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 Szetalo Plus MD 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. Szetalo plus MD is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

To be prescribed by Registered Medical Practitioner only

1. GENERIC NAME & BRAND NAME

Escitalopram Oxalate & Clonazepam Mouth Dissolving Tablets
Szetalo Plus® MD

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mouth dissolving tablet contains:
Escitalopram Oxalate I.P.
equivalent to Escitalopram 10 mg
Clonazepam I.P. 0.5 mg
Colour: Lake Erythrosine

3. DOSAGE FORM AND STRENGTH

Refer section 1 & 2.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of co-morbid depression with anxiety disorder.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

One Tablet once in a day orally or as directed by physician. Fixed dose combination may be replaced by Escitalopram after initial treatment of 2-3 weeks.

4.3 CONTRAINDICATIONS

• Hypersensitivity to benzodiazepines or to other ingredients of the medicinal product.

• Escitalopram is not recommended in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide or within 14 days of discontinuing treatment with a MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide.
• Escitalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome.
• Escitalopram is contraindicated together with medicinal products that are known to prolong the QT interval.
• Concomitant use in patients taking pimozide is contraindicated.
• Severe respiratory insufficiency
• Severe hepatic insufficiency
• Acute pulmonary insufficiency
• Sleep apnoea syndrome
• Myasthenia gravis
• Narrow angle glaucoma

4.4 SPEACIAL WARNINGS AND PRECAUTIONS FOR USE

It contains two drugs escitalopram and clonazepam. Hence warnings and precautions applicable to both the drugs must be considered

- Keep out of reach of children.
- Patients should be advised to avoid alcohol
- Patients should be cautioned when they undertake any jobs that require mental alertness such as driving, operating machinery.
- Avoid abrupt discontinuation of this drug. Gradual reduction over a period of 1 to 2 weeks is advised due to clonazepam in the formulation
- Breast feeding is not recommended when women are taking this drug due to clonazepam

Escitalopram

- Clinical Worsening and Suicide Risk- Monitor for clinical worsening, suicidality & unusual change in behavior, especially during the initial few months of therapy or at time of dose change.
- Serotonin Syndrome – During treatment initiation patients should be made aware of a potential increased risk for serotonin syndrome.
- Seizures- Use cautiously in patients with history of seizures.
- Activation of Mania/Hypomania – Use cautiously in patients with history of mania.
- Abnormal Bleeding – Use cautiously in concomitant use with NSAIDS, aspirin, warfarin or other drugs that effect coagulation.
- Hyponatremia- can occur in association with SIADH.
- Pregnancy- Caution should be exercised when administered during pregnancy.
- Pediatric Use - No data available. Escitalopram must not be used in children and adolescents under 18 years of age.
- Concomitant use with the following drugs is contraindicated: St Johns' wort, MAOI or within 14 days of discontinuing treatment with MAOI.

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.
Withdrawal Symptoms: Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines.
General:
A paradoxical increase in seizure activity or the appearance of new seizure types has occurred in a very few patients during treatment with clonazepam.
• The concomitant use of alcohol and/or CNS depressants should be avoided.
• Medical history of alcohol or drug abuse - clonazepam should be used with extreme caution in patients with a history of alcohol or drug abuse.
• Lactose intolerance- Lactose is a non-medicinal ingredient in clonazepam. Therefore, patients with rare hereditary problems of galactose intolerance &Lapp lactase deficiency or glucose-galactosemal absorption should not take this medicine.
• Hepatic- No safety & efficacy data available.
• Respiratory - Respiratory depression may occur following administration of drug.
• Special Populations Pregnant Women-Studies indicate anco relation between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy.
• Nursing Women- The mothers receiving clonazepam should not breast-feed their infants.
• Paediatrics (< 5 years of age): The risk-benefit consideration of the long-term use of clonazepam is important in paediatric patients.
• Geriatrics: There is no clinical trial experience with clonazepam in seizure disorder patients 65 years of age and older**.**
• Prolonged use of clonazepam may result in dependence and withdrawal symptoms on cessation of treatment

4.5 DRUG INTERACTIONS
Coadministration of Escitalopram with the following drugs:
Interaction with Monoamine Oxidase Inhibitors (MAOIs):
Escitalopram should not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should be allowed after stopping escitalopram, before starting a MAOI since there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma when selective serotonin reuptake inhibitors (SSRIs) were co-administered with MAOIs. Such reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on a MAOI.
CNS Drugs: Caution advised when concomitant use is necessary.
Alcohol: Concomitant use is not recommended.
NSAIDs, Aspirin, Warfarin: There is reported association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. It is also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, concurrent use of such drugs should be avoided.
Lithium: Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised, and plasma lithium levels should be monitored with appropriate adjustment to the lithium dose

Sumatriptan: Caution advised, and appropriate observation of the patient is warranted.
Carbamazepine: carbamazepine might increase the clearance of escitalopram.
Pimozide: Rarely increase in QTc values. The mechanism of this pharmacodynamic interaction is not known.
Drugs Metabolized by Cytochrome P4502D6: Caution is advised in the coadministration of escitalopram and drugs metabolized by CYP2D6.
Escitalopram Drug Interaction with Fluconazole
Coadministration clonazepam with the following drugs:
Alcohol: To be totally avoided. Since alcohol can provoke epileptic seizures, irrespective of therapy, patients must under no circumstances drink alcohol while under treatment. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects.
Anti-epileptic drugs: When clonazepam is used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy, and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment.
The combination of clonazepam and sodium valproate has, rarely, been associated with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered.
Inhibitors of hepatic enzymes: Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.
Phenytoin or primidone: In concurrent treatment with phenytoin or primidone, a change, usually a rise in the serum concentration of these two substances has occasionally been observed.
Centrally Acting Drugs: Concurrent use of clonazepam and other centrally acting medications, e.g. other anticonvulsant (antiepileptic) agents, anaesthetics, hypnotics, psychoactive drugs and some analgesics as well as muscle-relaxants may result in mutual potentiation of drug effects. This is especially true in the presence of alcohol. In combination therapy with centrally-acting medications, the dosage of each drug must be adjusted to achieve the optimum effect

4.6 USE IN SPECIAL POPULATIONS
Escitalopram:
Pregnancy
For escitalopram only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity. Escitalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.
Neonates should be observed if maternal use of Escitalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.
The following symptoms may occur in the neonate after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances, the complications begin immediately or soon (<24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Breastfeeding

It is expected that escitalopram will be excreted into human milk.
Consequently, breast-feeding is not recommended during treatment.

Clonazepam:

Pregnancy

During pregnancy, Clonazepam may be administered only if there is a compelling indication. Clonazepam has harmful pharmacological effects on pregnancy and the foetus/newborn child. Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heart beat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the post-natal period. It should be borne in mind that both pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy. Therefore, clonazepam should not be used in pregnancy unless clearly necessary.

Breast-feeding

Although clonazepam has been found to pass into the maternal milk in small amounts only, mothers undergoing treatment with this drug should not breastfeed. If there is a compelling indication for clonazepam, breastfeeding should be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Escitalopram

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

Clonazepam

clonazepam can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is impaired.
This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 UNDESIRABLE EFFECTS

Escitalopram

Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment.
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 (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (≤1/10000), 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, anorexia1
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams, libido decreased Female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalization, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour2,
Nervous system disorders	Very common	Headache
	Common	Insomnia, somnolence, dizziness, paresthesia, tremor
	Uncommon	Taste disturbance, sleep disorder, syncope
	Rare	Serotonin syndrome
	Not known	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/ akathisia 1
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged, ventricular arrhythmia including torsade de pointes
Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastroinstestinal disorders	Very common	Nausea

	Common	Diarrhoea, constipation, vomiting, dry mouth
	Uncommon	Gastrointestinal haemorrhages (including rectal haemorrhage)
Hepatobiliary disorders	Not known	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Sweating increased
	Uncommon	Urticaria, alopecia, rash, pruritus
	Not known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia
Renal and urinary disorders	Not known	Urinary retention
Reproductive system and breast disorders	Common	Male: ejaculation disorder, impotence
	Uncommon	Female: metrorrhagia, menorrhagia
	Not known	Galactorrhoea Male: priapism
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

1. These events have been reported for the therapeutic class of SSRIs
2. Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see section 4.4)

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 hypokalemia, 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.

Clonazepam
The following have been observed:
Immune System Disorders: Allergic reactions and very rare cases of anaphylaxis have been reported to occur with benzodiazepines. Angioedema may occur in rare cases.
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: Impaired concentration, restlessness, confusional state, disorientation have been observed. Depression may occur in patients treated with clonazepam, but it may be also associated with the underlying disease.
The following paradoxical reactions have been observed: excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams and psychotic disorders and activation of new types of seizures may be precipitated. If these occur, the benefit of continuing the drug should be weighed against the adverse effect. The addition to the regimen of another suitable drug may be necessary or, in some cases, it may be advisable to discontinue clonazepam therapy.
Nervous System Disorders: Somnolence, slowed reaction, muscular hypotonia, dizziness and ataxia. 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.
With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.
Although clonazepam has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients.
Eye Disorders: Particularly in long-term or high-dose treatment, reversible disorders of vision (diplopia) may occur. Common side effect is nystagmus.
Cardiac Disorders: Cardiac failure including cardiac arrest has been reported.
Respiratory, Thoracic and Mediastinal System Disorders: Respiratory depression may occur, particularly on i.v. administration of clonazepam. This effect may be aggravated by pre-existing airways obstruction or brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.
Gastrointestinal Disorders: The following effects have been reported in rare cases: nausea, gastrointestinal and epigastric symptoms.
Skin and Subcutaneous Tissue Disorders: The following effects may occur in rare cases: urticaria, pruritus, rash, transient hair loss and pigmentation changes.
Musculoskeletal and Connective Tissue Disorders: Muscle weakness, this undesirable effect occurs relatively frequently and is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.
Renal and Urinary Disorders: In rare cases urinary incontinence may occur.
Reproductive System and Breast Disorders: In rare cases erectile dysfunction or loss of libido may occur.
General Disorders and Administration Site Conditions: Fatigue (tiredness, lassitude), this undesirable effect occurs relatively frequently and is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.
Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Investigations: In rare cases decreased platelet count may occur. As with other benzodiazepines, isolated cases of blood dyscrasias and abnormal liver function tests have been reported.

4.9 OVERDOSAGE

Escitalopram

Toxicity

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

Symptoms

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

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/bradyarrhythmia's, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

Clonazepam

As with other benzodiazepine drugs, overdosage should not present undue problems of management or threat to life. Patients have recovered from overdoses in excess of 60mg without special treatment. Severe somnolence with muscle hypotonia will be present.

5.0 PHARMACOLOGIC PROPERTIES

5.1 MECHANISM OF ACTION

Escitalopram is a selective inhibitor of serotonin (5–HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000-fold lower affinity. Escitalopram has no or low affinity for a number of receptors including 5-HT1A, 5–HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. The inhibition of 5–HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram. 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. The precise mechanism by which clonazepam exerts its anxiolytic 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.

5.2 PHARMACODYNAMIC PROPERTIES

Escitalopram is a potent inhibitor of serotonin (5- HT)-uptake (in vitro IC50 2 nM). The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic

activity in the central nervous system (CNS) resulting from its inhibitory effect on the reuptake of 5-HT from the synaptic cleft.
Escitalopram has high affinity for the primary binding site and an allosteric modulating effect on the serotonin transporter. The Allosteric modulation of the serotonin transporter enhances binding of escitalopram to the primary binding site, resulting in more complete serotonin reuptake inhibition.
Clonazepam is an anticonvulsant which exhibits several pharmacological properties characteristic of the benzodiazepine class of medicines.
Benzodiazepines increase the polysynaptic inhibitory processes at all levels of the central nervous system. Clonazepam is more effective in blocking spread of electrical activity in the lesion itself.
The exact site and mode of action of the anticonvulsant action of clonazepam is unknown.

5.3 PHARMACOKINETIC PROPERTIES

	Escitalopram	**Clonazepam**
Absorption	Data specific to escitalopram are unavailable. Absorption is expected to be almost complete and independent of food intake (mean Tmax is 4 hours after multiple dosing).	Clonazepam is rapidly and almost completely absorbed after oral administration. Peak plasma concentrations of clonazepam are reached in 1-4 hours. The absorption half-life is around 25 minutes. The absolute bioavailability is 90%.
Distribution	The apparent volume of distribution (Vd,β/F) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%	Clonazepam distributes very rapidly to various organs and body tissues with preferential uptake by brain structures
Metabolism	Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites.	Clonazepam is extensively metabolized by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamino-clonazepam.
Excretion	Escitalopram and major metabolites are, like racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and renal routes with the major part of the dose excreted as metabolites in urine.	The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compound. 50-70% of the dose is excreted in the urine and 10-30% in feces as metabolites. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose.
Half life	The elimination half-life (t½β) after multiple dosing is about 30 hours and the oral plasma clearance (Cloral) is about 0.6 L/min.	The mean elimination half-life is 30-40 hours. The clearance is 55 ml/min.

6.NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Escitalopram

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

Clonazepam

Carcinogenicity: No 2-year carcinogenicity studies have been conducted with clonazepam. However, in an 18-month chronic study in rats no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

Mutagenicity: Genotoxicity tests using bacterial systems with in vitro or host mediated metabolic activation did not indicate a genotoxic liability for clonazepam.

Impairment of Fertility: Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and impaired pup survival at doses of 10 and 100 mg/kg/day.

Teratogenicity: No adverse maternal or embryo-fetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of up to 20 or 40 mg/kg/day, respectively.

In several rabbit studies following doses of clonazepam of up to 20 mg/kg/day, a low, non-dose-related incidence of a similar pattern of malformations (cleft palate, open eyelids, fused stern brae and limb defects) was observed.

7.0 DESCRIPTION

SZETALO PLUS MD is supplied for oral administration, as a mouth dissolving tablet of Escitalopram Oxalate & Clonazepam. Each mouth dissolving tablet of SZETALO PLUS MD contains Escitalopram Oxalate equivalent to Escitalopram 10 mg & Clonazepam 0.5 mg.

8.0 PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

Not Applicable

8.2 SHELF-LIFE

Refer pack

8.3 PACKAGING INFORMATION

Refer pack

8.4 STORAGE CONDITION AND HANDING INSTRUCTIONS

Refer pack

9. PATIENT COUNSELLING INFORMATION

It contains two drugs escitalopram and clonzepam. Hence warnings and precautions applicable to both the drugs must be considered

- Keep out of reach of children.
- Patients should be advised to avoid alcohol
- Patients should be cautioned when they undertake any jobs that require mental alertness such as driving, operating machinery.
- Avoid abrupt discontinuation of this drug. Gradual reduction over a period of 1 to 2 weeks is advised due to clonazepam in the formulation

- Breast feeding is not recommended when women are taking this drug due to clonazepam (refer section 4.4 for more details)

General Information about Medication Guide:
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with this tablet and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for this tablet (Escitalopram/Clonazepam).
The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents.
Pregnancy and Breast Feeding:
Patients should be advised to notify their physician if they
• become pregnant or intend to become pregnant during therapy.
• are breastfeeding an infant.
Alcohol:
Patients should be told that, although it has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of this tablet and alcohol is not advised.
Interference with Psychomotor Performance:
Because psychoactive drugs may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Escitalopram/Clonazepam therapy does not affect their ability to engage in such activities.
Abnormal Bleeding:
Patients should be cautioned about the concomitant use of 12 escitalopram and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.
Angle Closure Glaucoma:
Patients should be advised that taking this tablet can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma.
Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Information for patients:

- Do not stop the treatment without first talking to a healthcare provider.
- Tell your healthcare provider about all the medicines you take, including prescription and over-the counter medicines, vitamins, and herbal supplements.
- Taking this tablet with certain other medicines can cause side effects or affect how well the treatment or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.
- It can cause abuse and dependence.

- Do not stop taking this tablet all of a sudden. Stopping it 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 the treatment 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.
- Clonazepam is a benzodiazepine medicine. Benzodiazepines can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.
- Clonazepam 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 Clonazepam affects you.
- Clonazepam may cause problems with your coordination, especially when you are walking or picking things up.
- Do not use this tablet for a condition for which it was not prescribed. Do not give it to other people, even if they have the same condition. It may harm them.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

MARKETED BY
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER
Refer Pack for Permission/License details

12. DATE OF REVISION
Version 6.0 Dated 15th April 2025

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For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com