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

CLONOTRIL PLUS
(Escitalopram Oxalate and Clonazepam Tablets I.P.)

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 CLONOTRIL 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. CLONOTRIL 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: Information for Patients (9), and Use in Specific Populations: Paediatric Use (4.6)].***

1. Generic Name:

Escitalopram Oxalate and Clonazepam Tablets IP

2. Qualitative and quantitative composition:

Each film coated tablet contains:

Escitalopram Oxalate I.P. equivalent to Escitalopram 10 mg

Clonazepam I.P. 0.5 mg

Colours: Yellow Oxide of Iron and Titanium dioxide I.P.

The excipients used are Starch, Lactose, Acetone, Polyvinyl pyrrolidone, Sodium Starch glycollate, Magnesium stearate, Colloidal silicon dioxide, Ferric oxide yellow hydroxy propyl methyl cellulose, Talc, Colloidal silicon dioxide, Titanium dioxide, Poly ethylene glycol.

3. Dosage form and strength:

Dosage form: Film coated tablet

Strength: Escitalopram Oxalate 10 mg and Clonazepam Tablets 0.5 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Clonotril Plus is indicated for the treatment of patients with co-morbid depression and anxiety disorder.

4.2 Posology and method of administration:

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 CLONOTRIL PLUS 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.
- CLONOTRIL PLUS is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- CLONOTRIL PLUS 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.
- CLONOTRIL PLUS 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 nonpsychiatric.

Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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

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

Escitalopram

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.

Hyponatremia
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.

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.

4.5 Drug-Interaction:

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-steriodal 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 populations

Pregnancy: CLONOTRIL PLUS 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 CLONOTRIL PLUS 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 CLONOTRIL PLUS 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 CLONOTRIL PLUS and any potential adverse effects on the breastfed infant from CLONOTRIL PLUS or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of escitalopram-containing medicines have been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder. Although maintenance efficacy in adolescent patients with major depressive disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. The safety and effectiveness of escitalopram have not been established in pediatric (younger than 12 years of age) patients with major depressive disorder. In a reported 24-week, open- label safety study in 118 children (aged 7 to 11 years) who had major depressive disorder, the safety findings were consistent with the known safety and tolerability profile. Safety and effectiveness of escitalopram has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth

should be performed in children and adolescents treated with an SSRI.

Geriatric Use: Because CLONOTRIL PLUS undergoes hepatic metabolism, it is possible that liver disease will impair elimination. Metabolites of CLONOTRIL PLUS 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

System organ class	**Undesirable Effect**
Blood and the lymphatic system disorders	Isolated cases of blood dyscrasias
Immune system disorders	Allergic reaction and a very few cases of anaphylaxis and angioedema
Endocrine disorders	Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported
Psychiatric disorders and Paradoxical Reactions	Anterograde amnesia (risk increases at higher dosages). Amnestic effects may be associated with inappropriate behaviour. Depression, loss of libido, impotence. 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. 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.
Nervous system disorders	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. These undesirable effects occur relatively frequently and may disappear gradually in the course of the treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment. Headache was observed in rare cases. Causing of generalised fits was observed very rarely. 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.
Eye disorders	Double vision and nystagmus are reversible disorders and occur particularly in long term or high-dose treatment.
Cardiac Disorders	Cardiac failure including cardiac arrest has been reported
Respiratory, thoracic and mediastinal disorders	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. In infants and small children, and particularly those with a degree of mental impairment, salivary or bronchial hypersecretion with drooling may occur. Supervision of the airway may be required.
Gastrointestinal disorders	nausea, gastrointestinal symptoms
Hepato-biliary disorders	Isolated cases of abnormal liver function tests have been reported
Skin and subcutaneous tissue disorders	urticaria, pruritus, transient hair loss, pigmentation changes

Musculoskeletal, connective tissue and bone disorders	Muscle weakness, occasional muscular hypotonia
Renal and urinary disorders	urinary incontinence
Reproductive System and Breast Disorders	In rare cases erectile dysfunction or loss of libido may occur
General disorders and administration site conditions	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.
Injury, Poisoning and Procedural Complications	An increased risk for falls and fractures has been reported in elderly benzodiazepine users
Investigations	In rare cases decreased platelet count may occur. As with other benzodiazepines, isolated cases of blood dyscrasias.

Escitalopram

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

Psychiatric disorders	Anxiety, restlessness, abnormal dreams libido decreased Female: anorgasmia
	Bruxism, agitation, nervousness, panic attack, confusional state
	Aggression, depersonalisation, hallucination
	Mania, suicidal ideation, suicidal behaviour
Nervous system disorders	Headache
	Insomnia, somnolence, dizziness, paraesthesia, tremor
	Taste disturbance, sleep disorder, syncope
	Serotonin syndrome
	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia
Eye disorders	Mydriasis, visual disturbance
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Tachycardia
	Bradycardia
	Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes
Vascular disorders	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Sinusitis, yawning
	Epistaxis
Gastrointestinal disorders	Nausea
	Diarrhoea, constipation, vomiting, dry mouth
	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepatobiliary disorders	Hepatitis, liver function test abnormal

Skin and subcutaneous tissue disorders	Sweating increased
	Urticaria, alopecia, rash, pruritus
	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia
Renal and urinary disorders	Urinary retention
Reproductive system and breast disorders	Male: ejaculation disorder, impotence
	Female: metrorrhagia, menorrhagia
	Galactorrhoea Male: priapism
General disorders and administration site conditions	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 resedation, 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

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

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

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

5.2 Pharmacodynamic properties:

Clonazepam

The precise mechanism by which clonazepam exerts its anti-seizure and anti-panic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

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 Tmax) 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 (Vd,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 demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible. The elimination half-life (t½ β) after multiple dosing is about 30 hours and the oral plasma clearance (Cloral) 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.

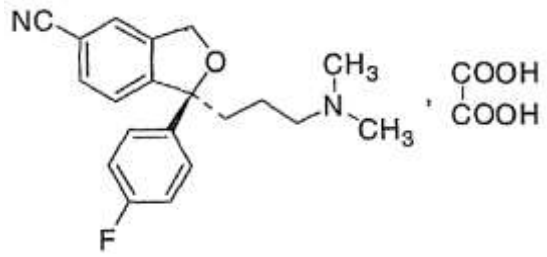
Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment 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.

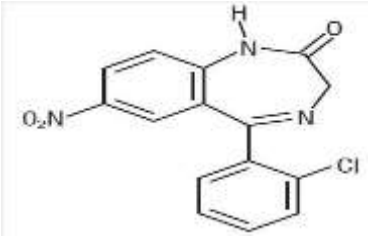
Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in implantation number and abnormal sperm at exposure well in excess of human exposure. No animal data related to this aspect are available for escitalopram.

7. Description:

Escitalopram Oxalate is (S)-1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrileoxalate. It is white to slightly yellow powder. Freely soluble in methanol, in dimethylsulphoxide; sparingly soluble in water, in ethanol; slightly soluble in ethyl acetate; practically insoluble in heptane. Its molecular formula is C20H21FN2O, C2H2O4 and its molecular weight is 414.4. The structural formula is:



Clonazepam is 5-(2-chlorophenyl)-7-nitro-1, 3-dihydro-2H-1,4-benzodiazepin-2-one. It is a slightly yellowish, crystalline powder. It is a slightly soluble in ethanol (95 per cent), in methanol and practically insoluble in water. Its molecular formula is C15H10ClN3O3 and its molecular weight is 315.7. The structural formula is:



Escitalopram Oxalate and clonazepam tablets are a reddish coloured, circular shaped, slightly biconvex, and film coated tablet contains plain on both sides. The excipients used are Starch,

Lactose, Acetone, Polyvinyl pyrrolidone, Sodium Starch glycollate, Magnesium stearate, Colloidal silicon dioxide, Ferric oxide yellow hydroxy propyl methyl cellulose, Talc, Colloidal silicon dioxide, Titanium dioxide, Poly ethylene glycol.

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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:

Clonotril Plus available in Blister pack 15 Tablets

8.4 Storage and handing instructions:

STORE AT A TEMPERATURE NOT EXCEEDING 30° C, PROTECTED FROM MOISTURE.

9. Patient Counselling Information

Package leaflet: Information for the user

CLONOTRIL PLUS

Escitalopram Oxalate and Clonazepam Tablets IP

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.
- 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. See section 4.

What is in this leaflet?

9.1 What CLONOTRIL PLUS is and what it is used for

The name of your medicine is CLONOTRIL 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)). These medicines act on the serotonin-system in the brain by increasing the serotonin level. Disturbances in the serotonin-system are considered an important factor in the development of depression and related diseases.) It is used to treat comorbid depression & anxiety disorders.

9.2 What you need to know before you take CLONOTRIL PLUS

Do not take CLONOTRIL 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

Talk to your doctor or pharmacist before taking CLONOTRIL PLUS if:

- 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 CLONOTRIL PLUS can harm your unborn baby.
- Tell your healthcare provider right away if you become pregnant while taking CLONOTRIL PLUS. You and your healthcare provider will decide if you should take CLONOTRIL PLUS while you are pregnant.
- Are breastfeeding or plan to breastfeed? CLONOTRIL PLUS can pass into breast milk. You and your healthcare provider should decide how you will feed your baby while you take CLONOTRIL PLUS.

If you have epilepsy. Treatment with CLONOTRIL PLUS should be stopped if seizures occur or if there is an increase in the seizure frequency.

- If you have diabetes. Treatment with CLONOTRIL PLUS may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.
- If you have a decreased level of sodium in the blood.
- If you have a tendency to easily develop bleedings or bruises.
- If you are receiving electroconvulsive treatment.
- If you have coronary heart disease.
- If you suffer or have suffered from heart problems or have recently had a heart attack.
- If you 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).
- If you experience a fast or irregular heartbeat, fainting, collapse or dizziness on standing up, which may indicate abnormal functioning of the heart rate.

- If you 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

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Other medicines and CLONOTRIL PLUS

Tell your healthcare provider about all the medicines you take, including prescription and over-the counter medicines, vitamins, and herbal supplements. Taking CLONOTRIL PLUS with certain other medicines can cause side effects or affect how well CLONOTRIL 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 CLONOTRIL PLUS. After stopping CLONOTRIL PLUS you must allow 7 days before taking any of these medicines.
- "Reversible, selective MAO-An 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 CLONOTRIL 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 (triclcylic 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 CLONOTRIL 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 CLONOTRIL 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 CLONOTRIL 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 CLONOTRIL PLUS, if you are pregnant or breast-feeding, unless you and your doctor have discussed the risks and benefits involved.

If you take CLONOTRIL 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 CLONOTRIL PLUS. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like CLONOTRIL 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 CLONOTRIL PLUS should never be stopped abruptly.

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

CLONOTRIL 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

You are advised not to drive a car or operate machinery until you know how CLONOTRIL PLUS affects you.

9.3 How to take CLONOTRIL PLUS

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

The recommended dose is **one tablet once a day with food**. Treatment should continue for as long as your doctor tells you. Usually this is for at least 6 to 12 months and may be for many years.

If you take more CLONOTRIL PLUS than you should

If you accidentally take more than the recommended dose of CLONOTRIL PLUS you may be at increased risk of experiencing possible side effects with this medicine (see section 4, *Possible side effects*).

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take CLONOTRIL PLUS

It is important not to miss a dose of CLONOTRIL PLUS. If you do miss a dose, work out how long since you should have taken it.

- **If it is less than 18 hours** after you usually take CLONOTRIL PLUS, take it as soon as you can, and then take your next dose at its regular time.

- **If it is more than 18 hours** after you usually take CLONOTRIL PLUS, then do not take the missed dose. Wait and take the next dose at the regular time. **Do not take a double dose** to make up for a forgotten tablet.

If you are sick (vomit) less than 1 hour after taking CLONOTRIL PLUS, take another tablet. You do not need to take another tablet if you are sick (vomit) more than 1 hour after taking CLONOTRIL PLUS.

If you stop taking CLONOTRIL PLUS

Do not stop taking CLONOTRIL PLUS without your doctor's advice. Stopping treatment with CLONOTRIL PLUS may cause your hepatitis B to get worse. In some patients with advanced liver disease or cirrhosis, this could be life-threatening. If you stop taking CLONOTRIL PLUS, you will need regular health checks and blood tests for several months to check your hepatitis B infection

- **Talk to your doctor** before you stop taking CLONOTRIL PLUS for any reason, particularly if you are experiencing any side effects or you have another illness.
- **Tell your doctor immediately** about new or unusual symptoms after you stop treatment,
- particularly symptoms you associate with hepatitis B infection.
- **Talk to your doctor** before you restart taking CLONOTRIL PLUS tablets.

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

9.4 Possible side effects

Changes Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor immediately if you experience any of the following serious side effects – you may need urgent medical treatment:

- 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 behavior (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.

Uncommon (may affect up to 1 in 100 people):
- Unusual bleeds, including gastrointestinal bleeds Rare (may affect up to 1 in 1000 people):
- 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. Not known (frequency cannot be estimate from the available data):
- 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) in addition to above the following side effects have been reported: Very common (may affect more than 1 in 10 people):
- Feeling sick (nausea)
- Headache

Common (may affect up to 1 in 10 people):

- 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 Uncommon (may affect up to 1 in 100 people):
- 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 (may affect up to 1 in 1000 people):
- Aggression, depersonalization, hallucination
- Slow heart beat Not known (frequency cannot be estimate from the available data):
- 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). In addition, a number of side effects are known to occur with drugs that work in a similar way to escitalopram (the active ingredient of CLONOTRIL PLUS). These are:
- Motor restlessness (akathisia)
- Loss of appetite
- drowsiness
- problems with walking and coordination
- problems with memory
- Depression

Withdrawal symptoms
Stopping CLONOTRIL PLUS 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 CLONOTRIL PLUS?
- CLONOTRIL PLUS contains Benzodiazepines which can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.

- CLONOTRIL 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 CLONOTRIL PLUS affects you.
- CLONOTRIL 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 CLONOTRIL PLUS until you talk to your healthcare provider.

When taken with alcohol or drugs that cause sleepiness or dizziness, CLONOTRIL PLUS may make your sleepiness or dizziness worse.

CLONOTRIL 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 o acting aggressive, being angry, or violent
- other unusual changes in behaviour 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 CLONOTRIL PLUS without first talking to a healthcare provider.

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

CLONOTRIL PLUS can cause abuse and dependence.

- Do not stop taking CLONOTRIL PLUS all of a sudden. Stopping CLONOTRIL 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 CLONOTRIL 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.

CLONOTRIL PLUS **can be abused or lead to dependence**. Keep CLONOTRIL PLUS in a safe place to prevent misuse and abuse. Selling or giving away CLONOTRIL 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, 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.

9.5 How to store CLONOTRIL PLUS

STORE AT A TEMPERATURE NOT EXCEEDING 30° C, PROTECTED FROM MOISTURE.

9.6 Contents of the pack and other information

What CLONOTRIL PLUS contains

Clonotril Plus available in Blister pack 15 Tablets

The active substance is **Clonazepam and Escitalopram.**

The excipients used are Starch, Lactose, Acetone, Polyvinyl pyrrolidone, Sodium Starch glycollate, Magnesium stearate, Colloidal silicon dioxide, Ferric oxide yellow hydroxy propyl methyl cellulose, Talc, Colloidal silicon dioxide, Titanium dioxide, Poly ethylene glycol.

10. Details of manufacturer

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.

11. Details of permission or licence number with date

Torrent Pharmaceuticals Ltd.

M/563/2010 Dated on 04.10.2017

Pure & cure Healthcare Pvt. Ltd.

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

12. Date of revision

March 2021

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/CLONOTRIL PLUS 10, 0.5 mg/Mar-21/04/PI