Front

Paraxyl®

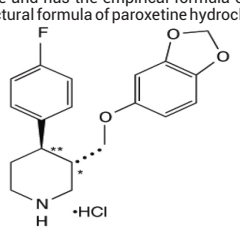
(PAROXETINE)

پراکسیل

COMPOSITION:
Each film coated tablet contains:
Paroxetine HCl USP equivalent to
Paroxetine ..... 20 mg.

Product Specs.: USP

DESCRIPTION:
PARAXYL (paroxetine hydrochloride) is an orally administered psychotropic drug. 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. 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.
Metabolism: 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).
Elimination: Approximately 64% of a 30-mg oral solution dose of paroxetine is excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% is 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.
Pharmacokinetics in Special Populations:
Renal Impairment and hepatic impairment: Patients with creatinine clearance of 30 to 60 mL/min and patients with hepatic functional impairment has a 2-fold increase in plasma concentrations (AUC, C_{max}). 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:
PARAXYL is indicated for the treatment of:
- Major Depressive Disorder
- Obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV.
- Social anxiety disorder, also known as social phobia, as defined in DSM-IV
- Generalized Anxiety disorder (GAD), as defined in DSM-IV.
- Posttraumatic Stress Disorder (PTSD) as defined by DSM-IV

DOSAGE AND ADMINISTRATION:
Major Depressive Disorder (MDD): The recommended initial dose is 20 mg/day as a single daily dose with or without food, usually in the morning. Patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.
Maintenance Therapy:
Acute episodes of MDD require several months or longer of sustained pharmacologic therapy. Systematic evaluation has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.
Obsessive Compulsive Disorder:
Usual Initial Dosage: The recommended initial dose of PARAXYL in the treatment of OCD is 40 mg daily as a single daily dose with or without food, usually in the morning. Patients should be started on 20 mg/day and the dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of atleast 1 week. The maximum dosage should not exceed 60 mg/day.
Maintenance Therapy: OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.
Panic Disorder:
Usual Initial Dosage: The target dose of PARAXYL in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day as a single daily dose with or without food, usually in the morning. Dose changes should occur in 10-mg/day increments and at intervals of at least 1 week. The maximum dosage should not exceed 60 mg/day.
Maintenance Therapy: Panic disorder is a chronic condition, it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.
Social Anxiety Disorder:
Usual Initial Dosage: Initial dosage is 20 mg/day as a single daily dose with or without food, usually in the morning.
Maintenance Therapy:
Social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.
Generalized Anxiety Disorder:
Usual Initial Dosage: PARAXYL should be administered as a single daily dose with or without food, usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.
Maintenance Therapy: Patients should be periodically reassessed to determine the need for maintenance treatment.
Posttraumatic Stress Disorder:
Usual Initial Dosage: PARAXYL should be administered as a single daily dose with or without food, usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at intervals of at least 1 week.
Maintenance Therapy: PTSD is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

DOSE MODIFICATION RECOMMENDATIONS:
Treatment of Pregnant Women: When treating pregnant women with paroxetine the physician should carefully consider the potential risks and benefits of treatment.
Elderly or Debilitated Patients and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

CONTRAINDICATIONS:
- The use of MAOIs intended to treat psychiatric disorders with PARAXYL or within 14 days of stopping treatment with PARAXYL is contraindicated because of an increased risk of serotonin syndrome.
- The use of PARAXYL within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.
- Starting PARAXYL 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 is contraindicated
- Concomitant use in patients taking pimozide is contraindicated. PARAXYL is contraindicated in patients with a hypersensitivity to paroxetine.

WARNINGS AND PRECAUTION:
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 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.

DRUG INTERACTIONS:
Tryptophan: As with other serotonin reuptake inhibitors and interaction between paroxetine and tryptophan nay occur and concomitant use of PARAXYL 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 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 is coadministered 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 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 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 after the 20 mg starting dose should be guided by clinical effect.
Phenobarbital and Phenytoin: No initial dosage adjustment of PARAXYL is considered necessary when co-administered; any subsequent adjustment should be guided by clinical effect.2
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 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, 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.
Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PARAXYL 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 coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.
Alcohol: PARAXYL does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PARAXYL.
Lithium: There is no pharmacokinetic interaction between PARAXYL and lithium carbonate. However, due to the potential for

serotonin syndrome, caution is advised when PARAXYL is coadministered 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 should be used cautiously in patients with a history of mania.
Seizures: PARAXYL 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:
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. 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. 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 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 and triptans, tramadol, or other serotonergic agents.
- Patients should be advised that taking PARAXYL 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 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 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 for some patients.
Body as a Whole: Allergic reaction, chills, face edema, malaise, neck pain.
Cardiovascular System: Hypertension, tachycardia; infrequent: Bradycardia, hematoma, hypotension, migraine, postural hypotension, syncope .
System:
Metabolic and Nutritional: Weight gain; infrequent: Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss.
Musculoskeletal System: Frequent: Arthralgia; infrequent: Arthritis, arthrosis.
Nervous System: Emotional lability, vertigo; infrequent: Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction.
Skin and Appendages: Pruritus; infrequent: Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria.

DRUG ABUSE AND DEPENDENCE:
Physical and Psychologic Dependence: Observe closely for signs of misuse or abuse of PARAXYL (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 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.
- For adults above 18 years only.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Paraxyl Tablet 20 mg : Pack of 1x10 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 ۱۸ سال سے زائد عمر افراد کیلئے۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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