Front

Paraxyl CR®

(Paroxetine HCl)

Tablets

پراکسیل سی آر

COMPOSITION:

Paraxyl CR Tablet 12.5 mg:
Each enteric film coated tablet contains:
Paroxetine HCl USP equivalent to
Paroxetine ..... 12.5 mg.

Product Specs.: CCL Pharmaceuticals

Paraxyl CR Tablet 25 mg:
Each enteric film coated tablet contains:
Paroxetine HCl USP equivalent to
Paroxetine ..... 25 mg.

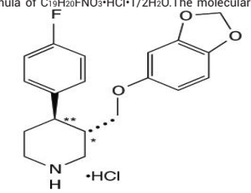
Product Specs.: CCL Pharmaceuticals

Paraxyl CR Tablet 37.5 mg:
Each enteric film coated tablet contains:
Paroxetine HCl USP equivalent to
Paroxetine ..... 37.5 mg.

Product Specs.: CCL Pharmaceuticals

DESCRIPTION:

PARAXYL CR (paroxetine hydrochloride) is an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic, or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[(3',4' methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate and has the empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot 1/2H_2O$.The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



CLINICAL PHARMACOLOGY:

Mechanism of action:
The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) 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). 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.

Pharmacokinetics:

Absorption and Distribution: Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. 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 PARAXYL CR (12.5 mg, 25 mg, 37.5 mg). Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. The metabolism of paroxetine is accomplished in part by CYP2D6. Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Specific Population: Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean 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.

INDICATIONS AND USAGE:

- ***Major Depressive Disorder:*** PARAXYL CR is indicated for the treatment of major depressive disorder.
- ***Panic Disorder:*** PARAXYL CR is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV.
- ***Social Anxiety Disorder:*** PARAXYL CR is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV
- ***Premenstrual Dysphoric Disorder:*** PARAXYL CR is indicated for the treatment of PMDD.

DOSAGE AND ADMINISTRATION:

Patients should be cautioned that PARAXYL CR should not be chewed or crushed, and should be swallowed whole:

- ***Major Depressive Disorder:*** Usual Initial Dosage: PARAXYL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Dose changes should occur at intervals of at least 1 week.
- ***Panic Disorder:*** Usual Initial Dosage: PARAXYL CR should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5 mg/day increments and at intervals of at least 1 week.
- ***Social Anxiety Disorder:*** Usual Initial Dosage: PARAXYL CR should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. If the dose is increased, this should occur at intervals of at least 1 week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.
- ***Premenstrual Dysphoric Disorder:*** Usual Initial Dosage: PARAXYL CR should be administered as a single daily dose, usually in the morning, with or without food. PARAXYL CR may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. The recommended initial dose is 12.5 mg/day. Both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least 1 week. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients should be periodically reassessed to determine the need for continued treatment.

Discontinuation of Treatment with Paraxyl CR: Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PARAXYL CR is being prescribed. 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.

Specific Populations:

Pregnant Women during the Third Trimester: Neonates exposed to PARAXYL CR and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding.

WARNINGS AND PRECAUTIONS:

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. All patients 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. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms, 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.

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. 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.

Potential for Interaction with Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOIs), including reversible MAOIs such as linezolid and methylene blue, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: Treatment with PARAXYL CR and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if NMS is suspected and supportive symptomatic treatment should be initiated.

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. It is recommended that paroxetine not be used in combination with thioridazine.

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

DRUG INTERACTIONS:

Tryptophan: As with other serotonin reuptake inhibitors and interaction between paroxetine and tryptophan nay occur and concomitant use of PARAXYL CR with tryptophan is not recommended.

Pimozide: Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and PARAXYL CR 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 PARAXYL CR is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, lithium, fentanyl, tramadol, amphetamines, or St. John's Wort.

Thioridazine: 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 co-administered.

Warfarin: the concomitant administration of PARAXYL CR and warfarin should be undertaken with caution.

Triptans: Serotonin syndrome with the use of an SSRI and a triptan may be expected. If concomitant use of PARAXYL CR with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increase.

Cimetidine: Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. Therefore, when these drugs are administered concurrently, dosage adjustment of PARAXYL CR after the 20-mg starting dose should be guided by clinical effect.

Phenobarbital and Phenytoin: No initial dosage adjustment of PARAXYL CR is considered necessary when co-administered; any subsequent adjustment should be guided by clinical effect.

Drugs Metabolized by CYP2D6: Many drugs, including drugs for treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P450 isozyme CYP2D6 Therefore, co-administration of PARAXYL CR 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. 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.

Tricyclic Antidepressants (TCAs): Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with PARAXYL CR, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced when co-administered with PARAXYL CR.

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Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PARAXYL CR 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. 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 co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

Alcohol: PARAXYL CR does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PARAXYL CR.

Lithium: Due to the potential for serotonin syndrome, caution is advised when PARAXYL CR is co-administered with lithium.

Digoxin: The concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam: Diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Theophylline: 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.

PRECAUTIONS:

General: Activation of Mania/Hypomania: As with all drugs effective in the treatment of major depressive disorder, PARAXYL CR should be used cautiously in patients with a history of mania.

Seizures: PARAXYL CR should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

DISCONTINUATION OF TREATMENT WITH PARAXYL CR:

There have been spontaneous reports of adverse events (generally self-limiting,) occurring upon the discontinuation of paroxitine 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.
Patients should be monitored for these symptoms when discontinuing treatment with PARAXYL CR.
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.

Akathisia: The use of paroxetine or other SSRIs may has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and 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.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PARAXYL CR. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate Antidiuretic hormone secretion (SIADH). Signs and symptoms associated with more severe include hallucination, syncope, seizure, coma, respiratory arrest, and death.

Abnormal Bleeding: Patients should be cautioned about the risk of bleeding associated with the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Bone Fracture: 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.

INFORMATION FOR PATIENTS:

- PARAXYL CR should not be chewed or crushed, and should be swallowed whole.
- Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of PARAXYL CR and triptans, tramadol, or other serotonergic agents.
- Patients should be advised that taking PARAXYL CR can cause mild pupillary dilation and episode of angle closure glaucoma in susceptible individuals.
- Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PARAXYL CR and should counsel them in its appropriate use.
- patients should be cautioned about operating hazardous machinery, including automobiles.
- patients may notice improvement with treatment with PARAXYL CR in 1 to 4 weeks, they should be advised to continue therapy as directed.
- 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 interaction.

ADVERSE REACTIONS:

Associated With Discontinuation of Treatment:

Commonly Observed Adverse Events:

The most commonly observed adverse events associated with the use of paroxetine are:

Major Depressive Disorder: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Social Anxiety Disorder: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

Generalized Anxiety Disorder: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Posttraumatic Stress Disorder: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

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 treatment with selective serotonin reuptake inhibitors (SSRIs).
Paroxetine treatment may be associated with priapism in male patients.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with PARAXYL CR for some patients.

Body as a Whole: Infrequent: Allergic reaction, chills, face edema, malaise, neck pain; rare: Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

DRUG ABUSE AND DEPENDENCE:

Physical and Psychologic Dependence: observe closely for signs of misuse or abuse of PARAXYL CR (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE:

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 consists of General supportive and symptomatic measures. Induction of emesis is not recommended. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, or exchange transfusion are unlikely to be of benefit. Accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

USE IN SPECIFIC POPULATIONS:

Pregnancy Category D: Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing Mothers: Patients should be advised to notify their physician if they are breastfeeding.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established anyone considering the use of PARAXYL CR in a child or adolescent must balance the potential risks with the clinical need. Decreased appetite and weight loss have been observed with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI.

Geriatric Use: SSRIs and SNRIs have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event.

INSTRUCTIONS:

Store below 30ºC. Protect from heat, sunlight & moisture. Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Paraxyl CR Tablet 12.5 mg	:	Pack of 2 x 15 tablets.
Paraxyl CR Tablet 25 mg	:	Pack of 2 x 15 tablets.
Paraxyl CR Tablet 37.5 mg	:	Pack of 1 x 10 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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