BIO-ANXIT CZ 0.25
Each tablet contains

Escitalopram oxalate equivalent to Escitalopram …..10 mg

Clonazepam ……0.25 mg

BIO-ANXIT CZ 0.5
Each tablet contains

Escitalopram oxalate equivalent to Escitalopram… 10 mg

Clonazepam …… 0.5 mg

Dosage Form

Film coated tablet

Pharmacology

Pharmacodynamics

Escitalopram
The mechanism of the antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to the potentiation of serotonergic activity in the central nervous system (CNS), resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

In vitro and *in vivo* studies suggests that escitalopram is a highly selective serotonin (5-HT) reuptake inhibitor (SSRI) with a high affinity for the primary binding site, and has minimal effects on norepinephrine and dopamine neuronal reuptake. It also binds to an allosteric site on the serotonin transporter, with a 1,000-fold lower affinity. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to the inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic (5-$HT_{1–7}$)or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1–5}$), histamine ($H_{1–3}$), muscarinic ($M_{1–5}$), benzodiazepine and opiod receptors. Escitalopram also does not bind to or has low affinity for various ion channels, including Sodium (Na^+), Potassium (K^+), Chloride ($Cl^–$) and Calcium (Ca^{++}) channels. Antagonism of the muscarinic, histaminergic and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular side effects of other psychotropic drugs.
Clonazepam
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.

Pharmacokinetics

Escitalopram

Absorption

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day.

Absorption is almost complete and independent of food intake (mean time to maximum concentration is 4 hours after multiple dosing). As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%. Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours.

Distribution

The binding of escitalopram to human plasma proteins is approximately 56%. The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12–26 L/kg. At the steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2–2.5 times the plasma concentrations observed after a single dose.

Metabolism

Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27–32 hours. Escitalopram is metabolized to S-demethylcitalopram (S-DCT) and S-didemethylcitalopram (S-DDCT). Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidized 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. In humans, unchanged escitalopram is the predominant compound in plasma. At the steady state, the concentration of the escitalopram metabolite, S-DCT, in plasma is approximately one-third that of escitalopram.

In vitro studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1-7}$) or other receptors, including alpha- and beta-adrenergic, dopamine (D_{1-5}), histamine (H_{1-3}), muscarinic (M_{1-5}) and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels, including Na^+, K^+, Cl^- and Ca^{++} channels. *In vitro* studies using human liver microsomes indicated that cytochrome (CY) P3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram. Some contribution by the enzymes, CYP3A4 and CYP2D6, is also possible.

Elimination

The elimination half-life ($t_{½\beta}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min. Following oral administration of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-DCT is about 8% and 10%, respectively. The major metabolites have a significantly longer half-life. Escitalopram and its 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. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

With once-daily dosing, steady-state plasma concentrations are achieved within approximately 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.

Special Populations

Adolescents
In a single-dose study of 10 mg escitalopram, the area under the concentration curve (AUC) of escitalopram decreased by 19% and the C_{max} increased by 26% in healthy adolescent subjects (12 to 17 years of age), compared to adults. Following multiple dosing of 40 mg/day escitalopram, the citalopram elimination half-life, steady-state C_{max} and the AUC were similar in patients with major depressive disorder (12 to 17 years of age), compared to adult patients. No adjustment of dosage is needed in adolescent patients.
Geriatric
Escitalopram pharmacokinetics in subjects who were ≥65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects and the C_{max} was unchanged. for elderly patients, 10 mg is the recommended dose. Escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients.
Gender
Based on data from single- and multiple-dose studies measuring escitalopram in the elderly, young adults and adolescents, no dosage adjustment on the basis of gender is needed.

Reduced Hepatic Function
Escitalopram oral clearance was reduced by 37%, the exposure was increased by 60% and the half-life was doubled in patients with mild or moderate hepatic impairment (Child-Pugh criteria A and B). the recommended dose of escitalopram for most hepatically impaired patients is10 mg.

Reduced Renal Function
In patients with mild-to-moderate renal function impairment, oral clearance of escitalopram was reduced by 17%. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance <20 mL/min). With racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (creatinine clearance 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 metabolizers. No significant change in exposure was observed in poor metabolizers with respect to CYP2D6.

Clonazepam
Absorption
Clonazepam is rapidly and completely absorbed after oral administration. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration. Routine monitoring of plasma

concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects.

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

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

Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabelled oral dose of clonazepam is excreted in the urine and 10 - 30% in the faeces, almost exclusively in the form of free or conjugated metabolites. Less than 0.5% appears as unchanged clonazepam in the urine.

Elimination
The elimination half-life is between 20 and 60 hours (mean 30 hours).

Special populations
Age and Gender
Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted.

Renal impairment
Controlled studies examining the influence of renal impairment on clonazepam pharmacokinetics have not been conducted.

Hepatic impairment
Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepamto these patients.

Indications

BIO-ANXIT CZ 0.25/0.5 Tablets are indicated for the treatment of patients with comorbid depression and anxiety disorder

Dosage and Administration

The administration of BIO-ANXIT CZ 0.25/0.5 Tablets is once daily for the specified indication in adults.
The recommended dose of escitalopram is 10 mg/day in adults. The dose should not be increased considering the presence of clonazepam.

Initial dose of clonazepam is 0.5 mg/day in the initial stages of treatment. Dosage of clonazepam should not exceed 1 mg/day.

Contraindications

Hypersensitivity to BIO-ANXIT CZ 0.25/0.5 Tablets and any of its component
Acute angle glaucoma

Concomitant use of monoamine oxidase inhibitors (MAOIs)

Concomitant use in patients taking pimozide.

In patients with clinical or biochemical evidence of significant liver disease.

Warnings and Precautions

General

Clinical Worsening and Suicide Risk
Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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

Families and caregivers of patients being treated with antidepressants and anxiolytics for both psychiatric and non-psychiatric indications, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behaviour, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for BIO-ANXIT CZ 0.25/0.5 Tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Screening Patients for Bipolar Disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the

symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression. It should be noted that BIO-ANXIT CZ 0.25/0.5 Tablets is not approved for use in treating bipolar depression.

Activation of Mania/Hypomania

In placebo-controlled trial of escitalopram in major depressive disorder, activation of mania/hypomania was reported in one patient treated with escitalopram and in none of the patients treated with placebo. Case of hypomania has been reported in association with escitalopram treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, BIO-ANXIT CZ 0.25/0.5 Tablets should be used cautiously in patients with a history of mania and should be discontinued in any patient entering the manic phase.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including escitalopram treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of BIO-ANXIT CZ 0.25/0.5 Tablets with MAOIs intended to treat depression is contraindicated. If concomitant treatment of BIO-ANXIT CZ 0.25/0.5 Tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of BIO-ANXIT CZ 0.25/0.5 Tablets with serotonin precursors (such as tryptophan) is not recommended. Treatment with BIO-ANXIT CZ 0.25/0.5 Tablets and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Seizures

Although clonazepam has anticonvulsant properties, escitalopram has not been systematically evaluated in patients with a seizure disorder. When used in patients in whom several different types of seizure disorders coexist, clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal).

In clinical trials of escitalopram, cases of convulsion have been reported in association with escitalopram treatment. Like other drugs effective in the treatment of major depressive disorder, BIO-ANXIT CZ 0.25/0.5 Tabletsshould be introduced with care in patients with a history of seizure disorder.

BIO-ANXIT CZ 0.25/0.5 Tablets 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.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including escitalopram. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when escitalopram was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients and patients suffering from cirrhosis may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of BIO-ANXIT CZ 0.25/0.5 Tablets should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest and death.

Abnormal Bleeding

SSRIs and SNRIs, including escitalopram, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin and other anticoagulants, with medicinal products known to affect platelet function (e.g. atypical antipsychotics phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and in patients with known bleeding tendencies) may add to the risk of 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. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, purpura, hematomas, epistaxis and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of BIO-ANXIT CZ 0.25/0.5 Tablets and NSAIDs, aspirin, or other drugs that affect coagulation. Caution is advised in patients taking BIO-ANXIT CZ 0.25/0.5 Tablets, particularly in concomitant use with oral anticoagulants.

Interference with Cognitive and Motor Performance

In a study in normal volunteers, escitalopram 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that escitalopram therapy does not affect their ability to engage in such activities. Since clonazepam produces CNS depression, patients receiving BIO-ANXIT CZ 0.25/0.5 Tablets 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 BIO-ANXIT CZ 0.25/0.5 therapy.

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.

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 when given concomitantly with BIO-ANXIT CZ 0.25/0.5 Tablets.
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.

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

Coronary Heart Disease
Caution is advisable in using BIO-ANXIT CZ 0.25/0.5 Tablets in patients with diseases or conditions that produce altered metabolism or hemodynamic responses e.g. coronary heart disease. Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease.
Laboratory Testing During Long-Term Therapy
Periodic blood counts and liver function tests are advisable during long-term therapy with BIO-ANXIT CZ 0.25/0.5 Tablets.
Hypersalivation
Clonazepammay produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, BIO-ANXIT CZ 0.25/0.5 Tablets should be used with caution in patients with chronic respiratory diseases.
Spinal and Cerebellar Ataxia
BIO-ANXIT CZ 0.25/0.5 Tablets may be used only with particular caution in patients with spinal or cerebellar ataxia.
Pulmonary Conditions
The dosage of S BIO-ANXIT CZ 0.25/0.5 Tablets must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease).
Galactose Intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactosemalabsorption, should not take this medicine.

Discontinuation
With SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with BIO-ANXIT CZ 0.25/0.5 Tablets. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered.
The abrupt withdrawal of clonazepam, particularly in those patients with epilepsy on long-term, high-dose therapy, may precipitate status epilepticus.

Abuse and Dependence

Escitalopram

Escitalopram has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The clinical experience with escitalopram did not reveal any drug seeking behaviour. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

Withdrawal symptoms were similar in character to those noted with barbiturates and alcohol (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence. Physicians should carefully evaluate patients receiving BIO-ANXIT CZ 0.25/0.5 Tablets for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behaviour).

Clonazepam

Clonazepam is a Schedule IV controlled substance. Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (eg, convulsions, psychosis, hallucinations, behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Following the short-term treatment of patients with panic disorder, patients were gradually withdrawn during a 7-week downward-titration (discontinuance) period. Overall, the discontinuance period was associated with good tolerability and a very modest clinical deterioration, without evidence of a significant rebound phenomenon. However, there are not sufficient data from adequate and well-controlled long-term clonazepam studies in patients with panic disorder to accurately estimate the risks of withdrawal symptoms and dependence that may be associated with such use.

Drug Interactions

Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs including escitalopram and the potential for serotonin syndrome, caution is advised when BIO-ANXIT CZ 0.25/0.5 Tablets are co-administered with other drugs that may affect the serotonergic

neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol or St. John's Wort. The concomitant use of BIO-ANXIT CZ 0.25/0.5 Tablets with other SSRIs, SNRIs or tryptophan is not recommended.
Triptans
There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. Concomitant treatment of BIO-ANXIT CZ 0.25/0.5 Tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
CNS Drugs
Given the primary CNS effects of escitalopram and clonazepam, caution should be used when BIO-ANXIT CZ 0.25/0.5 Tablets is taken in combination with other centrally acting drugs.
The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, anti-anxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs. The dose of BIO-ANXIT CZ 0.25/0.5 Tablets must be carefully adjusted in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents.
Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine, or Phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Alcohol
Although escitalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking BIO-ANXIT CZ 0.25/0.5 Tablets is not recommended. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects. Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.
Patients should be advised to avoid alcohol while taking BIO-ANXIT CZ 0.25/0.5 Tablets.
Monoamine Oxidase Inhibitors (MAOIs)
Irreversiblenon-selective MAOIs
Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective, irreversible 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.

BIO-ANXIT CZ 0.25/0.5 Tablets is contra-indicated in combination with non-selective, irreversible MAOIs. BIO-ANXIT CZ 0.25/0.5 Tablets 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 BIO-ANXIT CZ 0.25/0.5 Tablets with a MAO-A inhibitor such as moclobemide is contraindicated.
Reversible, non-selective MAO-inhibitor (linezolid)
The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with BIO-ANXIT CZ 0.25/0.5 Tablets.
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.

Drugs that Interfere with Haemostasis (NSAIDs, Aspirin, Warfarin, etc.)
Serotonin release by platelets plays an important role in haemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when BIO-ANXIT CZ 0.25/0.5 Tablets is initiated or discontinued.
Cimetidine
In subjects who had received 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Cimetidine (known inhibitor of hepatic enzymes), has shown to reduce the clearance of benzodiazepines and may potentiate their action. Caution must be exercised if cimetidine and BIO-ANXIT CZ 0.25/0.5 Tablets are used concomitantly.
Digoxin
In subjects who had received 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium
Coadministration of racemic citalopram (40 mg/day) and lithium (30 mmol/day) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when BIO-ANXIT CZ 0.25/0.5 Tabletsand lithium are coadministered.
Pimozide and Citalopram
In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec, compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max}ofpimozide. The mechanism of this pharmacodynamic interaction is not known.
Sumatriptan
There have been rare postmarketing reports describing patients with weakness, hyper-reflexia and in coordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and BIO-ANXIT CZ 0.25/0.5 Tablets is clinically warranted, appropriate observation of the patient is advised.
Theophylline
Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Carbamazepine
Combined administration of racemic citalopram (40 mg/day for 21 days) and carbamazepine (titrated to 400 mg/day) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were

unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered, if BIO-ANXIT CZ 0.25/0.5 Tablets and carbamazepine are co-administered.

Triazolam

Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole

Combined administration of racemic citalopram 40 mg and ketoconazole 200 mg, a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

Ritonavir

Combined administration of a single dose of ritonavir 600 mg, both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram 20 mg did not affect the pharmacokinetics of ritonavir.

CYP3A4 and CYP2C19 Inhibitors

In vitro studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of escitalopram. However, co-administration of escitalopram 20 mg and ritonavir 600 mg, a potent inhibitor of CYP3A4 and CYP2C19, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

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. Thus, caution should be exercised when BIO-ANXIT CZ 0.25/0.5 Tablets is used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine).

Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

Cytochrome P-450 inducers

Cytochrome P-450 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

Drugs Metabolized by Cytochrome P4502D6

In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in $C_{max}$and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

Metoprolol

Administration of 20 mg/day escitalopram for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Co-administration of BIO-ANXIT CZ 0.25/0.5 Tablets and metoprolol had no clinically significant effects on blood pressure or heart rate.
St. John´s Wort
Concomitant use of SSRIs and herbal remedies containing St. John´s Wort (Hypericumperforatum) may result in an increased incidence of adverse reactions.

Medicinal Products Lowering the Seizure Threshold
SSRIs can lower the seizure threshold. Caution is advised when concomitantly using BIO-ANXIT CZ 0.25/0.5 Tablets and other medicinal products capable of lowering the seizure threshold e.g., antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol.
Ranitidine
Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics. In a study in which the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with multiple effects on the GI tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the Cmax of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone.

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

Renal Impairment

Escitalopram is extensively metabolized; excretion of unchanged drug in urine is a minor route of elimination. In patients with severe renal impairment, treatment with BIO-ANXIT CZ 0.25/0.5 Tablets should be done with caution.
Metabolites of BIO-ANXIT CZ 0.25/0.5 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.

Hepatic Impairment

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. In patients with severe liver damage (e.g. cirrhosis of the liver), particular caution needs to be taken. The recommended dose of escitalopraminhepatically impaired patients is 10 mg/day.

Pregnancy

Pregnancy Category D

Neonates exposed to escitalopram and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome. 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.

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of women whose infants were born with PPHN and women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy.

When treating a pregnant woman with BIO-ANXIT CZ 0.25/0.5 Tablets, the physician should carefully consider both the potential risks and benefits of treatment. Physicians should note that in a prospective longitudinal study of women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.
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 sucking 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. Therefore,BIO-ANXIT CZ 0.25/0.5 Tablets should not be used in pregnancy unless clearly necessary.
Labour and Delivery
The effect of escitalopram on labour and delivery in humans is unknown. The effect of clonazepam on labor and delivery in humans has not been specifically studied; however, perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena. Therefore BIO-ANXIT CZ 0.25/0.5 Tablets should be used with cautions during labour and delivery.

Lactating Mothers

Escitalopram and clonazepam is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram

by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when BIO-ANXIT CZ 0.25/0.5 Tablets are administered to a lactating mother.

Paediatric Use

BIO-ANXIT CZ 0.25/0.5 Tablets should not be used in the treatment of children and adolescents below the age of 18 years. Safety and effectiveness of BIO-ANXIT CZ 0.25/0.5 Tablets has not been established in children and adolescents below the age of 18 years.

Geriatric Use

SSRIs and SNRIs, including escitalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event. Clonazepam is also advised to be used with caution; therefore BIO-ANXIT CZ 0.25/0.5 Tablets should be used with caution in this patient population.
Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of BIO-ANXIT CZ 0.25/0.5 Tablets and observed closely.

Undesirable Effects

Escitalopram

The most common set of undesirable effects observed with escitalopram are dry mouth, increased sweating, headache, par aesthesia, dizziness, nausea, diarrhoea, constipation, indigestion, abdominal pain, vomiting, flatulence, influenza-like symptoms, fatigue, abnormal dreaming, lethargy, insomnia, somnolence, decreased appetite, decreased libido, yawning, rhinitis, sinusitis, ejaculation disorder, impotence, anorgasmia and menstrual disorders.

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes
Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with escitalopram treatment. In addition, a comparison

of supine and standing vital sign measures in subjects receiving escitalopram indicated that escitalopram treatment is not associated with orthostatic changes.

Weight Changes
Patients treated with escitalopram in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes
Escitalopram and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with escitalopram treatment.

ECG Changes
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.

Post-Marketing Experience

Adverse Reactions Reported Subsequent to the Marketing of escitalopram
The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include:

Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolyticanemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia.
Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia.
Ear and labyrinth disorders: vertigo
Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH.
Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance.
Gastrointestinal Disorder: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage.
General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise.
Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis.

Immune System Disorders: allergic reaction, anaphylaxis.
Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased.
Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia.
Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis.
Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor.
Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion.
Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency.
Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention.
Reproductive System and Breast Disorders: menorrhagia, priapism.
Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn.
Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria.
*Vascular Disorders:*deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.
Adverse Reactions Reported Subsequent to the Marketing of Clonazepam
The most frequently occurring side effects of clonazepam are referable to CNS depression. Experience in treatments has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, ‘‘glassy-eyed’’ appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo
Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances). The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams
Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages
Cardiovascular: Palpitations
Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema
Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums
Genitourinary: Dysuria, enuresis, nocturia, urinary retention
Musculoskeletal: Muscle weakness, pains
Miscellaneous:Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia
Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatise

Overdosage

Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, include 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), gastrointestinal system (nausea, vomiting) and the cardiovascular system (hypotension, tachycardia, QT prolongation, arrhythmia, and very rare cases of torsade de pointes) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia) and sleep disturbances (insomnia somnolence). Acute renal failure has been very rarely reported accompanying overdose. In case of clonazepam, symptoms of overdosage are like those produced by other CNS depressants i.e., somnolence, confusion, coma and diminished reflexes.

Management of overdose includes establishing and maintaining an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control centre for additional information on the treatment of any overdose.

There is no specific antidotes for escitalopramoverdosage. However clonazepam being a benzodiazepine, 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.

Storage and Handling Instructions

Store in a cool dry place. Keep away from light.

BIOS LAB PVT. LTD.