UNIROX®

Paroxetine Hydrochloride

Description:
UNIROX® (Paroxetine Hydrochloride) is a potent and selective inhibitor of serotonin (5-HT) re-uptake and its antidepressant action and effectiveness in the treatment of Obsessive Compulsive Disorder (OCD), Social Anxiety Disorder (Social Phobia), General Anxiety Disorder, Post-traumatic Stress Disorder and Panic Disorder is thought to be related to its specific inhibition of 5-HT re-uptake in brain neurones.
Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants. Paroxetine has low affinity for muscarinic cholinergic receptors and have only weak anticholinergic properties. Paroxetine has little affinity for alpha1, alpha2 and beta-adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and histamine (H1) receptors. This lack of interaction with post-synaptic receptors demonstrates lack of CNS depressant and hypotensive properties.
Properties:
Absorption: Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. Due to first-pass metabolism, the amount of Paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Steady state systemic levels are attained by 7 to 14 days after starting treatment and pharmacokinetics do not appear to change during long-term therapy.
Distribution: Paroxetine is extensively distributed into tissues and only 1% of the Paroxetine resides in the plasma. Approximately 95% of the Paroxetine present is protein bound at therapeutic concentrations. Transfer to human breast milk occurs in small amounts.
Metabolism: The principal metabolites of Paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to Paroxetine therapeutic effects. Metabolism does not compromise Paroxetine selective action on neuronal 5-HT re-uptake.
Elimination: Urinary excretion of unchanged Paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in feces, probably via the bile, of which unchanged Paroxetine represents less than 1% of the dose. Thus Paroxetine is eliminated almost entirely by metabolism.
Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of Paroxetine. The elimination half-life is variable but is generally about 1 day.
Indications:
UNIROX® is indicated to treat:
Depression:
Treatment of symptoms of depressive illness of all types including reactive and severe depression and depression accompanied by anxiety following an initial satisfactory response, continuation with **UNIROX®** therapy is effective in preventing relapse at Depression.
Anxiety Disorder:
- Treatment of symptoms and prevention of relapse of Obsessive Compulsive Disorder (OCD).
- Treatment of symptoms and prevention of relapse of Panic Disorder with or without agoraphobia.
- Treatment of Social Anxiety disorder (Social Phobia).
- Treatment of symptoms and prevention of relapse of Generalized Anxiety Disorder (GAD).
- Treatment of Post-traumatic Stress Disorder.

Dosage and Administration:
Social Anxiety Disorder (Social Phobia) & Generalized Anxiety Disorder & Post-traumatic Stress Disorder:
The recommended dose of **UNIROX®** is 20 mg daily. Patients not responding to a 20 mg dose may benefit from dose increases in 10 mg increments as required, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.
Depression:
The recommended dose of **UNIROX®** is 20 mg daily. In some patients it may be necessary to increase the dose. This should be done gradually by 10 mg increments to a maximum of 50 mg according to the patient's response.
Obsessive Compulsive Disorder:
The recommended dose of **UNIROX®** is 40 mg daily. Patients should start on 20 mg daily and the dose may be increased weekly in 10 mg increments. Some patients will benefit from having their dose increased up to a maximum of 60 mg daily.
Panic disorder:
The recommended dose of **UNIROX®** is 40 mg daily. Patients should be started on 10 mg daily and the dose increased weekly in 10 mg increments according to the patient's response. Some patients may benefit from having their dose increased up to a maximum of 50 mg daily. As is generally recognized there is the potential for worsening of panic symptomatology during early treatment of panic disorder; a low initial starting dose is therefore recommended.
Patient notes:
o **UNIROX®** tablets should be swallowed whole rather chewed as once daily dose in the morning with food.
o As with all antidepressant drugs, dose of **UNIROX®** should be reviewed and adjusted if necessary within two to three weeks of initiation of therapy and thereafter as judged clinically appropriate.
o Patients should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months for depression and may be even longer for OCD and panic disorder.
o As with many psychoactive medications, abrupt discontinuation of Paroxetine should be avoided. The taper phase regimen used involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day is reached, patients are continued on this dose for one week before treatment is stopped.
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.
o Paroxetine is not indicated to treat children and adolescents; Paroxetine is used to treat adults only.
o Increased plasma concentrations of Paroxetine occur in elderly subjects. Dosing should commence at the adult starting dose and may be increased weekly in 10 mg increments to a maximum of 40 mg daily according to the patents response.
o Increased plasma concentrations of Paroxetine occur in patients with severe renal impairment (creatinine clearance <30 ml/min) or in those with hepatic impairment. The recommended dose is 20 mg daily. Incremental dosage, if required, should be restricted to the lower end of the range.
Contraindications:
o Known hypersensitivity to Paroxetine and excipients.
o Paroxetine should not be used in combination with monoamine oxidase inhibitors (MAOIs) or within 2 weeks of terminating treatment with MAOIs, Likewise, MAOIs should not be introduced within 2 weeks of cessation of therapy with Paroxetine.
o Paroxetine should not be used in combination with Thioridazine, as well as with other drugs which inhibit the hepatic enzyme CYP450 2D6, because Paroxetine can elevate plasma levels of Thioridazine. Administration of Thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.
Precautions:
o The use of Paroxetine in children below the age of 7years is not recommended as safety and efficacy have not been studied in this population.
o Children and adolescents aged 7 to 18 year the efficacy of Paroxetine has not been established, controlled clinical studies in depression failed to demonstrate efficacy and do not support the use of Paroxetine in the treatment of children under the age of 18 years with depression since in clinical trials side effects related to suicidality (suicide attempts and suicidal thoughts) and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in children and adolescents treated with Paroxetine compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioral development are lacking.
o **Clinical worsening and suicide risk associated with psychiatric disorders:** Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) and whether or not they are taking antidepressant medications. 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 for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. 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 suicidal behavior. In addition, these conditions may be comorbid 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 disorder.
Patients with a history of suicidal behavior or thoughts, young adults and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
o **Akathisia:** Rarely, the use of Paroxetine or other SSRIs has been associated with 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.
o **Serotonin syndrome / Neuroleptic malignant syndrome:** On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome like event may occur in association with Paroxetine treatment. Particularly when given in combination with other serotonergic and /or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with Paroxetine should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination with serotonin precursors (such as L-tryptophan, Oxitriptan) due to the risk of serotonergic syndrome.
o **Monoamine Oxidase Inhibitors:** Treatment with Paroxetine should be initiated cautiously at least 2 weeks after terminating treatment with MAO inhibitors and dosage of Paroxetine should be increased gradually until optimal response is reached.
o **Mania and Bipolar disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed / manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients 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 is not approved for use in treating bipolar, depression. As with all antidepressants, Paroxetine should be used with caution in patients with a history of mania.
o **Renal / hepatic impairment:** Caution is recommended in patients with severe renal impairment or in those with hepatic impairment.
o **Epilepsy:** As with other antidepressants, Paroxetine should be used with caution in patients with epilepsy.
o **Seizure:** Overall, the incidence of seizures is <0.1% in patients treated with Paroxetine. Paroxetine should be discontinued in any patient who develops seizures.
o **Glaucoma:** As with other SSRIs, Paroxetine infrequently caused mydriasis and should be used with caution in patients with narrow angle glaucoma.
o **Electroconvulsive therapy (ECT):** There is little clinical experience of the concurrent administration of Paroxetine with ECT. However, there have been rare reports of prolonged ECT-induced seizures and/or secondary seizures in patients on SSRIs.
o **Hyponatraemia:** Hyponatraemia has been reported rarely, predominantly in the elderly. The hyponatraemia generally reverses on discontinuation of Paroxetine.
o **Hemorrhage:** Skin and mucous membrane bleedings (including gastrointestinal bleeding) have been reported following treatment with Paroxetine. Paroxetine should therefore be used with caution in patients concomitantly treated with drugs that give an increased risk for bleeding and in patient's with a known tendency for bleeding or those with predisposing conditions.
o **Cardiac conditions:** The usual precautions should be observed in patients with cardiac conditions.
o **Effects on ability to drive and use machines:** Clinical experience has shown that therapy with Paroxetine is not associated with impairment of cognitive of psychomotor function. How-

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ever, as with all psychoactive drugs, patients should be cautioned about their ability to drive a car and operate machinery.

Use during pregnancy and lactation:

Pregnancy category **D**

Paroxetine has no teratogenic or selective embryotoxic effect. There have been reports of premature birth in pregnant women exposed to Paroxetine or others SSRIs, although a causal relationship with drug therapy has not been established.

Neonates should be observed if maternal use of Paroxetine continues into the later stages of pregnancy, because there have been reports of complications in neonates exposed to Paroxetine or other SSRIs late in the third trimester of pregnancy. However, a causal association with drug therapy has not been confirmed.

Reported clinical findings have included: Respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying and somnolence. In some instances the reported symptoms were described as neonatal withdrawal symptoms. In a majority of instances the complications were reported to have arisen either immediately or soon (< 24 hours) after delivery.

Paroxetine should not be used during pregnancy unless the potential benefit outweighs the possible risk.

Lactation: Paroxetine is known to be excreted in breast milk in Small amounts. No signs of drug effects were observed in these infants. Paroxetine should not be used during lactation unless the expected benefits to the mother justify the potential risks for the infant.

Drug interactions:

o **Serotonergic drugs:** As with other SSRIs, co administration with serotonergic drugs (including MAOIs, L-tryptophan, triptans, Tramadol, Linezolid, SSRIs, Lithium and St. johns Wort- Hypericum perforatum preparations) may lead to an incidence of serotonin syndrome. Caution should be advised and a closer clinical monitoring is required when these drugs are combined with Paroxetine.

o **Drug metabolizing enzymes:** The metabolism and pharmacokinetics of Paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes. When Paroxetine is to be co-administered with a known drug metabolizing enzyme inhibitor, consideration should be given to using doses at the lower end of the range. No initial dosage adjustment of Paroxetine is considered necessary when the drug is to be co-administered with known drug, metabolizing enzyme inducers (e.g. Carbamazepine, Rifampicin, Phenobarbital and Phenytoin). Any subsequent dosage adjustment should be guided by clinical effect (tolerability and efficacy).

o **Procyclidine:** Daily administration of Paroxetine increases significantly the plasma levels of Procyclidine. If anti-cholinergic effects are seen, the dose of Procyclidine should be reduced.

o **Anticonvulsants:** Concomitant administration of Carbamazepine, Phenytoin and Sodium Valproate does not seem to show any effect on pharmacokinetic / dynamic profile in epileptic patients.

o **CYP2D6 inhibitory potency of Paroxetine:** As with other antidepressants, including other SSRIs, Paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2C6. Inhibition of CYP2D6 may lead to increased plasma concentration of co-administered drugs metabolized by this enzyme. These include certain tricyclic antidepressants (e.g. Amitriptyline, Nortriptyline, Imipramine and Desipramine), Phenothiazine neuroleptics (e.g. Perphenazine and Thioridazine), Risperidon, certain Type 1c antiarrhythmics (e.g. Propafenone and Flecainide) and Metoprolol.

o **CYP3A4:** Concurrent administration of Paroxetine with Terfenadine, Alprazolam and other drugs that are CYP3A4 substrates would not be expected to cause a hazard. Clinical studies have shown the absorption and pharmacokinetics of Paroxetine to be unaffected or only marginally affected by:

- Food,
- Antacid,
- Digoxin,
- Propranolol,
- Alcohol: Paroxetine does not increase the impairment of mental and motor skills caused by Alcohol, however, the concomitant use of Paroxetine and alcohol is not advised.

Side effects:

Some of the side effects listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

- Blood and lymphatic system disorders:

Uncommon: Abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis).

Very rare: Thrombocytopenia.

- Immune system disorders:

Very rare: Allergic reactions (including urticaria and angioedema).

- Endocrine disorders:

Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

- Metabolism and nutrition disorders:

Common: Decreased appetite.

Rare: Hyponatraemia (hyponatraemia has been reported predominantly in elderly patients and sometimes due to syndrome of inappropriate anti-diuretic hormone (SIADH).

- Psychiatric disorders:

Common: Somnolence, insomnia.

Uncommon: Confusion, hallucinations.

Rare: Manic reactions.

These symptoms may be due to the underlying disease.

- Nervous system disorders:

Common: Dizziness, tremor.

Uncommon: Extrapyramidal disorders.

Rare: Convulsion, akathisia.

Very rare: Serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering tachycardia and tremor).

Reports of extrapyramidal disorders including orofacial dystonia have been received in patient sometimes with underlying movement disorders or who were using neuroleptic medication.

- Eye disorders:

Common: Blurred vision.

Very rare: Acute glaucoma.

- Cardiac disorders:

Uncommon: Sinus tachycardia.

- Vascular disorder:

Uncommon: Transient increase or decrease in blood pressure (usually in patients with pre-existing hypertension or anxiety).

- Respiratory, thoracic and mediastinal disorders:

Common: Yawning.

- Gastrointestinal disorders:

Very common: Nausea, constipation, diarrhea, dry mouth.

Very rare: Gastrointestinal weeding.

- Hepato-biliary disorders:

Rare: Elevation of hepatic enzymes.

Very rare: Hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

Discontinuation of Paroxetine should be considered if there is prolonged elevation of liver function test results.

- Skin and Subcutaneous tissue disorders:

Common: Sweating.

Uncommon: Skin rashes.

Very rare: Photosensitivity reactions.

- Renal and urinary disorders:

Uncommon: Urinary retention.

- Reproductive system and breast disorders:

Very common: Sexual dysfunction.

Rare: Hyper-prolactinemia / galactorrhea.

- General disorders and administration site conditions:

Common: Asthenia.

Very rare: Peripheral edema.

Symptoms seen on discontinuation of Paroxetine treatment:

Common: Dizziness, sensory disturbances, sleeps disturbances, anxiety and headache.

Uncommon: Agitation, nausea, tremor, confusion, sweating and diarrhea.

As with many psychoactive medicines, discontinuation of Paroxetine (particular when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including parasthesia and electric shock sensations), sleeps disturbances (including intense dreams), agitation or anxiety, nausea, headache, tremor, confusion, diarrhea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when Paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

Overdosage:

A wide margin of safety is evident from available data. Overdose attempts have been reported, when took up to 2000 mg alone or in combination with other drugs, including Alcohol.

Symptoms: Vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, anxiety and tachycardia have been reported besides to symptoms mentioned under side effect section.

Events such as coma or ECG changes have occasionally been reported and very rarely a fatal outcome, but generally when Paroxetine was taken in conjunction with other psychotropic drugs, with or without Alcohol.

Treatment: No specific antidote is Know. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Early administration of activated charcoal may delay the absorption of Paroxetine.

Storage conditions:

Store up to 30°C, in a dry place.

Presentation:

UNIROX© 20: Each film coated tablet contains Paroxetine Hydrochloride equivalent to 20 mg Paroxetine in packs of 30 tablets.

Hospital packs are also available.

This is a medicament

· Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
· Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
· The doctor and the pharmacist are experts in medicine, its benefits and risks.
· Do not by yourself interrupt the period of treatment prescribed for you.
· Do not repeat the same prescription without consulting your doctor.
· Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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