APO-PAROXETINE
Paroxetine HCl equivalent to Paroxetine 20mg
Antidepressant

Pharmacology
Paroxetine is a potent and selective serotonin (5-hydroxytryptamine), 5-HT reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant and anxiolytic action in the treatment of depression, obsessive-compulsive disorder (OCD), panic disorder, social phobia (social anxiety disorder), generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD). Paroxetine is a phenylpiperidine derivative which is chemically unrelated to the tricyclic or tetracyclic antidepressants. Pharmacokinetics: APO-PAROXETINE is well absorbed after oral administration. Paroxetine is subject to a biphasic process of metabolic elimination which involves presystemic (first-pass) and systemic pathways. First-pass metabolism is extensive, but may be partially saturable, accounting for the increased bioavailability observed with multiple dosing. Approximately 64% of an administered dose of paroxetine is eliminated by the kidneys and 36% in the faeces. Less than 2% of the dose is recovered in the form of the parent compound. The mean elimination half-life value for healthy subjects appears to be about 24 hours, although a range of 3 to 65 hours has been reported. Both the rate of absorption and the terminal elimination half-life appear to be independent of dose. Steady-state plasma concentrations of paroxetine are generally achieved in 7 to 14 days.

Indications
Depression including reactive and severe depression, depression with anxiety. Symptomatic treatment of Obsessive Compulsive Disorder (OCD) and Panic Disorder, with or without agoraphobia.

Recommended Dose
Depression
Usual adult dose: The administration of APO-PAROXETINE (paroxetine) should be initiated at 20 mg daily. For most patients, 20 mg daily will also be the optimum dose. The therapeutic response may be delayed until the third or fourth week of treatment. Dose range: For those patients who do not respond adequately to the 20 mg daily dose, a gradual increase in dosage up to 40 mg daily may be considered. The maximum recommended daily dose is 50 mg.
Obsessive-compulsive disorder (OCD)
Usual adult dose: The administration of APO-PAROXETINE (paroxetine) should be initiated at 20 mg/day. The recommended dose of APO-PAROXETINE in the treatment of OCD is 40 mg daily. Dose range: For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 50 mg.
Panic Disorder
Usual adult dose: The recommended starting dose of APO-PAROXETINE (paroxetine) in the treatment of panic disorder is 10 mg/day. The recommended dose of APO-PAROXETINE in the treatment of panic disorder is 40 mg/daily.
Dose range: For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.
Elderly: The recommended initial dose is 20 mg/day for elderly and/or debilitated patients. The dose may be increased if indicated up to a maximum of 40 mg daily.
Renal/Hepatic Impairment: APO-PAROXETINE should be used with caution in patients with renal or hepatic impairment. The recommended initial dose is 20 mg/day in patients with clinically significant renal or hepatic impairment (see Precautions). A maximum dose of 40 mg should not be exceeded. This product is not recommended for children and adolescents less than 18 years.

Mode of Administration
Oral

Contraindications
• Hypersensitivity to the paroxetine or to any of the excipients.
• Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with paroxetine provided that there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure.

Treatment with paroxetine can be initiated:
- 2 weeks after discontinuation of an irreversible MAOI, or

- at least 24hrs after discontinuation of a reversible MAOI (e.g. moclobemide, linezolid, methylthioninium chloride (methylene blue; a preoperative visualising agent which is a reversible non-selective MAOI)).

At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.

• Paroxetine should not be used in combination with thioridazine, because, as with other medicinal products, which inhibit the hepatic enzyme CYP450 2D6, 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.

• Paroxetine should not be used in combination with pimozide.

Warnings and Precautions

Monoamine oxidase inhibitor: Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached.

Suicidality in Children and Adolescents

• Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.

• Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.

• Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.

• Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

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 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.

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.

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.

Serotonin Syndrome/Neuroleptic Malignant Syndrome

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment of paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic medicinal products. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised 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.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

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.

Renal/hepatic impairment

Caution is recommended in patients with severe renal impairment or in those with hepatic impairment.

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.

Epilepsy

As with other antidepressants, paroxetine should be used with caution in patients with epilepsy.

Seizures

Caution is recommended when the drug is administered to patients with a history of seizures. The drug should be discontinued in any patient who develops seizures.

Cardiac Conditions

APO-PAROXETINE has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. The usual precautions should be observed in patients with cardiac conditions.

Electroconvulsive therapy (ECT)

Clinical experience of the concurrent administration of paroxetine with ECT is limited.

Opthtalmologic

Angle-Closure Glaucoma: Paroxetine infrequently causes mydriasis which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles glaucoma and should be used with caution in patients with untreated narrow angle. Open-Angle Glaucoma is not a risk factor for Angle-Closure Glaucoma. Patient should be informed to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eyes.

Hyponatraemia

Hyponatraemia has been occurred 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 upon 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 and gynaecological haemorrhage have been reported. Elderly patients may be at an increased risk for non-menses related events of bleeding.

Cautions is advised in patients taking SSRI's concomitantly with oral anticoagulants, drugs known to affect platelet function or other drugs may increase risk of bleeding (e.g. clozapine, phenothiazines, most TCA's, acetylsalicylic acid, NSAID's , COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

Withdrawal symptoms seen on discontinuation of paroxetine treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. 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, sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported . 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.

Renal and hepatic impairment: Caution is recommended in patients with severe renal impairment and those patients with hepatic impairment.

Interactions

Serotonergic drugs: As with other SSRIs, co-administration with serotonergic drugs may lead to an incidence of 5-HT associated effects. Caution should be advised and a closer clinical monitoring is required when these drugs (such as L-tryptophan, triptans, tramadol, linezolid, methylthioninium chloride (methylene blue), SSRIs, lithium, pethidine and St. John's Wort – Hypericum perforatum – preparations) are combined with paroxetine. Caution is also advised with fentanyl used in general anaesthesia or in the treatment of chronic pain. Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome.

Anticonvulsants: Co-administration of paroxetine with anticonvulsants (eg. carbamazepine, phenytoin, sodium valproate) does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

Litium: The co-administration of APO-PAROXETINE with litium should be undertaken with caution and litium levels should be monitored.

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 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.

Procycline: Daily administration of paroxetine increases significantly the plasma level of procycline. If anti-cholinergic effects are seen, the dose of procycline should be reduced.

Hepatic enzyme inhibitory potency of paroxetine: As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered drugs metabolised by this enzyme. These include certain tricyclic antidepressants (e.g. clomipramine, nortriptyline, and desipramine), phenothiazine neuroleptics (e.g. perphenazine), risperidone, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.

Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including paroxetine) should whenever possible be avoided.

Alcohol: Patients should be advised to avoid alcohol use while taking paroxetine.

Oral anticoagulants: A pharmacodynamic interaction between paroxetine and oral anticoagulants may occur. Concomitant use of paroxetine and oral anticoagulants can lead to an increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants.

NSAIDs and acetylsalicylic acid, and other antiplatelet agents: A pharmacodynamic interaction between paroxetine and NSAIDs/acetylsalicylic acid may occur. Concomitant use of paroxetine and NSAIDs/acetylsalicylic acid can lead to an increased haemorrhagic risk.

Cautions is advised in patients taking SSRIs, concomitantly with oral anticoagulants, drugs known to affect platelet function or increase risk of bleeding as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

Pravastatin: An interaction between paroxetine and pravastatin has been observed in studies suggesting that co-administration of paroxetine and pravastatin may lead to an increase in blood glucose levels. Patients with diabetes mellitus receiving both paroxetine and pravastatin may require dosage adjustment of oral hypoglycaemic agents and/or insulin.

Use in Pregnancy and Lactation

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

Neonates 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 neonates 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.

The concentrations of paroxetine detected in the breast milk of lactating women are similar to those in the mother's plasma. Lactating women should not nurse their infants while receiving paroxetine unless in the opinion of the treating physician, breast feeding is necessary, in which case the infant should be closely monitored.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

Effects on the Ability to Drive or Operate Machinery

Paroxetine has no or negligible influence on the ability to drive and use machines.

Clinical experience has shown that therapy with paroxetine is not associated with impairment of cognitive or psychomotor function.

However, as with all psychoactive medicinal products, patients should be cautioned about their ability to drive a car and operate machinery. Although paroxetine does not increase the mental and motor skill impairments caused by alcohol, the concomitant use of paroxetine and alcohol is not advised.

Adverse Reactions

Blood and lymphatic system disorders

abnormal bleeding, predominantly of the skin and mucous membranes (including ecchymosis and gynaecological bleeding), thrombocytopenia

Immune system disorders

Severe and potentially fatal allergic reactions (including anaphylactoid reactions and angioedema)

Endocrine disorders

Very rare: syndrome of inappropriate anti-diuretic hormone secretion. Metabolism and nutrition disorders Increases in cholesterol levels,decreased appetite, altered glycaemic control in diabetic patients, hyponatraemia Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Psychiatric disorders Somnolence, insomnia, agitation, confusion, hallucinations, manic reactions, anxiety, depersonalisation, panic attacks, akathisia, suicidal ideation, suicidal behaviour, aggression, bruxism. Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation. Cases of aggression were observed in post marketing experience. These symptoms may also be due to the underlying disease.

Nervous system disorders Dizziness, tremor, extrapyramidal disorders, convulsions, serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor). Reports of extrapyramidal disorder including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medication.

Eye disorders Blurred vision, mydriasis, acute glaucoma

Ear and labyrinth disorders

Tinnitus

Cardiac disorders

Sinus tachycardia, bradycardia.

Vascular disorders

Transient increases or decreases in blood pressure. Transient increases or decreases of blood pressure have been reported following treatment with paroxetine, usually in patients with pre-existing hypertension or anxiety.

Respiratory, thoracic and mediastinal disorders

Yawning

Gastrointestinal disorders

nausea, constipation, diarrhoea, dry mouth, gastrointestinal bleeding, colitis microscopic

Hepato-biliary disorders

Elevation of hepatic enzymes, hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure). Elevation of hepatic enzymes has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

Skin and subcutaneous tissue disorders
Sweating, skin rashes, pruritus, photosensitivity reactions, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, urticaria
Renal and urinary disorders
Urinary retention, urinary incontinence
Reproductive system and breast disorders sexual dysfunction, hyperprolactinaemia/galactorrhoea, priapism, menstrual disorders (including menorrhagia, metrorrhagia, amenorrhoea, menstruation delayed and menstruation irregular
Musculoskeletal and connective tissue disorders
Arthralgia, myalgia
General disorder and administration site conditions
Asthenia, body weight gain, peripheral oedema.
WITHDRAWAL SYMPTOMS SEEN ON DISCONTINUATION OF PAROXETINE TREATMENT
Dizziness, sensory disturbances, sleep disturbances, anxiety, headache, agitation, nausea, tremor, confusion, sweating, emotional instability, visual disturbances, palpitations, diarrhoea, irritability. Discontinuation of paroxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported.
Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

Symptoms and Treatment of Overdose
Symptoms and signs: Patients have generally recovered without serious sequelae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely with a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic medicinal products, with or without alcohol. Experience of paroxetine in overdose has indicated that, in addition to those symptoms mentioned under 'Adverse Reactions', vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, anxiety and tachycardia have been reported.
Treatment: No specific antidote is known. The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Administration of 20 - 30 g activated charcoal may be considered if possible within a few hours after overdose intake to decrease absorption of paroxetine. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated.

Availability of Dosage Forms
APO-PAROXETINE 20 mg: Each pink, oval, biconvex, film-coated tablet engraved "APO" on one side, and scored and engraved "20" on the other, contains paroxetine hydrochloride equivalent to 20 mg of paroxetine. Available in blisters of 30 tablets.

Storage condition
Store below 30˚C. Protect from moisture.

Manufacturer
Apotex Inc. 150 Signet Drive, Weston, Ontario, Canada M9L 1T9.

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