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 and 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:

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

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.

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.

4.6 Use in Special Populations

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.

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.

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

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	

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)
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, hyponatraemi a	

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)
Psychiatric disorders	Insomnia, depression	anxiety, agitation, libido decreased, nervousness, depersonalisation, nightmare, bruxism, Confusional state, disorientation , libido increased	suicidal ideation/behavi our, 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 nervous system imbalance, dystonia, teeth grinding or gait abnormalities) , paraesthesia, hypertonia, disturbance in attention, dysgeusia	amnesia, hypoaesthesia, muscle contractions involuntary, syncope, hyperkinesia, migraine, convulsion, dizziness postural, coordination abnormal, speech disorder	coma, akathisia, dyskinesia, hyperaesthesi a, cerebrovascul ar spasm (including reversible cerebral vasoconstricti on syndrome and Call-Fleming syndrome), psychomotor restlessness, sensory disturbance, choreoathetos is, also reported were signs and symptoms associated	

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)
				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		

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)
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	hyperventilati on, interstitial lung disease, laryngospasm, , dysphonia, stridor, hypoventilati on, 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, haematochezi a, tongue ulceration, stomatitis	

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)
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 oedema, cold sweat	rare reports of severe cutaneous adverse reactions (SCAR): e.g. Stevens-Johnson syndrome and 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	rhabdomyolysis, bone disorder	trismus

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)
			weakness		
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 results, semen abnormal, altered platelet	Intraocular pressure increased

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)
				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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

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

5.1 Mechanism of Action

Sertraline

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

Sertraline

Clinical efficacy and safety

Major Depressive Disorder

A study was conducted which involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on sertraline 50-200 mg/day. These patients (n=295) were randomized to continuation for 44 weeks on double-blind sertraline 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo. The mean dose for completers was 70 mg/day. The % of responders (defined as those patients that did not relapse) for sertraline and placebo arms were 83.4% and 60.8%, respectively.

Post-traumatic stress disorder (PTSD)

Combined data from the 3 studies of PTSD in the general population found a lower response rate in males compared to females. In the two positive general population trials, the male and female sertraline vs. placebo responder rates were similar (females: 57.2% vs 34.5%; males: 53.9% vs 38.2%). The number of male and female patients in the pooled general population trials was 184 and 430, respectively and hence the results in females are more robust and males were associated with other baseline variables (more substance abuse, longer duration, source of trauma etc.) which are correlated with decreased effect.

Paediatric OCD

The safety and efficacy of sertraline (50-200 mg/day) was examined in the treatment of nondepressed children (6-12 years old) and adolescent (13-17 years old) outpatients with obsessive compulsive disorder (OCD). After a one week single blind placebo lead-in, patients were randomly assigned to twelve weeks of flexible dose treatment with either sertraline or placebo. Children (6-12 years old) were initially started on a 25 mg dose. Patients randomized to sertraline showed significantly greater improvement than those randomised to placebo on the Children's Yale-Brown Obsessive Compulsive Scale CYBOCS (p =0.005) the NIMH Global Obsessive Compulsive Scale (p=0.019), and the CGI Improvement (p =0.002) scales. In addition, a trend toward greater improvement in the sertraline group than the placebo group was also observed on the CGI Severity scale (p=0.089). For CY-BOCs the mean baseline and change from baseline scores for the

placebo group was 22.25 ± 6.15 and -3.4 ± 0.82, respectively, while for the sertraline group, the mean baseline and change from baseline scores were 23.36 ± 4.56 and -6.8 ± 0.87, respectively. In a post-hoc analysis, responders, defined as patients with a 25% or greater decrease in the CY-BOCs (the primary efficacy measure) from baseline to endpoint, were 53% of sertralinetreated patients compared to 37% of placebo- treated patients (p=0.03). Long term safety and efficacy data are lacking for this paediatric population.

Paediatric population

No data is available for children under 6 years of age.

Alprazolam

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).

5.3 Pharmacokinetic Properties

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.

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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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.

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

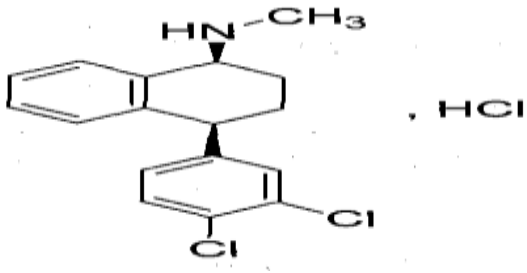
Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile 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.

7. DESCRIPTION

Sertraline Hydrochloride

Sertraline Hydrochloride is (1 S,4S)-4-(3,4-dichlorophenyl)-Nmethyl-l,2,3,4-tetrahydronaphthalen-1-amine hydrochloride. Having molecular Formula $C_{17}H_{17}ChN$, HCl and Molecular weight 342.7. The empirical formula $C_{17}H_{17}ChN$, HCl is represented by the following structural formula:



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

Alprazolam

Alprazolam is 8-chloro-1-methyl-6-phenyl -4H-1,2,4-triazolo[4,3-a] [1,4]benzodiazepine. Having molecular Formula $C_{17}H_{13}CLN_4$ and Molecular weight 308.8. The empirical formula $C_{17}H_{13}CLN_4$ is represented by the following structural formula:

Alprazolam is a white to off-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

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal Products)

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 0.5 mg and 25 mg /SEP-2019/01/PI