaking, and stomach and muscle cramps.

- Talk to your healthcare provider about slowly stopping FELIZ S PLUS to avoid withdrawal symptoms.
- Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

FELIZ S PLUS can be abused or lead to dependence.

Keep FELIZ S PLUS in a safe place to prevent misuse and abuse. Selling or giving away FELIZ S PLUS may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

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 PLUS

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

9.6 Contents of the pack and other information

FELIZ S PLUS is available Blister strips of 15 tablets.
FELIZ S PLUS 5 is available strips of 10 tablets.

10. Details of manufacturer

FELIZ S PLUS

TORRENT PHARMACEUTICALS LTD.

32 No. Middle Camp, NH-10,
East District, Gangtok, Sikkim-737 135.

OR

Pure & Cure Healthcare Pvt. Ltd.
Plot No. : 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar – 249403 (Uttarakhand).

FELIZ S PLUS 5

TORRENT PHARMACEUTICALS LTD.

Vill. Bhud & Makhnu Majra,
Teh. Baddi-173 205, Dist. Solan (H.P.), INDIA.

11. Details of permission or licence number with date

FELIZ S PLUS

Mfg Lic No. M/563/2010 issued on 23.12.2016

OR

Mfg Lic No. 31/UA/2013 issued on 06.10.2020

FELIZ S PLUS 5

MNB/05/183 issued on 09.12.2020

12. Date of revision

Sep-2022

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/FELIZ S PLUS 5, 10 mg/Sep-2022/06/PI