Generic Name Paroxetine extended release + Clonazepam

Trade Name Depaxil CR Plus

1. NAME OF THE MEDICINAL PRODUCT: Paroxetine and clonazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-coated bilayer tablet contains:
Paroxetine Hydrochloride IP (As Hemihydrate)
Equivalent to Paroxetine …….12.5mg (As extended release form)
Clonazepam IP……0.5mg

Each Film-coated bilayer tablet contains:
Paroxetine Hydrochloride IP (As Hemihydrate)
Equivalent to Paroxetine ……25mg (As extended release form)
Clonazepam IP……..0.5mg

3. PHARMACEUTICAL FORM: Film-coated bilayer tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
The combination is indicated for the treatment of patients with co-morbid depression and anxiety disorders.

4.2 Posology and Method of Administration
For the treatment of patients with co-morbid depression with anxiety disorder, should be administered as starting single daily dose of 12.5mg/0.5mg per day. Dose can be increased up to25mg/0.5mg at intervals of at least 1 week. Dosage should not be increased more than two tablets of 25mg/0.5mg per day.

4.3 Contraindications
Hypersensitivity to clonazepam or Paroxetine or any of the excipients.
The use of MAOIs intended to treat psychiatric disorders with FDC or within 14 days of stopping treatment with FDC is contraindicated because of an increased risk of serotonin syndrome. The use of FDC within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

In a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

Concomitant use with thioridazine, pimozide is contraindicated.

History of sensitivity to benzodiazepines

In patients with clinical or biochemical evidence of significant liver disease

Acute narrow angle glaucoma (May be used in patients with open angle glaucoma who are receiving appropriate therapy)

4.4 Special Warnings and Special Precautions for Use

Paroxetine CR:

Warnings:

Suicide/suicidal thoughts or clinical worsening:

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

Other psychiatric conditions for which paroxetine 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 a 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.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during

the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Paroxetine controlled release should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Paroxetine controlled release is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Paroxetine controlled release, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Paroxetine controlled release with MAOIs intended to treat psychiatric disorders is contraindicated. Paroxetine controlled release should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Paroxetine controlled release. Paroxetine controlled release should be discontinued before initiating treatment with the MAOI.

If concomitant use of Paroxetine controlled release with certain other serotonergic drugs, i.e., triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, be aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases. Treatment with Paroxetine controlled release and any concomitant

serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including Paxil may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Potential Interaction With Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be dose related. An in vivo study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine.

Clonazepam:

Interference With Cognitive and Motor Performance: Since Clonazepam produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during Clonazepam therapy.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including Clonazepam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed**.**

Anyone considering prescribing Clonazepam or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Pregnancy Risks: Data from several sources raise concerns about the use of Clonazepam during pregnancy.

Animal Findings: In three studies in which Clonazepam was administered orally to pregnant rabbits at doses of 0.2, 1, 5 or 10 mg/kg/day (low dose approximately 0.2 times the maximum recommended human dose of 20 mg/day for seizure disorders and equivalent to the maximum dose of 4 mg/day for panic disorder, on a mg/m2 basis) during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were observed in mice and rats following administration during organogenesis of oral doses up to 15 mg/kg/day or 40 mg/kg/day, respectively (4 and 20 times the maximum recommended human dose of 20 mg/day for seizure disorders and 20 and 100 times the maximum dose of 4 mg/day for panic disorder, respectively, on a mg/m2 basis).

General Concerns and Considerations About Anticonvulsants: Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

In children of women treated with drugs for epilepsy, reports suggesting an elevated incidence of birth defects cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors (eg, genetic factors or the epileptic condition itself) may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

General Concerns About Benzodiazepines: An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Clonazepam in Women of Childbearing Potential: In general, the use of Clonazepam in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants for epilepsy in women of childbearing potential should be weighed in treating or counseling these women.
Because of experience with other members of the benzodiazepine class, Clonazepam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency in the treatment of panic disorder, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

Withdrawal Symptoms: Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines

PRECAUTIONS
Mania: As with all antidepressants, paroxetine should be used with caution in patients with a history of mania. Paroxetine should be discontinued in any patient entering a manic phase.

Seizures:
Overall the incidence of seizures is less than 0.1% in patients treated with paroxetine. The medicinal product should be discontinued in any patient who develops seizures.

Discontinuation of Treatment With Paroxetine controlled release: Adverse events while discontinuing therapy with Paroxetine controlled release were not systematically evaluated in most clinical trial.
However, in recent placebo-controlled clinical trials utilizing daily doses of Paroxetine controlled release up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with Paroxetine controlled release were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for 1 week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for Paroxetine controlled release, at an incidence of 2% or greater for Paroxetine controlled release and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing Paroxetine controlled release (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with Paroxetine controlled release.

During marketing of Paroxetine controlled release and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Paroxetine controlled release. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION). See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia/psychomotor restlessness

The use of paroxetine has been associated with the development of akathisia, which is characterised by an inner sense of restlessness and by psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. 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.

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted. Additionally, there have been studies suggesting that an increase in blood glucose levels may occur when paroxetine and pravastatin are co-administered

ECT

There is little clinical experience of the concurrent administration of paroxetine with ECT.

Cardiac Conditions

The usual precautions should be observed in patients with cardiac conditions.

Hyponatraemia

Hyponatraemia has been reported rarely, predominantly in the elderly. Caution should also be exercised in those patients at risk of hyponatraemia e.g. from concomitant medications and cirrhosis. The hyponatraemia generally reverses on discontinuation of paroxetine.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Other haemorrhagic manifestations e.g. gastrointestinal haemorrhage have been reported. Elderly patients may be at an increased risk.

Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, medicinal products known to affect platelet function or other medicinal products that may increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

Interaction with tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a result of paroxetine's irreversible inhibition of CYP2D6. Paroxetine should whenever possible be avoided during tamoxifen use for treatment or prevention of breast cancer.

Withdrawal symptoms seen on discontinuation of paroxetine treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In clinical trials adverse events seen on treatment discontinuation occurred in 30% of patients treated with paroxetine compared to 20% of patients treated with placebo. The occurrence of withdrawal symptoms is not the same as the drug being addictive or dependence producing.
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 and electric shock sensations and tinnitus), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Bone Fracture: Epidemiological studies on bone fracture risk following exposure to some antidepressants, including SSRIs, have reported an association between antidepressant treatment and fractures. There are multiple possible causes for this observation and it is unknown to what extent fracture risk is directly attributable to SSRI treatment. The possibility of a pathological fracture, that is, a fracture produced by minimal trauma in a patient with decreased bone mineral density, should be considered in patients treated with paroxetine who present with unexplained bone pain, point tenderness, swelling, or bruising.

Use in Patients With Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using Paroxetine controlled release in patients with diseases or conditions that could affect metabolism or hemodynamic responses. As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when Paroxetine controlled release is prescribed for patients with narrow angle glaucoma. Paroxetine controlled release or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure. Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance)

Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference With Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies immediate-release paroxetine hydrochloride has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with Paroxetine controlled release does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with use of Paroxetine controlled release in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Although immediate-release paroxetine hydrochloride has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paroxetine controlled release.

Laboratory Tests: There are no specific laboratory tests recommended

General: Worsening of Seizures: When used in patients in whom several different types of seizure disorders coexist, Clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and Clonazepam may produce absence status.

Laboratory Testing During Long-Term Therapy: Periodic blood counts and liver function tests are advisable during long-term therapy with Clonazepam.

Risks of Abrupt Withdrawal: The abrupt withdrawal of Clonazepam, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing Clonazepam, gradual withdrawal is essential. While Clonazepam is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.

Caution in Renally Impaired Patients: Metabolites of Clonazepam are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Hypersalivation: Clonazepam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of

respiratory depression, Clonazepam should be used with caution in patients with chronic respiratory diseases.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Paroxetine CR

Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of Paroxetine controlled release with tryptophan is not recommended.

Monoamine Oxidase Inhibitors: The use of MAOIs intended to treat psychiatric disorders with Paroxetine controlled release or within 14 days of stopping treatment with Paroxetine controlled release is contraindicated because of an increased risk of serotonin syndrome. The use of Paroxetine controlled release within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Pimozide: In a controlled study of healthy volunteers, after immediate-release paroxetine hydrochloride was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and Cmax of 62%, compared to pimozide administered alone. The increase in pimozide AUC and Cmax is due to the CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and Paroxetine controlled release is contraindicated.

Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs, including paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when Paroxetine controlled release is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, lithium, fentanyl, tramadol, or St. John's Wort). The concomitant use of Paroxetine controlled release with MAOIs (including linezolid and intravenous methylene blue) is contraindicated. The concomitant use of Paroxetine controlled release with other SSRIs, SNRIs or tryptophan is not recommended.

Thioridazine: Concomitant use with thioridazine is contraindicated

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin.

Since there is little clinical experience, the concomitant administration of Paroxetine controlled release and warfarin should be undertaken with caution.

Triptans: There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of Paroxetine controlled release with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine: Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of Paroxetine controlled release after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital: Phenobarbital induces many cytochrome P450 (oxidative) enzymes. When a single oral 30-mg dose of immediate-release paroxetine was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and T½ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with Paroxetine controlled release is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect

Phenytoin: When a single oral 30-mg dose of immediate-release paroxetine was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and T½ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when Paroxetine controlled release is coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect.

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P450 isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme In most patients (>90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In 1 study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) Cmax, AUC, and T½ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately

1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine Cmax values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

Concomitant use of Paroxetine controlled release with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either Paroxetine controlled release or the other drug.

Therefore, coadministration of Paroxetine controlled release with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered

Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite (endoxifen) and hence reduced efficacy of tamoxifen.

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P450 isozymes that, unlike CYP2D6, show no evidence of saturation.

Drugs Metabolized by Cytochrome CYP3A4: An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine’s in vitro Ki and its lack of effect on terfenadine's in vivo clearance predicts its effect on other CYP3A4 substrates, paroxetine’s extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of TCAs with Paroxetine controlled release, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with Paroxetine controlled release

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of Paroxetine controlled release to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking Paroxetine controlled release.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of Paroxetine controlled release and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state AUC0-24, Cmax, and Cmin values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS: Postmarketing Reports).

Theophylline: Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and Paroxetine controlled release.

Clonazepam

Effect of Clonazepam on the Pharmacokinetics of Other Drugs: Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Effect of Other Drugs on the Pharmacokinetics of Clonazepam: Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics.

In a study in which the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with multiple effects on the GI tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the Cmax of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone. Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme ystem, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

Pharmacodynamic Interactions: The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

4.6 Fertility, Pregnancy and Lactation

Paroxetine CR

Pregnancy

Some epidemiological studies suggest an increased risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septum defects) associated with the use of paroxetine during the first trimester. The mechanism is unknown. The data suggest that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less then 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant.

Abrupt discontinuation should be avoided during pregnancy.

New-born infants should be observed if maternal use of paroxetine continues into the later stages of pregnancy, particularly the third trimester.

The following symptoms may occur in the new-born infants after maternal paroxetine 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, particularly in late pregnancy, may have an increased risk of persistent pulmonary hypertension of 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
Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (<2 ng/ml) or very low (<4 ng/ml). No signs of drug effects were observed in these infants. Since no effects are anticipated, breast-feeding can be considered.

Fertility
Animal data have shown that paroxetine may affect sperm quality (see section 5.3). In vitro data with human material may suggest some effect on sperm quality, however, human case reports with some SSRIs (including paroxetine) have shown that an effect on sperm quality appears to be reversible.
Impact on human fertility has not been observed so far.

Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development

Clonazepam:

Pregnancy: Teratogenic Effects: Pregnancy Category D

Labor and Delivery: The effect of Clonazepam on labor and delivery in humans has not been specifically studied; however, perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena.

Nursing Mothers: Mothers receiving Clonazepam should not breastfeed their infants.

4.7 Effects on Ability to Drive and Use Machines

Patients Should not drive, operate heavy machinery, or do other dangerous activities until it is known how the combination affects them

4.8 Undesirable Effects

Paroxetine CR

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With Paroxetine controlled release:

Adverse Events Associated With Discontinuation of Treatment: Major Depressive Disorder –
The most common events (≥1%) associated with discontinuation and considered to be drug related: Nausea, asthenia, dizziness, somnolence.

In a placebo-controlled study of elderly patients with major depressive disorder, adverse events leading to discontinuation of an adverse event- Nausea, Headache, Depression, LFT's abnormal.

Adverse events leading to discontinuation in panic disorder: Nausea, Insomnia, Headache, Asthenia

Adverse events leading to discontinuation in social anxiety disorder: nausea, headache, diarrhoea

The most common events (≥1%) associated with discontinuation in either group treated with Paroxetine controlled release with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen: Nausea, Asthenia, Somnolence, Insomnia, Concentration Impaired, Dry mouth, Dizziness, Decreased Appetite, Sweating, Tremor, Yawn, Diarrhoea.

Commonly Observed Adverse Events: Depression
The most commonly observed adverse events associated with the use of Paroxetine controlled release incidence of 5.0% or greater and incidence for Paroxetine controlled release at least twice that for placebo, were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of Paroxetine controlled release in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder: In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder: The most commonly observed adverse events associated with the use of Paroxetine controlled release either during continuous dosing or luteal phase dosing incidence of 5% or greater and incidence for Paroxetine controlled release at least twice that for placebo- Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation.

Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With Paroxetine controlled release in a Pool of 2 Studies in Depression

Body as a Whole: Headache, Asthenia, Infection, Abdominal pain, back pain, trauma, pain, allergic reaction.

Cardiovascular System: Tachycardia, Vasodilatation

Digestive System: Nausea, Diarrhea, Dry Mouth, constipation, Flatulence, Decreased Appetite, Vomiting

Nervous System: Somnolence, insomnia, dizziness, decreased libido, tremor, hypertonia, paresthesia, agitation, confusion

Respiratory system: Yawn, rhinitis, increased cough, bronchitis

Skin and appendages: Sweating, photosensitivity

Special senses: abnormal vision, taste perversion

Urogenital system: Abnormal Ejaculation (Mostly anorgasmia or delayed ejaculation), Female Genital Disorder (Mostly anorgasmia or delayed orgasm), Impotence, Urinary Tract Infection, Menstrual Disorder, vaginitis

Adverse events for which the Paroxetine controlled release reporting incidence was less than or equal to the placebo. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.

Treatment-Emergent Adverse Events Occurring in ≥5% of Patients Treated With Paroxetine controlled release in a Study of Elderly Patients With Depression

Body as a Whole: Headache, asthenia, trauma, infection

Digestive system: Dry mouth, diarrhoea, constipation, dyspepsia, decreased appetite, flatulence

Nervous system: Somnolence, insomnia, dizziness, decreased libido, tremor

Skin and Appendage: Sweating

Urogenital System: Abnormal Ejaculation (Mostly anorgasmia or delayed ejaculation), Impotence

Adverse events for which the Paroxetine controlled release reporting incidence was less than or equal to the placebo. These events are nausea and respiratory disorder.

Treatment-Emergent Adverse Events Occurring in ≥1% of Patients Treated With Paroxetine controlled release in a Pool of 3 Panic Disorder Studies

Body as a Whole: Asthenia, Abdominal Pain, Trauma

Cardiovascular System: Vasodilation

Digestive System: Nausea, dry mouth, diarrhoea, constipation, decreased appetite

Metabolic/ nutritional disorders: Weight loss

Musculoskeletal System: Myalgia

Nervous system: Insomnia, Somnolence, Libido Decreased, Nervousness, tremor, anxiety, agitation, hypertonia, myoclonus

Respiratory system: Sinusitis, Yawn

Skin and Appendages: Sweating

Special senses: abnormal vision

Urogenital System: abnormal ejaculation (Mostly anorgasmia or delayed ejaculation), impotence, female genital disorders (Mostly anorgasmia or difficulty achieving orgasm.), urinary frequency, urination impaired, vaginitis

Adverse events for which the reporting rate for Paroxetine controlled release was less than or equal to the placebo rate. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.

Treatment-Emergent Adverse Effects Occurring in ≥1% of Patients Treated With Paroxetine controlled release in a Social Anxiety Disorder Study

Body as a Whole: headache, asthenia, abdominal pain, back pain, trauma, allergic reaction, chest pain

Cardiovascular system: hypertension, migraine, tachycardia

Digestive system: Nausea, diarrhoea, constipation, dry mouth, dyspepsia, decreased appetite, tooth disorder

Metabolic/nutritional disorders: weight gain, weight loss

Nervous system: insomnia, somnolence, decreased libido, dizziness, tremor, anxiety, concentration impaired, depression, myoclonus, paresthesia

Respiratory system: Yawn

Skin and appendages: sweating, eczema

Special senses: abnormal vision, abnormality of accommodation

Urogenital system: abnormal ejaculation (Mostly anorgasmia or delayed ejaculation), impotence, female genital disorders (Mostly anorgasmia or difficulty achieving orgasm)

Adverse events for which the reporting rate for Paroxetine controlled release was less than or equal to the placebo rate. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.

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

Symptoms of sexual dysfunction reported in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

Males: Decreased libido, ejaculatory disturbance, impotence

Females: decreased libido, Orgasmic Disturbance

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment. Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with Paroxetine controlled release or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with Paroxetine controlled release, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Test: In a pool of 2 placebo-controlled clinical trials, patients treated with Paroxetine controlled release or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities. In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with Paroxetine controlled release and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with Paroxetine controlled release dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated with Paroxetine controlled release and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all 4 patients decreased substantially after discontinuation of Paroxetine controlled release. The clinical significance of these findings is unknown. In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients receiving placebo.

Other Events Observed During the Clinical Development of Paroxetine: Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.
Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea* ; infrequent were albuminuria, amenorrhea* , breast pain* , cystitis, dysuria, prostatitis* , urinary retention; rare were breast enlargement* , breast neoplasm* , female lactation, hematuria, kidney calculus, metrorrhagia* , nephritis, nocturia, pregnancy and puerperal disorders* , salpingitis, urinary incontinence, uterine fibroids enlarged* ; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

* Based on the number of men and women as appropriate.

Postmarketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), vasculitic syndromes (such as Henoch-Schönlein purpura) and premature births in pregnant women. There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment

Clonazepam:

The adverse experiences for Clonazepam are provided separately for patients with seizure disorders and with panic disorder.

Seizure Disorders: The most frequently occurring side effects of Clonazepam are referable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, ‘‘glassy-eyed’’ appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo

Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances).

The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages

Cardiovascular: Palpitations

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums

Genitourinary: Dysuria, enuresis, nocturia, urinary retention

Musculoskeletal: Muscle weakness, pains

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

Panic disorder
Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:

Adverse Events Associated With Discontinuation of Treatment:

Most Common Adverse Events (≥1%) Associated with Discontinuation of Treatment- somnolence, depression, dizziness, nervousness, ataxia, intellectual ability reduced.

Adverse Events Occurring at an Incidence of 1% or More Among Clonazepam-Treated Patients:
Central & Peripheral Nervous System- somnolence, dizziness, coordination abnormal, ataxia, dysarthria
Psychiatric: Depression, Memory Disturbance, nervousness, intellectual ability reduced, emotional lability, libido decreased, confusion.

Respiratory system: upper respiratory tract infection: Infection, sinusitis, rhinitis, coughing, pharyngitis, bronchitis

Gastrointestinal system: constipation, decreased appetite, abdominal pain
Body as a whole: Fatigue, allergic reaction

Musculoskeletal: Myalgia

Resistance mechanism disorders: Influenza

Urinary system: micturition frequency, urinary tract infecrion

Vision disorders: blurred vision

Reproductive disorders: Female- Dysmenorrhoea, colpitis
Male: ejaculation delayed and impotence

Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6- to 9-Week Trials

Somnolence, Depression, Coordination Abnormal, ataxia

* Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

Other Adverse Events Observed During the Premarketing Evaluation of Clonazepam in Panic Disorder:

Body as a Whole: weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized

Cardiovascular Disorders: chest pain, hypotension postural

Central and Peripheral Nervous System Disorders: migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching

Gastrointestinal System Disorders: abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, haemorrhoids

Hearing and Vestibular Disorders: vertigo, otitis, earache, motion sickness

Heart Rate and Rhythm Disorders: palpitation

Metabolic and Nutritional Disorders: thirst, gout

Musculoskeletal System Disorders: back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee

Platelet, Bleeding and Clotting Disorders: bleeding dermal

Psychiatric Disorders: insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased, aggressive reaction, apathy, attention lack, excitement, feeling mad, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning

Reproductive Disorders, Female: breast pain, menstrual irregularity Reproductive Disorders, Male: ejaculation decreased

Resistance Mechanism Disorders: infection mycotic, infection viral, infection streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis

Respiratory System Disorders: sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy

Skin and Appendages Disorders: acne flare, alopecia, xeroderma, dermatitis contact, flushing, pruritus, pustular reaction, skin burns, skin disorder

Special Senses Other, Disorders: taste loss

Urinary System Disorders: dysuria, cystitis, polyuria, urinary incontinence, bladder dysfunction, urinary retention, urinary tract bleeding, urine discoloration

Vascular (Extracardiac) Disorders: thrombophlebitis leg

Vision Disorders: eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia

4.9 Overdose

Paroxetine CR

Human Experience: Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: No specific antidotes for paroxetine are known. Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, or exchange perfusion are unlikely to be of benefit. A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a

tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

Clonazepam

Human Experience: Symptoms of clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma and diminished reflexes.

Overdose Management: Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

Flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Paroxetine CR

The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha1-, alpha2-, beta-adrenergic-, dopamine (D2)-, 5-HT1-, 5-HT2-, and histamine (H1)-receptors; antagonism of

muscarinic, histaminergic, and alpha1-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Clonazepam

The precise mechanism by which clonazepam exerts its antiseizure and antipanic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

5.2 Pharmacokinetic Properties:

Paroxetine CR

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The elimination half-life is approximately 15 to 20 hours after a single dose of Paroxetine controlled release. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution: Tablets of Paroxetine controlled release contain a degradable polymeric matrix designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release in vivo, an enteric coat delays the start of drug release until tablets of Paroxetine controlled release have left the stomach. Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma. Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or warfarin.

Metabolism and Excretion: The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of Paroxetine controlled release (12.5 mg, 25 mg, 37.5 mg, and 50 mg).

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic

acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions.

Other Clinical Pharmacology Information: Specific Populations: Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic plasma concentrations in patients with creatinine clearance below 30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, Cmax). The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals.

Elderly Patients: In a multiple-dose study in the elderly at daily doses of 20, 30, and 40 mg of the immediate-release formulation, Cmin concentrations were about 70% to 80% greater than the respective Cmin concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced.

Drug-Drug Interactions: In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine

Clonazepam

Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States: Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients.

5.3 Preclinical Safety Data

Paroxetine CR

Toxicology studies have been conducted in rhesus monkeys and albino rats; in both, the metabolic pathway is similar to that described for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one-year duration at doses that were 6 times higher than the recommended range of clinical doses.

Carcinogenesis: In two-year studies conducted in mice and rats, paroxetine had no tumorigenic effect.

Genotoxicity: Genotoxicity was not observed in a battery of in vitro and in vivo tests.

Reproduction toxicity studies in rats have shown that paroxetine affects male and female fertility by reducing fertility index and pregnancy rate. In rats, increased pup mortality and delayed ossification were observed. The latter effects were likely related to maternal toxicity and are not considered a direct effect on the foetus/neonate.

Clonazepam:

Carcinogenicity studies have not been conducted with clonazepam. The data currently available are not sufficient to determine the genotoxic potential of clonazepam. In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 M

6.2 Special Precautions for Storage

Store in a cool dry place and temperature not exceeding at 30°C, Protected from Light and Moisture

6.3 Nature and Contents of Container

10 x 10's

Marketed By:

Alkem Laboratories Limited,
Alkem House, S.B. Road,
Lower Parel (West)
Mumbai 400013