

To be sold by retail on the prescription of a Registered Medical Practitioner only

FELIZ S PLUS/CLONOTRIL PLUS

1. Generic Name

Escitalopram Oxalate and Clonazepam Tablets I.P.

2. Qualitative and quantitative Composition:

FELIZ S PLUS 20/CLONOTRIL PLUS 20 mg/0.5 mg

Each film coated tablet contains:

Escitalopram Oxalate I.P.

Eq. to Escitalopram.....20 mg

Clonazepam I.P.....0.5 mg

Excipients.....q.s.

Colour: Titanium Dioxide I.P.

The List of excipients used are Starch, Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Mannitol, Polyvinyl Pyrolidone, Iso Propyl Alcohol, Methylene Chloride, Purified Talc, Colloidal Silicon Dioxide, Magnesium Sterate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol and Titanium Dioxide.

FELIZ S PLUS 5/CLONOTRIL PLUS 5/0.5

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, Acetone, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Hydroxy Propyl Methyl Cellulose, Talc, Titanium dioxide, PEG-6000

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: Escitalopram 5 mg/20 mg and Clonazepam 0.5 mg

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the treatment of patients with comorbid depression & anxiety disorders.

4.2. Posology and method of administration

Posology

Escitalopram:

Adults, the Elderly:

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.

Generalised anxiety disorder:

Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. Long term treatment of responders has been studied for at least 6 months in patients receiving 20 mg/day. Treatment benefits and dose should be re-evaluated at regular intervals.

Obsessive-Compulsive Disorder:

Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. Treatment benefits and dose should be re-evaluated at regular intervals.

Elderly patients (> 65 years of age)

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

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

Paediatric population:

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

Reduced renal function:

Dosage adjustment is not necessary in patients with mild or moderate renal impairment. Caution is advised in patients with severely reduced renal function (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.

Clonazepam:

Adults:

Initial dosage should not exceed 1 mg/day.

The maintenance dosage for adults normally falls within the range 4 to 8 mg. Elderly: The elderly are particularly sensitive to the effects of centrally depressant drugs and may experience confusion. It is recommended that the initial dose should not exceed 0.5 mg/day. These are total daily dosages which should be divided into 3 or 4 doses taken at intervals throughout the day. If necessary, larger doses may be given at the discretion of the physician, up to a maximum of 20 mg daily. The maintenance dose should be attained after 2 to 4 weeks of treatment.

Paediatric population:

To ensure optimum dosage adjustment, children should be given the 0.5 mg tablets.

Initial dosage should not exceed 0.25 mg/day for infants and small children (1 to 5 years) and 0.5 mg/day for older children and children aged 12 years and over: Do not take more medicine than the label tells you to.

Method of administration

For oral use. Take a single daily dose and may be taken with or without food.

4.3. Contraindications

Escitalopram

- Hypersensitivity to escitalopram or to any of the excipients.
- Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc.
- The combination of escitalopram with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome.
- Escitalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Escitalopram is contraindicated together with medicinal products that are known to prolong the QT interval.

Clonazepam

- Known hypersensitivity to benzodiazepines
- Hypersensitivity to the active substance or to any of the excipients.
- Acute pulmonary insufficiency
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Myasthenia gravis
- Severe hepatic insufficiency

Clonazepam 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

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.

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

Hyponatraemia:

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

Haemorrhage:

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

ECT (electroconvulsive therapy):

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

Serotonin syndrome:

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

St. John's wort:

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

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

Escitalopram

Contraindicated combinations:

Irreversible non-selective MAOIs

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective, irreversible monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued SSRI treatment and have been started on such MAOI treatment. In some cases, the patient developed serotonin syndrome. Escitalopram is contraindicated in combination with non-selective, irreversible MAOIs. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective, irreversible MAOI. Reversible, selective MAO-A inhibitor (moclobemide): Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO-A inhibitor such as moclobemide is contraindicated. If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.

Reversible, non-selective MAO-inhibitor (linezolid):

The antibiotic linezolid is a reversible non-selective MAO-inhibitor and should not be given to patients treated with escitalopram. If the combination proves necessary, it should be given with minimum dosages and under close clinical monitoring. Irreversible, selective MAO-B inhibitor (selegiline): In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome. Selegiline doses up to 10 mg/day have been safely co administered with racemic citalopram.

QT interval prolongation:

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

Combinations requiring precautions for use:

Serotonergic medicinal products:

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

Medicinal products lowering the seizure threshold:

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

Lithium, tryptophan:

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

St. John's Wort:

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

Haemorrhage:

Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped.

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency.

Alcohol:

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

Medicinal products inducing hypokalaemia/hypomagnesaemia:

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

Clonazepam

Since alcohol can provoke epileptic seizures, irrespective of therapy, patients must under no circumstances drink alcohol while under treatment with antiepileptic drugs. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy, or give rise to unpredictable side-effects.

Enhanced effects on sedation, respiration and haemodynamics may occur when clonazepam is co-administered with any centrally acting depressants e.g. alcohol, and other anticonvulsant (antiepileptic) agents, anaesthetics, hypnotics, psychoactive drugs and some analgesics as well as muscle relaxants and may result in mutual potentiation of drug effects.

In combination therapy with centrally-acting medications, the dosage of each drug must be adjusted to achieve the optimum effect. There is an increased sedative effect when clonazepam is given with tricyclic and tricyclic-related antidepressants, antihistamines (less so for non-sedating antihistamines and not usually for topically applied antihistamines), antipsychotics, baclofen, lofexidine, mirtazapine, nabilone, tizanidine.

Antiepileptic drugs

When clonazepam is 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. In concurrent treatment with phenytoin or primidone, a change, usually a rise, in the serum concentration of these two substances has occasionally been observed. Clonazepam itself does not induce the enzymes responsible for its own metabolism.

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.

Hepatic enzyme inhibitors and inducers

Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action. Metabolism of clonazepam is inhibited (i.e. plasma concentration is increased) by disulfiram, fluvoxamine and ritonavir.

Known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines. The selective serotonin reuptake inhibitors sertraline and fluoxetine do not affect the pharmacokinetics of clonazepam when administered concomitantly.

Special Precautions

The plasma concentration of clonazepam is possibly reduced by theophylline. Clonazepam may possibly antagonise effects of levodopa. There are enhanced hypotensive and sedative effects when clonazepam is given with alpha-blockers or with moxonidine.

There is an enhanced hypotensive effect when clonazepam is given with ACE inhibitors, adrenergic neurone blockers, angiotensin-II receptor antagonists, beta blockers, calcium channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates or nitroprusside.

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

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 paediatric 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

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. As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on clonazepam, it should be remembered that any increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility. Even if taken as directed, clonazepam can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is impaired. This effect is aggravated by consumption of alcohol. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment.

4.8. Undesirable effects

Most side effects do not require any medical attention and disappear as your body adjusts to the medicine. Consult your doctor if they persist or if you're worried about them.

- Delayed ejaculation
- Confusion
- Vomiting
- Memory impairment
- Drowsiness
- Tiredness
- Anorgasmia (decreased orgasm)
- Low sexual desire
- Nausea
- Diarrhea
- Uncoordinated body movements.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

Escitalopram

Toxicity

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Fatal cases of escitalopram overdose have rarely been reported with escitalopram alone; the

majority of cases have involved overdose with concomitant medications. Doses between 400 and 800mg of escitalopram alone have been taken without any severe symptoms.

Symptoms

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

Management

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures. ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

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 using 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.

5. Pharmacological properties

5.1. Mechanism of Action

Escitalopram

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.

Clonazepam

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

5.2. Pharmacodynamic properties

Escitalopram

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

Clinical efficacy

Major Depressive Episodes

Escitalopram has been found to be effective in the acute treatment of major depressive episodes in three out of four double-blind, placebo controlled short-term (8-weeks) studies. In a long-term relapse prevention study, 274 patients who had responded during an initial 8-week open label treatment phase with escitalopram 10 or 20 mg/day, were randomised to continuation with escitalopram at the same dose, or to placebo, for up to 36 weeks. In this study, patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

Social Anxiety Disorder:

Escitalopram was effective in both three short-term (12- week) studies and in responders in a 6-month relapse prevention study in social anxiety disorder. In a 24-week dose-finding study, efficacy of 5, 10 and 20 mg escitalopram has been demonstrated.

Generalised anxiety disorder:

Escitalopram in doses of 10 and 20 mg/day was effective in four out of four placebo-controlled studies. In pooled data from three studies with similar design comprising 421 escitalopram treated patients and 419 placebo-treated patients there were 47.5% and 28.9% responders respectively and 37.1% and 20.8% remitters. Sustained effect was seen from week 1. Maintenance of efficacy of escitalopram 20mg/day was demonstrated in a 24- to 76 week, randomised, maintenance of efficacy study in 373 patients who had responded during the initial 12-week open-label treatment.

Obsessive-compulsive disorder:

In a randomized, double-blind, clinical study, 20 mg/day escitalopram separated from placebo on the Y-BOCS total score after 12 weeks. After 24 weeks, both 10 and 20 mg/day escitalopram were superior as compared to placebo.

Prevention of relapse was demonstrated for 10 and 20 mg/day escitalopram in patients who responded to escitalopram in a 16-week open-label period and who entered a 24 week, randomized, double blind, placebo-controlled period.

Clonazepam

Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

Generalised EEG abnormalities are more readily suppressed by clonazepam than are focal EEG abnormalities such as focal spikes. Clonazepam has beneficial effects in generalised and focal epilepsies.

5.3. Pharmacokinetic properties

Escitalopram

Absorption:

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

Distribution:

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

Biotransformation:

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

Elimination:

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

Linearity:

There is linear pharmacokinetics. Steady-state plasma levels are achieved in about 1 week. Average steady-state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Elderly patients (> 65 years):

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

Reduced hepatic function:

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long, and the exposure was about 60% higher than in subjects with normal liver function. Reduced renal function: With racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (CL_{Cr} 10-53 ml/min). Plasma concentrations of the metabolites have not been studied, but they may be elevated.

Polymorphism:

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

Clonazepam

Absorption:

Clonazepam is quickly and completely absorbed after oral administration. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration. Routine monitoring of plasma concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects.

Distribution:

The mean volume of distribution of clonazepam is estimated at about 3 L/kg. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk.

Metabolism:

The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7 acetylamino compounds, with trace amounts of 3-hydroxy derivatives of all three compounds, and their glucuronide and sulfate conjugates. The nitro compounds are pharmacologically active, whereas the amino compounds are not.

Elimination:

The elimination half-life is between 20 and 60 hours (mean 30 hours). Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabelled oral dose of clonazepam is excreted in the urine and 10 - 30% in the faeces, almost exclusively in the form of free or conjugated metabolites. Less than 0.5% appears as unchanged clonazepam in the urine.

Pharmacokinetics in special clinical situations: Based on kinetic criteria no dose adjustment is required in patients with renal failure.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Escitalopram

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

In comparative toxicological studies in rats, escitalopram and citalopram caused cardiac toxicity, including congestive heart failure, after treatment for some weeks, when using dosages that caused general toxicity. The cardiotoxicity seemed to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at no-effect-level were in excess (8-fold) of those achieved in clinical use, while AUC for escitalopram was only 3- to 4-fold higher than the exposure achieved in clinical use. For citalopram AUC values for the S enantiomer were 6- to 7-fold higher than exposure achieved in clinical use. The findings are probably related to an exaggerated influence on biogenic amines i.e. secondary to the primary pharmacological effects, resulting in hemodynamic effects (reduction in coronary flow) and 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.

Clonazepam

Carcinogenicity:

Conventional studies of carcinogenic potential have not been conducted with clonazepam. However, in an 18-month chronic study in rats no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

Mutagenicity:

Genotoxicity tests using bacterial systems with in vitro, or host mediated metabolic activation did not indicate a genotoxic liability for clonazepam. Impairment of Fertility: Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and impaired pup survival at doses of 10 and 100 mg/kg/day.

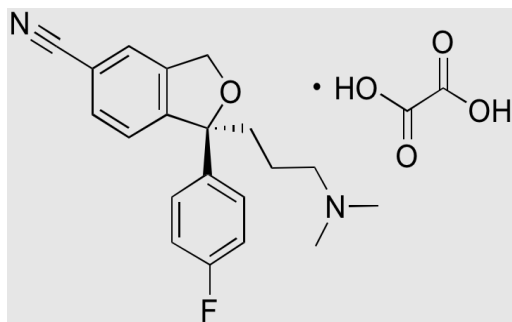
Teratogenicity:

No adverse maternal or embryo-foetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of up to 20 or 40 mg/kg/day, respectively. In several rabbit studies following doses of clonazepam of up to 20 mg/kg/day, a low, non-dose-related incidence of a similar pattern of malformations (cleft palate, open eyelids, fused sternebrae and limb defects) was observed.

As toxicokinetic evaluations have not been performed with clonazepam, it is not possible to determine the safety margin for the adverse effects observed in the nonclinical studies. The relevance of these findings to the patient population is unclear therefore a potential risk to man cannot be ruled out.

7. Description

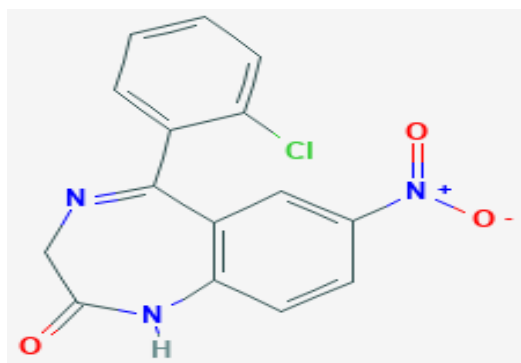
Escitalopram oxalate is designated (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate. C₂H₂O₄



Escitalopram oxalate is a white to slightly yellow powder. The molecular weight of Escitalopram oxalate is 414.4. It is freely soluble in methanol, in dimethyl-sulphoxide,

sparingly soluble in water, in ethanol, slightly soluble in ethyl acetate, practically insoluble in heptane.

Clonazepam is 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one having molecular formula of $C_{15}H_{10}ClN_3O_3$. and molecular weight is 315.71g/mol. The chemical structure is:



Clonazepam is a slightly yellowish, crystalline powder. It is slightly soluble in ethanol (95 percent), in methanol and practically insoluble in water.

FELIZ S PLUS 20/CLONOTRIL PLUS 20 /0.5

Escitalopram Oxalate and Clonazepam Tablets are white to off-white coloured, round, biconvex, film coated tablets, having both sides Plain.

The excipients used are Starch, Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Mannitol, Polyvinyl Pyrrolidone, Iso Propyl Alcohol, Methylene Chloride, Purified Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol and Titanium Dioxide.

FELIZ S PLUS 5/CLONOTRIL PLUS 5/0.5

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, Acetone, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Hydroxy Propyl Methyl Cellulose, Talc, Titanium dioxide, PEG-6000.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

FELIZ S PLUS 20/CLONOTRIL PLUS 20/0.5 is available in pack of 10 Tablets.

FELIZ S PLUS 5/CLONOTRIL PLUS 5/0.5 is available 10 strips of 10 Tablets each.

8.4. Storage and handing instructions

FELIZ S PLUS 20/CLONOTRIL PLUS 20 /0.5

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

FELIZ S PLUS 5/CLONOTRIL PLUS 5/0.5

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

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

FELIZ S PLUS 20/CLONOTRIL PLUS 20 /0.5

East African (India) Overseas

8 & 8A, Pharmacy, Selaqui,

Dehradun- 248011 (U.K.)

(WHO-GMP Certified Company)

FELIZ S PLUS 5/CLONOTRIL PLUS 5/0.5

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 20 /CLONOTRIL PLUS 20 /0.5

Mfg. License No.: 70/UA/2009 Issued on 18.06.2024.

FELIZ S PLUS 5/CLONOTRIL PLUS 5/0.5

MNB/05/183 issued on 09.12.2020.

12. Date of revision

NA

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IN/FELIZ S PLUS /CLONOTRIL PLUS 20/5 mg and 0.5 mg/APR 2026/01/PI