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

C-PRAM S PLUS

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

1. **Generic Name**

   Escitalopram and Clonazepam Tablets I.P.

2. **Qualitative and quantitative composition**

   C-PRAM S PLUS

   Each film-coated tablet contains:

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

   Clonazepam I.P. ……..0.5 mg

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

   The Excipients used are Lactose, Starch, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Ferric Oxide Yellow,Acetone, Propylene Glycol, Hydroxy Propyl Methyl Celu, Pigment Mix-A IH, Talc IP.

   C-PRAM S PLUS 0.25

   Each film-coated tablet contains:

   Escitalopram Oxalate IP

Equivalent to Escitalopram……. 10 mg

Clonazepam IP …… 0.25 mg

Excipients……. q.s.

Colour: Ferric Oxide Red NF

The excipients are Starch, Microcrystalline Cellulose, Povidone K 30, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Talc, Magnesium stearate, hydroxy propyl methyl cellulose, Methylene dichloride, Titanium dioxide, Polyethylene glycol, Castor oil.

3. Dosage form and strength

C-PRAM S PLUS

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

C-PRAM S PLUS 0.25

Film coated (Escitalopram 10 mg + Clonazepam 0.25 mg) tablets

4. Clinical particulars

4.1 Therapeutic indication

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

4.2 Posology and method of administration

Posology
As directed by the physician

4.3 Contraindications

- Hypersensitivity to the active substance (Clonazepam and Escitalopram)
- History of sensitivity to benzodiazepines. Hypersensitivity to any of the excipients.
- Clinical or biochemical evidence of significant liver disease.
- Acute narrow angle glaucoma (it may be used in patients with open angle glaucoma who are receiving appropriate therapy).
- Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors) is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc.
- The combination of Escitalopram and Clonazepam tablets with reversible MAO-an inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome.
- Escitalopram and Clonazepam tablets is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
- Escitalopram and Clonazepam tablets is contraindicated together with medicinal products that are known to prolong the QT interval.
- Acute pulmonary insufficiency; severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency.

- Escitalopram and Clonazepam tablets must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol.

4.4 Special warnings and precautions for

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

Use in children and adolescents under 18 years of age

Escitalopram should not be used in the treatment of children and adolescents under the age of 18 years. Suicide related behaviours (suicide attempt and suicidal thoughts) and hostility (predominately aggression, oppositional behaviour and anger) were more frequently observed in clinical trials - among children and adolescents 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 children and adolescents 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.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which escitalopram is prescribed can also be associated with an increased risk of Suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than

25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and care givers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Akathisia/psychomotor restlessness

The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is more 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.

SSRIs/SNRIs may increase the risk of postpartum haemorrhage.

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, opioids (such as buprenorphine and 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.

Herb of St. John (St. John´s Wort)

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

Discontinuation symptoms seen when stopping treatment

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on treatment discontinuation occurred in approximately 25% of patients treated with escitalopram and 15% of patients taking placebo.

The risk of discontinuation symptoms may be dependent on several factors, including the duration and dose of therapy, and the rate of dose reduction. Dizziness, sensory disturbances (including

paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity.

They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose.

Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that escitalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

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 hypokalemia, 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 hypokalemia 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.

Sexual dysfunction

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

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 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 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 and Clonazepam tablets is used with opioids.

Interference with Cognitive and Motor Performance: Since Escitalopram 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 and Clonazepam tablets therapy.

PRECAUTIONS

Worsening of Seizures: When used in patients in whom several different types of seizure disorders coexist, Escitalopram 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 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 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 and Clonazepam tablets, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing Escitalopram and Clonazepam tablets, gradual withdrawal is essential.

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

Caution in Renally Impaired Patients: Metabolites of Escitalopram 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 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 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 and Clonazepam tablets may have a porphyrogenic effect and should be used with care in patients with porphyria.

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.

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

<u>Clonazepam</u>

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

Pharmacokinetic interactions:

Influence of other medicinal products on the pharmacokinetics of Escitalopram:

The metabolism of escitalopram is mainly mediated by CYP2C19. CYP3A4 and CYP2D6 may also contribute to the metabolism although to a smaller extent. The metabolism of the major metabolite S-DCT (demethylated escitalopram) seems to be partly catalysed by CYP2D6.

Co-administration of escitalopram with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram.

Co-administration of escitalopram with cimetidine 400 mg twice daily (moderately potent general enzyme-inhibitor) resulted in a moderate (approximately 70%) increase in the plasma concentrations of escitalopram. Caution is advised when administering escitalopram in combination with cimetidine. Dose adjustment may be warranted.

Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluconazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment.

Effect of escitalopram on the pharmacokinetics of other medicinal products:

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-

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

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

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

4.6 Use in special populations

Pregnancy: Escitalopram 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 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 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 and Clonazepam tablets and any potential adverse effects on the breastfed infant from Escitalopram and Clonazepam tablets or from the underlying maternal condition.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clonazepam

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

System organ class	Undesirable Effect
	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.

System organ class	Undesirable Effect
Gastrointestinal	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

Adverse reactions known for SSRIs and also reported for escitalopram in either placebo-controlled clinical studies or as spontaneous post-marketing events are listed below by system organ class and frequency.
Frequencies are taken from clinical studies; they are not placebo-corrected. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (≤1/10,000), or not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Rare	Anaphylactic reaction
Endocrine disorders	Not known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Decreased appetite, increased appetite, weight increased
	Uncommon	Weight decreased
	Not known	Hyponatraemia, anorexia[2]
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams libido decreased Female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalisation, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour[1]
Nervous system disorders	Very common	headache
	Common	Insomnia, somnolence, dizziness, paraesthesia, tremor
	Uncommon	Taste disturbance, sleep disorder, syncope
	Rare	Serotonin syndrome
	Not known	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia[2]
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes
Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea, constipation, vomiting, dry mouth
	Uncommon	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepatobiliary disorders	Not known	Hepatitis, liver function test abnormal

Skin and subcutaneous tissue disorders	Common	Sweating increased
	Uncommon	Urticaria, alopecia, rash, pruritus
	Not known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia
Renal and urinary disorders	Not known	Urinary retention
Reproductive system and breast disorders	Common	Male: ejaculation disorder, impotence
	Uncommon	Female: metrorrhagia, menorrhagia
	Not known	Postpartum haemorrhage* Galactorrhoea Male: priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

[1] Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation.
[2] These events have been reported for the therapeutic class of SSRIs.
[*] This event has been reported for the therapeutic class of SSRIs/SNRIs.

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.

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.

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

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000

fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-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 exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects.

Escitalopram

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

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 months 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 reported 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 reported 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.

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

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 (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.

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% 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.

Elimination

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.

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, when compared with younger patients. Systemic exposure (AUC) is about 50 % higher in elderly compared to young healthy volunteers.

Impaired 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.

Impaired renal function

With racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (CLcr 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 CYP_2D_6.

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.

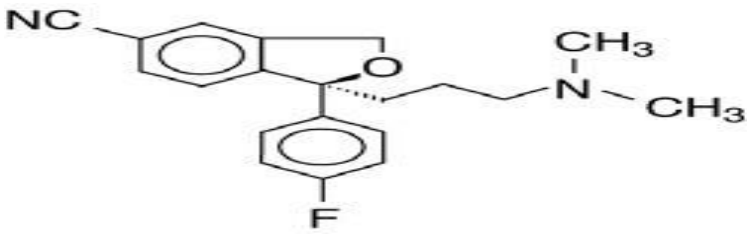
Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment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

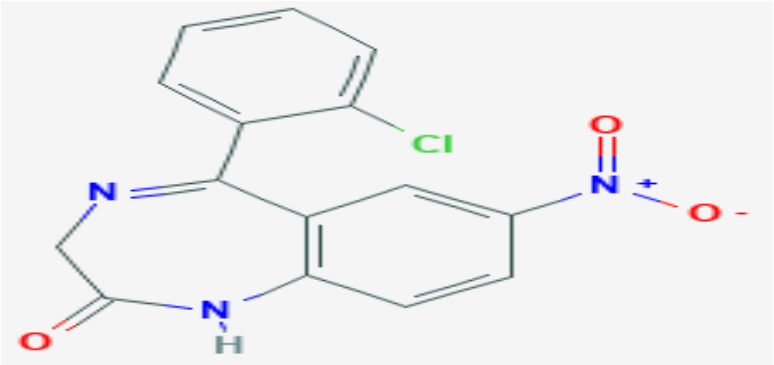
7. Description

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



•$C_2H_2O_4$

Clonazepam is 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-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:



C-PRAM S PLUS

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

C-PRAM S PLUS 0.25

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, Microcrystalline Cellulose, Povidone K 30, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Talc, Magnesium stearate, hydroxy propyl methyl cellulose, Methylene dichloride, Titanium dioxide, Poly ethylene glycol, Castor oil.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

C-PRAM S PLUS is available in blister strips of 10 tablets

C-PRAM S PLUS 0.25 is available in Blister pack of 10 tablets.

8.4 Storage and handing instructions

C-PRAM S PLUS

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

C-PRAM S PLUS 0.25

Store in a cool & dry place. Protect from light.

9. Patient counselling information

C-PRAM S PLUS

Escitalopram and Clonazepam Tablets I.P.

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

• Keep this leaflet. You may need to read it again.

• Keep all medicines out of reach of children

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What C-PRAM S PLUS is and what it is used for

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

9.2 What you need to know before you take C-PRAM S PLUS

Do not take C-PRAM S PLUS

- If you are allergic to clonazepam or any of the other ingredients of this medicine.
- If you are allergic to other benzodiazepine medicines and Escitalopram or any of the other ingredients of this medicine.
- Have significant liver disease.
- Have an eye disease called acute narrow angle glaucoma.
- If you take other medicines which belongs to a group called MAO inhibitors, including selegiline (used in the treatment of Parkinson's disease), moclobemide (used in the treatment of depression) and linezolid (an antibiotic).

- If you are born with or have had an episode of abnormal heart rhythm (Seen at ECG; an examination to evaluate how the heart is functioning).
- If you take medicines for heart rhythm problems or that may affect the heart's rhythm.

Warnings and precautions

Tell your healthcare provider if you,

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

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 C-PRAM S PLUS

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

Do not start or stop other medicines without talking to your healthcare provider.

Tell your doctor if you are taking any of the following medicines:.

- Non-selective monoamine oxidase inhibitors (MAOIs)", containing phenelzine, iproniazid, isocarboxazid, nialamide, and tranylcypromine as active ingredients. If you have taken any of these medicines you will need to wait 14 days before you start taking C-PRAM S PLUS. After stopping C-PRAM S 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 mayincrease 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 C-PRAM S PLUS in order to verify that your dose of anticoagulant is still adequate.
- Mefloquine (used to treat Malaria), bupropion (used to treat depression) and tramadol (used to treat severe pain) due to a possible risk of a lowered threshold for seizures.
- Neuroleptics (medicines to treat schizophrenia, psychosis) and antidepressants (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 C-PRAM S PLUS may need to be adjusted.
- Medicines that decrease blood levels of potassium or magnesium, as these conditions increase the risk of life-threatening heart rhythm disorders. Do not take C-PRAM S PLUS if you take medicines for heart rhythm problems or medicines that may affect the heart's rhythm, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine). If you have any further questions about this, you should speak to your doctor.
- Do not take C-PRAM S PLUS if you take medicines for heart rhythm problems or medicines that may affect the heart's rhythm, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine). If you have any further questions about this you should speak to your doctor.

Pregnancy and breast-feeding

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

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

Make sure your midwife and/or doctor know you are on C-PRAM S PLUS. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like C-PRAM S PLUS may increase the risk of a serious condition in babies, called persistent pulmonary

hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens

to your baby, you should contact your midwife and/or doctor immediately.

If used during pregnancy C-PRAM S PLUS should never be stopped abruptly. It

is expected that escitalopram will be excreted into breast milk.

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

Driving and using machines

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

9.3 How to take C-PRAM S 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 C PRAM S than you should

If you accidentally take more than the recommended dose of C PRAM PLUS you may be at increased risk of experiencing possible side effects with this medicine.

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 C PRAM PLUS

It is important not to miss a dose of C PRAM 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 C PRAM 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 C PRAM 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 C PRAM PLUS, take another tablet. You do not need to take another tablet if you are sick (vomit) more than 1 hour after taking C PRAM PLUS.

If you stop taking C PRAM PLUS

Do not stop taking C PRAM PLUS without your doctor's advice. Stopping treatment with C PRAM 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 C PRAM 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 C PRAM 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 C PRAM PLUS tablets.

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

9.4 Possible side effects

Clonazepam:

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects below may sometimes happen.

Important side effects to look out for-

See a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- thoughts of harming or killing yourself
- allergic reactions – the signs may include skin rash, flaking skin, boils, sore lips and mouth, swelling of the face, fever, sudden wheezing, fluttering or tightness of the chest or collapse.

Effects on the heart

If you notice any of the following effects, see a doctor straight away.

The signs may include:

- 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.

Effects on behaviour

If you notice any of the following effects, talk to your doctor as they may want you to stop taking Clonazepam. The signs may include:

- being aggressive, excited, irritable, nervous, agitated, hostile or anxious
- problems sleeping, nightmares or vivid dreams
- mental problems such as seeing or hearing things that are not really there (hallucinations), believing in things that are not real (delusions) or problems with your speech
- types of fits (seizures) that you have not had before.

Elderly patients

- Older patients taking benzodiazepine medicines have a higher risk of falling and breaking bones.

Other possible side effects-

When you start taking Clonazepam you may notice the following effects:

- feeling drowsy and tired
- feeling dizzy and light-headed
- weak or floppy muscles or jerky movements (poor coordination)
- feeling unsteady when walking.

If you notice any of these effects, talk to your doctor. Your doctor may be able to help you by giving you a lower dose of Clonazepam and then increasing it slowly.

The following may occur at any time during your treatment:

Mind and nervous system

- poor concentration, confusion or a feeling of being lost (disorientation)
- feeling restless
- difficulty remembering new things
- headache
- depression
- slowing or slurring of speech
- poor coordination, including feeling unsteady when walking
- an increase in how often you have fits.

Liver, kidney and blood

- changes in how well your liver is working (shown by blood tests)

loss of bladder control

blood problems - the signs may include feeling tired, bruising easily, being short of breath and nose bleeds. Your doctor may want to give you blood tests from time to time.

Stomach and gut

- feeling sick (nausea)
- stomach upset.

Eyes

- double vision
- jerky movements of the eyes (nystagmus).

<u>Escitalopram;</u>

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

The side effects usually disappear after a few weeks of treatment. Please beware that many of the effects may also be symptoms of your illness and therefore will improve when you start to get better.

If you experience any of the following symptoms you should contact your doctor or go to the hospital straight away:

Uncommon (may affect up to 1 in 100 people):

• Unusual bleeds, including gastrointestinal bleeding

Rare (may affect up to 1 in 1,000 people):

• If you experience swelling of skin, tongue, lips, pharynx or face, hives or have difficulties breathing or swallowing (serious allergic reaction).

• If you have a 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 estimated from the available data):

• Difficulties urinating

• Seizures (fits), see also section 2 "Warnings and precautions"

• Thoughts of harming yourself or thoughts of killing yourself, see also section 2 "Warnings and precautions"

• Yellowing of the skin and the white in the eyes are signs of liver function impairment/ hepatitis.

• Fast, irregular heart beat, fainting which could be symptoms of a life-threatening condition known as torsade de pointes.

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 and 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 attacks, confusion state

• 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

• Vaginal bleeding

• Decreased weight

• Fast heartbeat

• Swelling of the arms or legs

• Nosebleeds

Rare (may affect up to 1 in 1,000 people):

• Aggression, depersonalisation, hallucination

• Slow heart beat

Not known (frequency can not be estimated 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)

• Bleeding disorders including skin and mucous bleeding (ecchymosis) and low level of blood platelets (thrombycytopenia)

• Heavy vaginal bleeding shortly after birth (postpartum haemorrhage), see Pregnancy in section 2 for more information

• Sudden swelling of skin or mucosa (angioedemas)

• Increase 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 medicine

• Alteration 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 similar way to escitalopram (the active ingredient of Escitalopram Tablets). These are :

• Motor restlessness (akathisia)

• Loss of appetite (Anorexia)

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 C-PRAM S PLUS

C-PRAM S PLUS

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

C-PRAM S PLUS 0.25

Store in a cool & dry place. Protect from light.

9.6 Contents of the pack and other information

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

C-PRAM S PLUS:

The excipients used are Lactose, Starch, Magnesium Stearate, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Ferric oxide Yellow, Acetone, Propylene Glycol, HYDROXY PROPYL METHYL CELU, PIGMENT MIX-A IH, TALC IP.

C-PRAM S PLUS 0.25:

The excipients used are Starch, Microcrystalline Cellulose, Povidone K 30, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Talc, Magnesium stearate, hydroxy propyl methyl cellulose, Methylene dichloride, Titanium dioxide, Polyethylene glycol, Castor oil.

Pack Details:

C-PRAM S PLUS is available in blister strips of 10 tablets

C-PRAM S PLUS 0.25 is available in Blister pack of 10 tablets.

10. Details of manufacturer

C-PRAM S PLUS

Torrent pharmaceuticals Ltd.

32 No. Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135.

OR

Pure & Cure Healthcare Pvt. Ltd

Plot no. 26A, 27-30, Sector-8A, IIE, SIDCUL,

Ranipur, Haridwar (Uttarakhand)-249403

C-PRAM S PLUS 0.25

M/S. GKM NEW PHARMA

Spl. Type Plot No. 5,6,7,8

PIPDIC Electronic Park, Thirubuvanai, Puducherry- 605 107

11. Details of permission or licence number with date

C-PRAM S PLUS

M/563/2010 issued on 17.12.2018

OR

Pure & Cure Healthcare Pvt. Ltd

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

C-PRAM S PLUS 0.25

Mfg Lic. No. 09 13 2634 issued on 09 Feb. 2018

12. Date of revision

MAR-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/C-PRAM S PLUS 10mg, 0.5mg/0.25mg /Mar-22/02/PI