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

ALPRAX PLUS

1. Generic Name
Sertraline and Alprazolam SR Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each uncoated bilayered tablet contains:
Alprazolam I.P. 0.5 mg
(In sustained release form)
Colour: Lake of Brilliant Blue
Sertraline Hydrochloride I.P.
Equivalent to sertraline 25 mg
Colour: Quinoline Yellow

Other inactive ingredients are Lake of Brilliant Blue, Dibasic Calcium, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Hydroxypropyl methylcellulose, Iso propyl Alcohol, microcrystalline Cellulose, Diabasic calcium, Magnesium stearate, Sodium starch glycollate, Polysorbate, Colloidal silicon dioxide, Hydroxy Propyl cellulose, Iso propyl alcohol, Sodium starch Glycollate.

3. DOSAGE FORM AND STRENGTH
Dosage Form: Uncoated bilayered tablet
Strength: Alprazolam 0.5 mg
Sertraline Hydrochloride 25 mg

4. CLINICAL PARTICULARS
4.1 Therapeutic Indication
For the treatment of panic disorders with or without agoraphobia.

4.2 Posology and Method of Administration
Posology:
As directed by physician

Method of administration
For oral use.
Treatment should be as short as possible. It is recommended that the patient be reassessed at the end of no longer than 4 weeks of treatment and the need for continued treatment established, especially in case the patient is symptom free. The overall duration of treatment should not be more than 8-12 weeks, including a tapering off process. In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

Elderly patients
There is a reduced clearance of the drug and, as with other benzodiazepines, an increased sensitivity to the drug in elderly patients. Elderly should be dosed carefully, as elderly may be more at risk for hyponatraemia.

Patients with hepatic impairment

The use of Alprax Plus in patients with hepatic disease should be approached with caution. A lower or less frequent dose should be used in patients with hepatic impairment. Alprax Plus should not be used in cases of severe hepatic impairment as no clinical data are available.

Abrupt discontinuation should be avoided. When stopping treatment, Alprax Plus should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serotonin syndrome with symptoms such as agitation, tremor and hyperthermia. Alprax Plus must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Alprax Plus must be discontinued for at least 7 days before starting treatment with an irreversible MAOI. Concomitant intake of pimozide is contraindicated.

Alprax plus is also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Renal and hepatic impairment

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency.

Paediatric population

Safety and efficacy of Alprax Plus have not been established in children and adolescents below the age of 18 years; therefore, is not recommended.

Elderly patients

Alprax Plus should be used with caution in elderly, due to the risk of sedation and / or musculoskeletal weakness that can promote falls, often with serious consequences in this population. Alprax plus should be used with extreme caution in patients with a history of alcohol or drug abuse).

Risk from concomitant use of opioids

Concomitant use of ALPRAX PLUS and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as

ALPRAX PLUS with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe ALPRAX PLUS concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptom).

Dependence

Use of Alprax plus may lead to the development of physical and psychic dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol and drug abuse. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of Pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported.

Withdrawal symptoms: Once physical dependence has developed; abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and insomnia. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. During discontinuation, the dosage should be reduced slowly in keeping with good medical practice.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications, that in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Alprax Plus may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours.

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using Alprax Plus. Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

Serotonin Syndrome (SS) or Neuroleptic Malignant Syndrome (NMS)

The development of potentially life-threatening syndromes like serotonin syndrome (SS) or Neuroleptic Malignant Syndrome (NMS) has been reported. The risk of SS or NMS is increased with concomitant use of other serotonergic drugs (including other serotonergic antidepressants, amphetamines, triptans), with drugs which impair metabolism of serotonin (including MAOIs e.g. methylene blue), antipsychotics and other dopamine antagonists, and with opiate drugs. Patients should be monitored for the emergence of signs and symptoms of SS or NMS syndrome.

Other serotonergic drugs e.g. tryptophan, fenfluramine and 5-HT agonists

Co-administration of Alprax Plus with other drugs which enhance the effects of serotonergic neurotransmission such as amphetamines, tryptophan or fenfluramine or 5-HT agonists, or the herbal medicine, St John's Wort (*hypericum perforatum*), should be undertaken with caution and avoided whenever possible due to the potential for a pharmacodynamic interaction.

QTc Prolongation/Torsade de Pointes (TdP)

Cases of QTc prolongation and Torsade de Pointes (TdP) have been reported. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Therefore, Alprax Plus should be used with caution in patients with risk factors for QTc prolongation.

Activation of hypomania or mania

Manic/hypomanic symptoms have been reported to emerge in a small proportion of patients treated with marketed antidepressant and anti-obsessional drugs. Therefore, Alprax plus should be used with caution in patients with a history of mania/hypomania. Close surveillance by the physician is required. Alprax Plus should be discontinued in any patient entering a manic phase.

Seizures

Seizures may occur with Alprax plus therapy: Alprax plus should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Alprax plus should be discontinued in any patient who develops seizures.

Suicide/suicidal thoughts/suicide attempts or clinical worsening

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

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

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

Abnormal bleeding/Haemorrhage

There have been reports of bleeding abnormalities with SSRIs including cutaneous bleeding (ecchymoses and purpura) and other haemorrhagic events such as gastrointestinal or gynaecological bleeding, including fatal haemorrhages. Caution is advised in patients taking Alprax plus, particularly in concomitant use with drugs known to affect platelet function (e.g. anticoagulants, atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs)) as well as in patients with a history of bleeding disorders.

Hyponatraemia

Hyponatraemia may occur as a result of treatment with Alprax plus. In many cases, hyponatraemia appears to be the result of a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases of serum sodium levels lower than 110 mmol/L have been reported.

Elderly patients may be at greater risk of developing hyponatraemia. Also patients taking diuretics or who are otherwise volume-depleted may be at greater risk. Discontinuation should be considered in patients with symptomatic hyponatraemia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatraemia 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.

Withdrawal symptoms seen on discontinuation of treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Alprax Plus should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Akathisia/psychomotor restlessness

The use of Alprax Plus 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.

Hepatic impairment

Sertraline is extensively metabolised by the liver. A multiple dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and approximately three-fold greater AUC and Cmax in comparison to normal subjects. There were no significant differences in plasma protein binding observed between the two groups. The use of sertraline in patients with hepatic disease must be approached with caution. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. Sertraline should not be used in patients with severe hepatic impairment.

Renal impairment

Sertraline is metabolised, and excretion of unchanged drug in urine is a minor route of elimination. In studies of patients with mild to moderate renal impairment (creatinine clearance 30-60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple-dose pharmacokinetic parameters (AUC_{0-24} or Cmax) were not significantly different compared with controls. Sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Diabetes

In patients with diabetes, treatment with Alprax plus may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Grapefruit juice

The administration of Alprax plus with grapefruit juice is not recommended.

Angle-Closure glaucoma

Alprax plus including sertraline may have an effect on pupil size resulting in mydriasis. This mydriasis effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. Alprax plus should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

4.5 Drugs Interactions
Alprazolam

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as ALPRAX PLUS with opioids increases the risk of sedation, respiratory depression, coma and death because of additive central nervous system (CNS) depressant effect. The dosage and duration of concomitant use should be limited. Concomitant intake with alcohol is not recommended. Alprazolam should be used with caution when combined with CNS depressants. Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence. Pharmacokinetic interactions can occur when alprazolam is administered along

with drugs that interfere with its metabolism.

CYP3A Inhibitors

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, in-vitro studies with alprazolam and clinical studies with drugs metabolised similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

• The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended.

• The co-administration of nefazodone or fluvoxamine increases the AUC of alprazolam by approximately 2-fold. Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine and cimetidine.

• Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

CYP3A4 Inducers

Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam. Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Short term, low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

Digoxin

Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Sertraline

Monoamine Oxidase Inhibitors

Irreversible MAOIs (e.g. selegiline)

Sertraline must not be used in combination with irreversible MAOIs such as selegiline. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of sertraline with a reversible and selective MAOI, such as moclobemide, should not be given. Following treatment with a reversible MAO-inhibitor, a shorter withdrawal period than 14 days may be used before

initiation of sertraline treatment. It is recommended that sertraline should be discontinued for at least 7 days before starting treatment with a reversible MAOI.

Reversible, non-selective MAOI (linezolid)

The antibiotic linezolid is a weak reversible and non-selective MAOI and should not be given to patients treated with sertraline.

Severe adverse reactions have been reported in patients who have recently been discontinued from an MAOI (e.g. methylene blue) and started on sertraline, or have recently had sertraline therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, and hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death.

Pimozide

Increased pimozide levels of approximately 35% have been demonstrated in a study of a single low dose pimozide (2 mg). These increased levels were not associated with any changes in EKG. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide, concomitant administration of sertraline and pimozide is contraindicated.

Co-administration with sertraline is not recommended

CNS depressants and alcohol

The co-administration of sertraline 200 mg daily did not potentiate the effects of alcohol, carbamazepine, haloperidol, or phenytoin on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of sertraline and alcohol is not recommended.

Other serotonergic drugs

Caution is also advised with fentanyl (used in general anaesthesia or in the treatment of chronic pain), other serotonergic drugs (including other serotonergic antidepressants, amphetamines, triptans), and with other opiate drugs.

Special Precautions

Drugs that Prolong the QT Interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. TdP) may be increased with concomitant use of other drugs which prolong the QTc interval (e.g. some antipsychotics and antibiotics).

Lithium

In a placebo-controlled trial in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with lithium, patients should be appropriately monitored.

Phenytoin

A placebo-controlled trial in normal volunteers suggests that chronic administration of sertraline 200 mg/day does not produce clinically important inhibition of phenytoin metabolism. Nonetheless, as some case reports have emerged of high phenytoin exposure in patients using sertraline, it is recommended that plasma phenytoin concentrations be monitored following initiation of sertraline therapy, with appropriate adjustments to the phenytoin dose. In addition, co-administration of phenytoin may cause a reduction of sertraline plasma levels.

It cannot be excluded that other CYP3A4 inducers, e.g. phenobarbital, carbamazepine, St John´s Wort, rifampicin may cause a reduction of sertraline plasma levels.

Triptans

There have been rare post-marketing reports describing patients with weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following the use of sertraline and sumatriptan. Symptoms of serotonergic syndrome may also occur with other products of the same class (triptans). If concomitant treatment with sertraline and triptans is clinically warranted, appropriate observation of the patient is advised.

Warfarin

Co-administration of sertraline 200 mg daily with warfarin resulted in a small but statistically significant increase in prothrombin time, which may in some rare cases unbalance the INR value.

Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped.

Other drug interactions, digoxin, atenolol, cimetidine

Co-administration with cimetidine caused a substantial decrease in sertraline clearance. The clinical significance of these changes is unknown. Sertraline had no effect on the beta-adrenergic blocking ability of atenolol. No interaction of sertraline 200 mg daily was observed with digoxin.

Drugs affecting platelet function

The risk of bleeding may be increased when medicines acting on platelet function (e.g. NSAIDs, acetylsalicylic acid and ticlopidine) or other medicines that might increase bleeding risk are concomitantly administered with SSRIs, including sertraline.

Neuromuscular Blockers

SSRIs may reduce plasma cholinesterase activity resulting in a prolongation of the neuromuscular blocking action of mivacurium or other neuromuscular blockers.

Drugs Metabolized by Cytochrome P450

Sertraline may act as a mild-moderate inhibitor of CYP 2D6. Chronic dosing with sertraline 50 mg daily showed moderate elevation (mean 23%-37%) of steady-state desipramine plasma levels (a marker of CYP 2D6 isozyme activity). Clinical relevant interactions may occur with other CYP 2D6 substrates with a narrow therapeutic index like class 1C antiarrhythmics such as propafenone and flecainide, TCAs and typical antipsychotics, especially at higher sertraline dose levels.

Sertraline does not act as an inhibitor of CYP 3A4, CYP 2C9, CYP 2C19, and CYP 1A2 to a clinically significant degree. This has been confirmed by *in-vivo* interaction studies with CYP3A4 substrates (endogenous cortisol, carbamazepine, terfenadine, alprazolam), CYP2C19 substrate diazepam, and CYP2C9 substrates tolbutamide, glibenclamide and phenytoin. *In vitro* studies indicate that sertraline has little or no potential to inhibit CYP 1A2.

Intake of three glasses of grapefruit juice daily increased the sertraline plasma levels by approximately 100% in a cross-over study in eight Japanese healthy subjects. Therefore, the intake of grapefruit juice should be avoided during treatment with sertraline.

Based on the interaction study with grapefruit juice, it cannot be excluded that the concomitant administration of sertraline and potent CYP3A4 inhibitors, e.g. protease inhibitors, ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin and nefazodone, would result in even larger increases in exposure of sertraline. This also concerns moderate CYP3A4 inhibitors, e.g. aprepitant, erythromycin, fluconazole, verapamil and diltiazem. The intake of potent CYP3A4 inhibitors should be avoided during treatment with sertraline.

Sertraline plasma levels are enhanced by about 50% in poor metabolizers of CYP2C19 compared to rapid metabolizers. Interaction with strong inhibitors of CYP2C19, e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole, fluoxetine, fluvoxamine cannot be excluded.

4.6 Use in Special Populations

Alprazolam

Pregnancy

The data concerning teratogenicity and effects on postnatal development and behaviour following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found a twofold increased risk of oral clefts. Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of fetal active movements and a variability of fetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half-life of the product. At high doses, respiratory depression or apnoea and hypothermia in new born may appear. Moreover, neonatal withdrawal symptoms with hyper excitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The apparition of withdrawal symptoms after birth depends on the half-life of the substance.

Alprazolam should not be used during pregnancy unless the clinical condition of the woman requires treatment with alprazolam. If alprazolam is used during pregnancy, or of the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the fetus.

If alprazolam treatment is necessary during last part of pregnancy, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in

newborn.

Breast-feeding

Alprazolam is excreted in breast milk at low level. However, alprazolam is not recommended during breast-feeding.

Sertraline

Pregnancy

There are no well controlled studies in pregnant women. However, a substantial amount of data did not reveal evidence of induction of congenital malformations by sertraline. Animal studies showed evidence for effects on reproduction probably due to maternal toxicity caused by the pharmacodynamic action of the compound and/or direct pharmacodynamic action of the compound on the foetus.

Use of sertraline during pregnancy has been reported to cause symptoms, compatible with withdrawal reactions, in some neonates, whose mothers had been on sertraline. This phenomenon has also been observed with other SSRI antidepressants. Sertraline is not recommended in pregnancy, unless the clinical condition of the woman is such that the benefit of the treatment is expected to outweigh the potential risk.

Neonates should be observed if maternal use of sertraline continues into the later stages of pregnancy, particularly the third trimester. The following symptoms may occur in the neonate after maternal sertraline use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal 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, particular 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.

Breast-feeding

Published data concerning sertraline levels in breast milk show that small quantities of sertraline and its metabolite N-desmethylsertraline are excreted in milk. Generally negligible to undetectable levels were found in infant serum, with one exception of an infant with serum levels about 50% of the maternal level (but without a noticeable health effect in this infant). To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.

Fertility

Animal data did not show an effect of sertraline on fertility parameters.

Human case reports with some SSRI's have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive and use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased.

These effects are potentiated by alcohol.
Patients should be cautioned about operating motor vehicles or engaging in other dangerous activities while taking ALPRAX PLUS.
This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable Effects

Table 1: Adverse Reactions
Frequency of adverse reactions observed from placebo-controlled clinical trials in depression, OCD, panic disorder, PTSD and social anxiety disorder. Pooled analysis and post-marketing experience.

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency Not Known (Cannot be Estimated From the Available Data)**
Infections and infestations		upper respiratory tract infection, pharyngitis, rhinitis	gastroenteritis, otitis media	diverticulitis	
Neoplasms benign, malignant and unspecified (including cysts and polyps)			neoplasm		
Blood and lymphatic system disorders				lymphadenopathy, thrombocytopenia, leukopenia	

Immune system disorders			hypersensitivity, seasonal allergy	anaphylactoid reaction	
Endocrine disorders			hypothyroidism	hyperprolactinaemia, inappropriate antidiuretic hormone secretion	
Metabolism and nutrition disorders		decreased appetite, increased appetite		hypercholesterolaemia, diabetes mellitus, hypoglycaemia, hyperglycaemia, hyponatraemia	
Psychiatric disorders	Insomnia, depression	anxiety, agitation, libido decreased, nervousness, depersonalisation, nightmare, bruxism, Confusional state, disorientation, libido increased	suicidal ideation/behaviour, psychotic disorder, thinking abnormal, apathy, hallucination, aggression, euphoric mood, paranoia, mania, anger	conversion disorder, paroniria, drug dependence, sleep walking, premature ejaculation	Hypomania, hostility, psychomotor hyperactivity
Nervous system disorders	dizziness, headache, somnolence, ataxia, memory impairment, dysarthria	Balance disorder, coordination abnormal, hypersomnia, lethargy, tremor, movement disorders (including extrapyramidal symptoms such as hyperkinesia, hypertonia, Autonomic	amnesia, hypoaesthesia, muscle contractions involuntary, syncope, hyperkinesia, migraine, convulsion, dizziness postural, coordination abnormal, speech disorder	coma, akathisia, dyskinesia, hyperaesthesia, cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome), psychomotor	

		nervous system imbalance, dystonia, teeth grinding or gait abnormalities), paraesthesia, hypertonia, disturbance in attention, dysgeusia		restlessness, sensory disturbance, choreoathetosis, also reported were signs and symptoms associated with serotonin syndrome or neuroleptic malignant syndrome: In some cases associated with concomitant use of serotonergic drugs that included agitation, confusion, diaphoresis, diarrhoea, fever, hypertension, rigidity and tachycardia	
Eye disorders		visual disturbance, vision blurred	mydriasis	scotoma, glaucoma, diplopia, photophobia, hyphaemia, pupils unequal, vision abnormal, lacrimal disorder	
Ear and labyrinth disorders		tinnitus	ear pain		
Cardiac disorders		palpitations	tachycardia, cardiac disorder	myocardial infarction, Torsade de Pointes,	

				bradycardia, QTc prolongation	
Vascular disorders		hot flush	abnormal bleeding (such as gastrointestinal bleeding), hypertension, flushing, haematuria	peripheral ischaemia	
Respiratory, thoracic and mediastinal disorders		yawning	dyspnoea, epistaxis, bronchospasm	hyperventilation, interstitial lung disease, laryngospasm, dysphonia, stridor, hypoventilation, hiccups	
Gastrointestinal disorders	nausea, diarrhoea, dry mouth, constipation	dyspepsia, abdominal pain, vomiting, flatulence	melaena, tooth disorder, oesophagitis, glossitis, haemorrhoids, salivary hypersecretion, dysphagia, eructation, tongue disorder	mouth ulceration, pancreatitis, haematochezia, tongue ulceration, stomatitis	
Hepatobiliary disorders				hepatic function abnormal, serious liver events (including hepatitis, jaundice and hepatic failure)	
Skin and subcutaneous tissue disorders		hyperhidrosis, rash, dermatitis	periorbital oedema, urticaria, alopecia, pruritus, purpura, dermatitis, dry skin, face	rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome an	

			oedema, cold sweat	d epidermal necrolysis, skin reaction, photosensitivity, angioedema, hair texture abnormal, skin odour abnormal, dermatitis bullous, rash follicular	
Musculoskeletal and connective tissue disorders		back pain, arthralgia, myalgia	osteoarthritis, muscle twitching, muscle cramps, muscular weakness	rhabdomyolysis, bone disorder	trismus
Renal and urinary disorders			pollakiuria, micturition disorder, urinary retention, urinary incontinence, polyuria, nocturia	urinary hesitation, oliguria	
Reproductive system and breast disorders	ejaculation failure	menstruation irregular, erectile dysfunction	sexual dysfunction, menorrhagia, vaginal haemorrhage, female sexual dysfunction	Galactorrhoea, atrophic vulvovaginitis, genital discharge, balanoposthitis, gynaecomastia, priapism	
General disorders and administration site conditions	fatigue, irritability	malaise, chest pain, asthenia, pyrexia	oedema peripheral, chills, gait disturbance, thirst	hernia, drug tolerance decreased	
Investigations		weight increased, weight decreased	alanine aminotransferase increased, aspartate aminotransferase increased,	blood cholesterol increased, abnormal clinical laboratory	Intraocular pressure increased

				results, semen abnormal, altered platelet function	
Injury, poisoning and procedural complications		injury			
Surgical and medical procedures				vasodilation procedure	

Withdrawal symptoms seen on discontinuation of treatment

Discontinuation of Alprax plus (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported. 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 sertraline treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

4.9 Overdose
Sertraline
Toxicity

Sertraline has a margin of safety dependent on patient population and/or concomitant medication. Deaths have been reported involving overdoses of sertraline, alone or in combination with other drugs and/or alcohol. Therefore, any overdosage should be medically treated aggressively.

Symptoms

Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbances (e.g. nausea and vomiting), tachycardia, tremor, agitation and dizziness. Coma has been reported although less frequently.

QTc prolongation/Torsade de Pointes has been reported following sertraline overdose; therefore, ECG-monitoring is recommended in all ingestions of sertraline overdoses.

Management

There are no specific antidotes to sertraline. It is recommended to establish and maintain an airway and, if necessary, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with a cathartic, may be as, or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended. Cardiac (e.g. ECG) and vital sign monitoring is also recommended, along with general symptomatic and supportive measures. Due to the large volume of distribution of sertraline, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

Alprazolam
As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents have been taken.
Following overdose with oral benzodiazepines, vomiting may be induced (within 1 hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption.

Special attention should be paid to respiratory and cardiovascular functions in intensive care.
Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES

Sertraline
5.1 Mechanism of Action
Sertraline is a potent and specific inhibitor of neuronal serotonin (5 HT) uptake in vitro, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs. Sertraline has not demonstrated potential for abuse. In a placebo-controlled, double-blind randomized study of the comparative abuse liability of sertraline, alprazolam and d-amphetamine in humans, sertraline did not produce positive subjective effects indicative of abuse potential. In contrast, subjects rated both alprazolam and d-amphetamine significantly greater than placebo on measures of drug liking, euphoria and abuse potential. Sertraline did not produce either the stimulation and anxiety associated with d-amphetamine or the sedation and psychomotor impairment associated with alprazolam. Sertraline does not function as a positive reinforce in rhesus monkeys trained to self-administer cocaine, nor does it substitute as a discriminative stimulus for either d-amphetamine or pentobarbital in rhesus monkeys.

Alprazolam

The exact mechanism of action of alprazolam is unknown. Benzodiazepines bind to gamma aminobutyric acid (GABA) receptors in the brain and enhance GABA mediated synaptic inhibition; such actions may be responsible for the efficacy of alprazolam in anxiety disorder and panic disorder.

5.2 Pharmacodynamic Properties

Alprazolam

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid, which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).

Sertraline

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors (SSRI), ATC code: N06 AB06

5.3 Pharmacokinetic Properties

Alprazolam

Alprazolam is readily absorbed. Following oral administration peak concentration in the plasma occurs after 1 - 2 hours.

The mean half-life is 12 - 15 hours. Repeated dosage may lead to accumulation and this should be borne in mind in elderly patients and those with impaired renal or hepatic function. Alprazolam and its metabolites are excreted primarily in the urine.

In vitro alprazolam is bound (80%) to human serum protein.

Sertraline

Absorption

In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Distribution

Approximately 98% of the circulating drug is bound to plasma proteins.

Biotransformation

Sertraline undergoes extensive first-pass hepatic metabolism.

Based on clinical and in-vitro data, it can be concluded that sertraline is metabolized by multiple pathways including CYP3A4, CYP2C19 and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrate of P-glycoprotein in-vitro.

Elimination

The mean half-life of sertraline is approximately 26 hours (range 22-36 hours). Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after one week of once-daily dosing. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in the urine.

Linearity/non-linearity

Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Alprazolam

Mutagenesis and Carcinogenesis

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Ocular Effects
When rats were treated orally with alprazolam for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

Fertility
In reproductive toxicity studies administration of alprazolam in rats and rabbits is associated at very high doses with developmental delay and an increased incidence of fetal death and skeletal malformations. In fertility studies, treatment of male rats at high doses prior to mating resulted in a decrease in the percentage of dams conceiving.

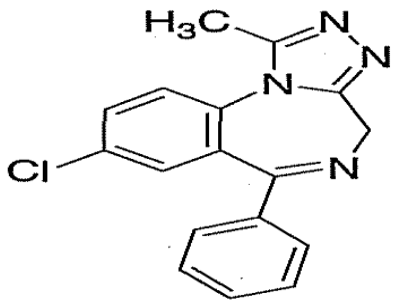
Effect of anesthetic and sedative drugs
Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with alprazolam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

Sertraline
Preclinical data does not indicate any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenesis. Reproduction toxicity studies in animals showed no evidence of teratogenicity or adverse effects on male fertility. Observed fetotoxicity was probably related to maternal toxicity. Postnatal pup survival and body weight were decreased only during the first days after birth. Evidence was found that the early postnatal mortality was due to in-utero exposure after day 15 of pregnancy. Postnatal developmental delays found in pups from treated dams were probably due to effects on the dams and therefore not relevant for human risk.
Animal data from rodents and non-rodents does not reveal effects on fertility.

Juvenile animal studies
A juvenile toxicology study in rats has been conducted in which sertraline was administered orally to male and female rats on Postnatal Days 21 through 56 (at doses of 10, 40, or 80 mg/kg/day) with a nondosing recovery phase up to Postnatal Day 196. Delays in sexual maturation occurred in males and females at different dose levels (males at 80 mg/kg and females at ≥10 mg/kg), but despite this finding there were no sertraline-related effects on any of the male or female reproductive endpoints that were assessed. In addition, on Postnatal Days 21 to 56, dehydration, chromorhinorrhea, and reduced average body weight gain was also observed. All of the aforementioned effects attributed to the administration of sertraline were reversed at some point during the nondosing recovery phase of the study. The clinical relevance of these effects observed in rats administered sertraline has not been established.

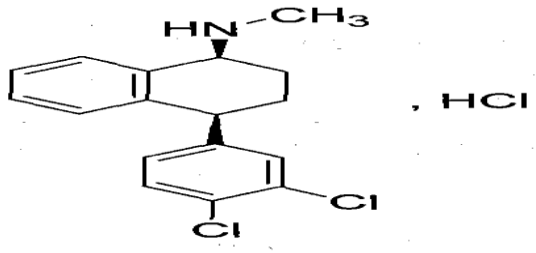
7. DESCRIPTION

Alprazolam is 8-chloro-1-methyl-6-phenyl -4H-1,2,4-triazolo[4,3-a][1,4]benzodiazepine. Having molecular Formula C17H13CLN4 and Molecular weight 308.8. The chemical structure is



Alprazolam is a white to off-white, crystalline powder.

Sertraline Hydrochloride is (1 S,4S)-4-(3,4-dichlorophenyl)-Nmethyl-l,2,3,4-tetrahydronaphthalen-1-amine hydroch\oride. . Having molecular Formula C17H17ChN, HCl and Molecular weight 342.7. The chemical structure is



Sertraline Hydrochloride is a white or almost white, crystalline powder.

Product Description:

ALPRAX PLUS: Blue and yellow coloured, uncoated bilayered, round flat tablets.

8. PHARMACEUTICAL PARTICULAR

8.1 Incompatibilities

Not available

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

ALPRAX PLUS Available in Blister strip of 10 tablets.

8.4 Storage and Handing Instructions

STORE IN A DRY PLACE AT A TEMPERATURE NOT EXCEEDING 30°C, PROTECTED FROM LIGHT.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

ALPRAX PLUS

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

 Keep this leaflet. You may need to read it again.
 If you have any further questions, ask your doctor or pharmacist.
 This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
 If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What ALPRAX PLUS is and what it is used for

ALPRAX PLUS is combination of Alprazolam and Sertraline; it is used for the treatment of panic disorder, with or without agarophobia.

2. What you need to know before you take Alprax plus

Do not take Alprax plus:
 If you are allergic to the active substances or any of the other ingredients of this medicine
 If you are taking or have taken medicines called monoamine oxidase inhibitors (MAOIs such as selegiline, moclobemide) or MAOI like drugs (such as linezolid). If you stop treatment with sertraline, you must wait until at least one week before you start treatment with a MAOI. After stopping treatment with a MAOI, you must wait at least 2 weeks before you can start treatment with sertraline.
 If you are taking another medicine called pimozide (a medicine for mental disorders such as psychosis).
- If you suffer from a disease called ‘myasthenia gravis’ where you suffer from very weak and tired muscles.
- If you have severe chest problems or breathing difficulties (e.g. chronic bronchitis or emphysema).
- If you have ‘sleep apnoea’ - this is a condition where your breathing becomes irregular, even stopping for short periods, while you are asleep.
- If you have severe liver problems.

- If you are pregnant, think you might be pregnant now, are planning to become pregnant or if you are breast-feeding (see also the sections on ‘Pregnancy’ and ‘Breast-feeding’ for more information).

Warnings and precautions
Talk to your doctor or pharmacist before taking Alprax plus
.
Medicines are not always suitable for everyone. Tell your doctor before you take Alprax plus, if you suffer from or have suffered in the past from any of the following conditions:
 If you have epilepsy (fit) or a history of seizures. If you have a fit (seizure), contact your doctor immediately.
 If you have suffered from manic depressive illness (bipolar disorder) or schizophrenia. If you have a manic episode, contact your doctor immediately.
 If you have or have previously had thoughts of harming or killing yourself (see Below-Thoughts of suicide and worsening of your depression or anxiety disorder).
 If you have Serotonin Syndrome. In rare cases this syndrome may occur when you are taking certain medicines at the same time as sertraline. Your doctor will have told you whether you have suffered from this in the past.
 If you have low sodium level in your blood, since this can occur as a result of treatment with ALPRAX PLUS. You should also tell your doctor if you are taking certain medicines for hypertension, since these medicines may also alter the sodium level in your blood.
 If you are elderly as you may be more at risk of having low sodium level in your blood (see above).
 If you have liver disease; your doctor may decide that you should have a lower dose of ALPRAX PLUS.
 If you have diabetes; your blood glucose levels may be altered due to ALPRAX PLUS and your diabetes medicines may need to be adjusted.
 If you have suffered from bleeding disorders or have been taking medicines which thin the blood (e.g. acetylsalicylic acid (aspirin), or warfarin) or may increase the risk of bleeding.
 If you are a child or adolescent under 18 years old.
 If you are having electro-convulsive therapy (ECT).
 If you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
 If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.
 If you have heart disease, low potassium levels or low magnesium levels, family history of QT prolongation, low heart rate and concomitant use of medications which prolong QT interval. - Have ever felt so depressed that you have thought about taking your own life.
- Have ever suffered any mental illness that required hospital treatment.
- Have problems with your lungs, kidneys or liver.
- Have abused drugs or alcohol in the past or find it difficult to stop taking medicines, drinking or taking drugs. Your doctor may want to give you special help when you need to stop taking these tablets.
- Have been prescribed medicines for severe anxiety before, because your body can quickly become used to this type of medicine so that it no longer helps you

Benzodiazepines and related products should be used with caution in elderly, due to the risk of sedation and / or musculoskeletal weakness that can promote falls, often with serious consequences in this population.

Restlessness/Akathisia:
The use of sertraline has been linked to a distressing restlessness and need to move, often being unable to sit or stand still (akathisia). This is most likely to occur during the first few weeks of treatment. Increasing the dose may be harmful so if you develop such symptoms you should talk to your doctor.
Withdrawal reactions:
Side effects relating to stopping treatment (withdrawal reactions) are common, particularly if the treatment is stopped suddenly. The risk of withdrawal symptoms depends on the length of treatment, dosage, and the rate at which the dose is reduced. Generally, such symptoms are mild to moderate. However, they can be serious in some patients. They normally occur within the first few days after stopping treatment. In general, such symptoms disappear on their own and wear off within 2 weeks. In some patients they may last longer (2-3 months or more). When stopping treatment with Alprax plus it is recommended to reduce the dose gradually over a period of several weeks or months, and you should always discuss the best way of stopping treatment with your doctor.
Thoughts of suicide and worsening of your depression or anxiety disorder:
If you are depressed and/or have anxiety disorders, you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:
 If you have previously had thoughts about killing or harming yourself.
 If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.
Children and adolescents:
Alprax plus should not usually be used in children and adolescents less than 18 years old. Patients under 18 have an increased risk of undesirable effects, such as suicide attempt, thoughts of harming or killing themselves (suicidal thoughts) and hostility (mainly aggressiveness, oppositional behaviour and anger) when they are treated with this class of medicines. Nevertheless, it is possible that your doctor decides to prescribe ALPRAX PLUS to a patient under 18 if it is in the patient's interest. If your doctor has prescribed ALPRAX PLUS to you and you are less than 18 years old and you want to discuss this, please contact him/her. Furthermore, if any of the symptoms listed above appear or worsen while you are taking ALPRAX PLUS, you should inform your doctor. Also, the long-term safety of ALPRAX PLUS in regard to growth, maturation and learning (cognitive) and behavioural development in this age group has not yet been demonstrated.

Other medicines and ALPRAX PLUS:
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Some medicines can affect the way ALPRAX PLUS works, or ALPRAX PLUS itself can reduce the effectiveness of other medicines taken at the same time.
Taking ALPRAX PLUS together with the following medicines may cause serious side effects:

 Medicines called monoamine oxidase inhibitors (MAOIs), like moclobemide (to treat depression) and selegiline (to treat Parkinson's disease), the antibiotic linezolid and methylene blue (to treat high levels of met haemoglobin in the blood). Do not use ALPRAX PLUS together with these medicines.
 Medicines to treat mental disorders such as psychosis (pimozide). Do not use ALPRAX PLUS together with pimozide.
 Medicines containing amphetamines (used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity).
 Herbal medicine containing St. John's Wort (Hypericum perforatum). The effects of St. John's Wort may last for 1-2 weeks.
 Products containing the amino acid tryptophan.
 Medicines to treat severe pain (e.g. tramadol).
 Medicines to treat migraines (e.g. sumatriptan).
 Blood thinning medicine (warfarin).
 Medicines to treat pain/arthritis (Non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen, acetylsalicylic acid (aspirin)).
 Sedatives (diazepam).
 Diuretics (also called 'water' tablets).
 Medicines to treat epilepsy (phenytoin, phenobarbital, carbamazepine).
 Medicines to treat diabetes (tolbutamide).
 Medicines to treat excessive stomach acid, ulcers and heartburn (cimetidine, omeprazole, lansoprazole, pantoprazole, rabeprazole).
 Medicines to treat mania and depression (lithium).
 Other medicines to treat depression (such as amitriptyline, nortriptyline, nefazodone, fluoxetine, fluvoxamine).
 Medicines to treat schizophrenia and other mental disorders (such as perphenazine, levomepromazine and olanzapine).
 Medicines used to treat high blood pressure, chest pain or regulate the rate and rhythm of the heart (such as verapamil, diltiazem, flecainide, propafenone).
 Medicines used to treat bacterial infections (such as rifampicin, clarithromycin, telithromycin, erythromycin).
 Medicines used to treat fungal infections (such as ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole).
 Medicines used to treat HIV/AIDS and Hepatitis C (protease inhibitors such as ritonavir, telaprevir).
 Medicines used to prevent nausea and vomiting after an operation or chemotherapy (aprepitant).
 Medicines known to increase the risk of changes in the electrical activity of the heart (e.g. some antipsychotics and antibiotics).

- Any other medicines to treat anxiety or depression or to help you sleep (e.g. nefazodone, fluvoxamine, fluoxetine).
- Some strong pain killers (e.g. opioids such as - morphine, codeine or propoxyphene).
- Antipsychotic medicines used to treat mental illnesses like schizophrenia.
- Medicines to treat epilepsy.
- Antihistamines for relief of allergies.
- Medicines for treating fungal infections (e.g. ketoconazole).
- Oral contraceptives ('the pill').
- Certain antibiotics (e.g. erythromycin).
- Cimetidine (for treating stomach ulcers).

- Diltiazem (used for angina and high blood pressure).
- Digoxin (used to treat various heart conditions).
- Ritonavir or other similar medicines used for treating HIV.

If you are going to have an operation where you will be given a general anaesthetic, tell your doctor or anaesthetist that you are taking ALPRAX PLUS.

Concomitant use of ALPRAX PLUS and opioids (strong pain killers, medicines for substitution therapy and some cough medicines) increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However, if your doctor does prescribe ALPRAX PLUS together with opioids the dosage and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all opioid medicines you are taking, and follow your doctor's dosage recommendation closely. It could be helpful to inform friends or relatives to be aware of sign and symptoms stated above. Contact your doctor when experiencing such symptoms.

ALPRAX PLUS with food, drink and alcohol:
ALPRAX PLUS tablets can be taken with or without food. as alcohol increases the effects of the medicine Alcohol should be avoided whilst taking ALPRAX PLUS.
Sertraline should not be taken in combination with grapefruit juice, as this may increase the level of sertraline in your body.

Pregnancy, breast-feeding and fertility:
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not breast-feed while taking ALPRAX PLUS, as the drug may pass into breast milk.

The safety of sertraline has not fully been established in pregnant women. Sertraline will only be given to you when pregnant if your doctor considers that the benefit for you is greater than any possible risk to the developing baby.
Make sure your midwife and/or doctor know you are on ALPRAX PLUS. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like ALPRAX PLUS may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby, you should contact your midwife and/or doctor immediately.
Your newborn baby might also have other conditions, which usually begin during the first 24 hours after birth. Symptoms include:
 trouble with breathing,
 a blueish skin or being too hot or cold,
 blue lips,
 vomiting or not feeding properly,
 being very tired, not able to sleep or crying a lot,
 stiff or floppy muscles,
 tremors, jitters or fits,
 increased reflex reactions,
 irritability,

 low blood sugar.

If your baby has any of these symptoms when it is born, or you are concerned about your baby's health, contact your doctor or midwife who will be able to advise you.
There is evidence that sertraline passes into human breast milk. Sertraline should only be used in women during breast-feeding, if your doctor considers that the benefit exceeds any possible risk to the baby.
Some medicines like sertraline may reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.
Driving and using machines:
Alprax plus may influence your ability to drive or use machines. You should therefore not drive or operate machinery, until you know how this medication affects your ability to perform these activities. ALPRAX PLUS can affect your ability to drive as it may make you sleepy or dizzy.

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

3. How to take ALPRAX PLUS

Always take this medicine exactly as your doctor or pharmacist has told you.

If you take more ALPRAX PLUS than you should:
If you accidentally take too much ALPRAX PLUS contact your doctor at once or go to the nearest hospital casualty department. Always take the labelled medicine package with you, whether there is any medication left or not.
Symptoms of overdose may include drowsiness, nausea and vomiting, rapid heart rate, shaking, agitation, dizziness and in rare cases unconsciousness.

If you forget to take ALPRAX PLUS:
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, do not take the missed dose. Just take the next dose at the right time.

If you stop taking ALPRAX PLUS:
Do not stop taking ALPRAX PLUS unless your doctor tells you to. Your doctor will want to gradually reduce your dose of ALPRAX PLUS over several weeks, before you finally stop taking this medicine. If you suddenly stop taking this medicine you may experience side effects such as dizziness, numbness, sleep disturbances, agitation or anxiety, headaches, feeling sick, being sick and shaking. If you experience any of these side effects, or any other side effects whilst stopping taking ALPRAX PLUS, please speak to your doctor.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Nausea is the most common side effect. The side effects depend on the dose and often disappear or lessen with continued treatment.
Tell your doctor immediately:

If you experience any of the following symptoms after taking this medicine, these symptoms can be serious.
- Memory loss (amnesia).
- Yellowing of the skin and whites of the eyes (jaundice).
 If you develop a severe skin rash that causes blistering (erythema multiforme), (this can affect the mouth and tongue). These may be signs of a condition known as Stevens Johnson Syndrome, or Toxic Epidermal Necrolysis (TEN). Your doctor will stop your treatment in these cases.
 Allergic reaction or allergy, which may include symptoms such as an itchy skin rash, breathing problems, wheezing, swollen eyelids, face or lips.
 If you experience agitation, confusion, diarrhoea, high temperature and blood pressure, excessive sweating and rapid heartbeat. These are symptoms of Serotonin Syndrome. In rare cases this syndrome may occur when you are taking certain medicines at the same time as sertraline. Your doctor may wish to stop your treatment.
 If you develop yellow skin and eyes which may mean liver damage.
 If you experience depressive symptoms with ideas of harming or killing yourself (suicidal thoughts).
 If you start to get feelings of restlessness and are not able to sit or stand still after you start to take ALPRAX PLUS. You should tell your doctor if you start to feel restless.
 If you have a fit (seizure).
 If you have a manic episode.

The following side effects were seen in clinical trials in adults and after marketing.

Dependence and withdrawal symptoms
It is possible to become dependent on medicines like ALPRAX PLUS while you are taking them which increases the likelihood of getting withdrawal symptoms when you stop treatment.

Withdrawal symptoms are more common if you:
- stop treatment suddenly
- have been taking high doses
- have been taking this medicine for long time
- have a history of alcohol or drug abuse.

This can cause effects such as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, mood changes, difficulty sleeping and irritability.

In severe cases of withdrawal, you can also get the following symptoms: nausea (feeling sick), vomiting, sweating, stomach cramps, muscle cramps, a feeling of unreality or detachment, being unusually sensitive to sound, light or physical contact, numbness and tingling of the feet and hands, hallucinations (seeing or hearing things which are not there while you are awake), tremor or epileptic fits.

Very common (may affect more than 1 in 10 people):
Insomnia, dizziness, sleepiness, headache, diarrhoea, feeling sick, dry mouth, ejaculation failure, fatigue. - Depression- Sleepiness and drowsiness
- Jerky, uncoordinated movements
- Inability to remember bits of information
- Slurred speech

Common (may affect up to 1 in 10 people):
 chest cold, sore throat, runny nose,
 decreased appetite, increased appetite,
 anxiety, depression, agitation, decreased sexual interest, nervousness, feeling strange, nightmare, teeth grinding,
 shaking, muscular movement problems (such as moving a lot, tense muscles, difficulty walking and stiffness, spasms and involuntary movements of muscles), numbness and tingling, muscle tense, lack of attention, abnormal taste,
 visual disturbance,
 ringing in ears,
 palpitations,
 hot flush,
 yawning,
 upset stomach, constipation, abdominal pain, vomiting, gas,
 increased sweating, rash,
 back pain, joint pain, muscle pain,
 menstrual irregularities, erectile dysfunction,
 malaise, chest pain, weakness, fever,
 weight increased,
 injury.
- Loss of appetite
- Confusion and disorientation
- Increased sex drive (men and women) and erectile dysfunction
- Nervousness or feeling anxious or agitated
- Insomnia (inability to sleep or disturbed sleep)
- Problems with balance, and unsteadiness (similar to feeling drunk) especially during the day
- Loss of alertness or concentration
- Inability to stay awake, feeling sluggish
- Shakiness or trembling
- Double or blurred vision
- Feeling sick
- Skin reactions
- Change in your weight

Uncommon (may affect up to 1 in 100 people):
 gastroenteritis, ear infection,
 tumour,
 hypersensitivity, seasonal allergy,
 low thyroid hormones,
 suicidal thoughts, suicidal behaviour, psychotic disorder, thinking abnormal, lack of caring, hallucination, aggression, euphoric mood, paranoia,
 amnesia, decreased feeling, involuntary muscle contractions, passing out, moving a lot, migraine, convulsion, dizziness while standing up, abnormal coordination, speech disorder,
 enlarged pupils,
 ear pain,
 fast heartbeat, heart problem
 bleeding problems (such as stomach bleeding), high blood pressure, flushing, blood in urine,
 shortness of breath, nose bleed, breathing difficulty, possible wheezing,

 tarry stools, tooth disorder, inflammation of the oesophagus, tongue problem, haemorrhoids, increased saliva, difficulty swallowing, burping, tongue disorder,
 eye swelling, hives, hair loss, itching, purple spots on skin, skin problem with blisters, dry skin, face oedema, cold sweat,
 osteoarthritis, muscle twitching, muscle cramps, muscular weakness,
 increase in frequency of urination, problem urinating unable to urinate, urinary incontinence, increase in urination, night-time urination,
 sexual dysfunction, excessive vaginal bleeding, vaginal haemorrhage, female sexual dysfunction,
 swelling in legs, chills, difficulty walking, thirst,
 increase in liver enzyme levels, weight decreased.
- Feeling elated or over-excited, which causes unusual behaviour
- Hallucination (seeing or hearing things that do not exist)
- Feeling agitated or angry
- Incontinence
- Cramping pain in the lower back and thighs, which may indicate menstrual disorder
- Muscle spasms or weakness

 Cases of suicidal ideation and suicidal behaviours have been reported during sertraline therapy or early after treatment discontinuation.
Rare (may affect up to 1 in 1,000 people):
 diverticulitis, swollen lymph glands, decrease in clotting cells, decrease in white blood cells,
 severe allergic reaction,
 endocrine problems,
 high cholesterol, problems controlling blood sugar levels (diabetes), low blood sugar, increase in blood sugar levels, low blood salt,
 physical symptoms due to stress or emotions, terrifying abnormal dreams, drug dependence, sleep walking, premature ejaculation,
 coma, abnormal movements, difficulty moving, increased sensation, sudden severe headache (which may be a sign of a serious condition known as Reversible Cerebral Vasoconstriction Syndrome (RCVS)), sensory disturbance,
 spots in front of eyes, glaucoma, double vision, light hurts eye, blood in the eye, unequal sized pupils, vision abnormal, tear problem,
 heart attack, light-headedness, fainting, or chest discomfort which could be signs of changes in the electrical activity (seen on electrocardiogram) or abnormal rhythm of the heart*, slow heartbeat,
 poor circulation of arms and legs,
 breathing fast, progressive scarring of lung tissue (Interstitial Lung Disease), closing up of throat, difficulty talking, breathing slow, hiccups,
 mouth ulceration, pancreatitis, blood in stool, tongue ulceration, sore mouth,
 problems with liver function, serious liver function problems, yellow skin and eyes (jaundice),
 skin reaction to sun, skin oedema, hair texture abnormal, skin odour abnormal, hair rash,
 breakdown of muscle tissue, bone disorder,
 urinary hesitation, decreased urination,
 breast discharge, dry vaginal area, genital discharge, red painful penis and foreskin, breast enlargement*, prolonged erection,
 hernia, drug tolerance decreased,
 increase in blood cholesterol levels, abnormal laboratory tests, semen abnormal, problems with clotting,

 relaxation of blood vessels procedure.

Not known: frequency cannot be estimated from the available data:
 lockjaw,
 bedwetting
- In women, irregular periods or production of too much prolactin (the hormone that stimulates milk production)
- Feeling hostile or aggressive
- Abnormal thoughts
- Twisting or jerking movements
- Being hyperactive
- Stomach upsets
- Problems with liver function (this shows up in blood tests), inflammation of the liver (hepatitis)
- Imbalance to part of nervous system. Symptoms may include: fast heart beat and unstable blood pressure (feeling dizzy, light-headed or faint)
- Serious allergic reaction which causes swelling of the face or throat
- Swelling of the ankles, feet or fingers
- Skin reaction caused by sensitivity to sunlight
- Difficulty urinating or bladder control problems
- Increased pressure in the eyes, which can also affect your vision

5. How to store ALPRAX PLUS

STORE IN A DRY PLACE AT A TEMPERATURE NOT EXCEEDING 30°C, PROTECTED FROM LIGHT.

6. Contents of the pack and other information

What ALPRAX PLUS contains

The active substances in this product are Alprazolam and sertraline. Other inactive ingredients are Lake of Brilliant Blue, Dibasic Calcium, Magnesium Stearate, Talc, Polyvinyl Pyrrolidone, Hydroxypropyl methylcellulose, Iso propyl Alcohol, microcrystalline Cellulose, Diabasic calcium, Magnesium stearate, Sodium starch glycollate, Polysorbate, Colloidal silicon dioxide, Hydroxy Propyl cellulose, Iso propyl alcohol, Sodium starch Glycollate.

10. DETAILS OF MANUFACTURER

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle camp, NH-10, East District, Gangtok, Sikkim-737 135

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

M/563/2010 issued on 26.04.2014

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN /ALPRAX PLUS 0.5mg and 25 mg /SEP-19/01/PI