DRUG PROFILE
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Paroxetine hydrochloride

Chemical Name: (3S,4R)-3-(1,3-benzodioxol-5-yloxyethyl)-4-(4-fluorophenyl)piperidine

Structure:

Molecular Formula: C_{19}H_{20}FNO_{3}

Molecular Weight: 329.3654 gm/mole

Category: Antidepressants Selective Serotonin Reuptake Inhibitors (SSRIs)

Description: Paroxetine hydrochloride is an odorless, off-white powder

Solubility: Slightly soluble in water (5.4 mg/ml), freely soluble in Methanol, sparingly soluble in alcohol and in methylene chloride

Melting Range: 129-131°C
Protein Binding: 95 %, binding is independent of concentration

Storage/stability: Store at ≤25°C for suspensions or 15-30°C for tablets.

Pharmacology

Absorption: completely absorbed after oral dosing

Oral Bioavailability: Completely absorbed from GI, but extensive first-pass metabolism in the liver; Tmax 4.9 (with meals) to 6.4 hours (fasting)

Effect of Food: Although the rate (C_{max}) and extent (AUC) of paroxetine absorption from the capsules are reduced by 16% and 10%, respectively, when given with a high-fat meal, the magnitude of these reductions is not likely to be clinically significant. Therefore, paroxetine may be taken without regard to food.

Distribution: Owing to the extensive distribution of paroxetine into the tissues, less than 1% of the total drug in the body is believed to reside in the systemic circulation. 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.

Biotransformation: Paroxetine is subject to a biphasic process of metabolic elimination which involves presystemic (first-pass) and systemic pathways.
Metabolism and Excretion:

First-pass metabolism is extensive, but may be partially saturable, accounting for the increased bioavailability observed with multiple dosing. Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions.

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.
Mechanism of Action: Paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake. Paroxetine likely inhibits the reuptake of serotonin at the neuronal membrane, enhances serotonergic neurotransmission by reducing turnover of the neurotransmitter, therefore it prolongs its activity at synaptic receptor sites and potentiates 5-HT in the CNS; paroxetine is more potent than both sertraline and fluoxetine in its ability to inhibit 5-HT reuptake. Compared to the tricyclic antidepressants, SSRIs have dramatically decreased binding to histamine, acetylcholine, and norepinephrine receptors.

Adverse Reactions:

Cardiovascular: Frequent: Hypertension, syncope, tachycardia. Infrequent: Bradycardia, conduction abnormalities, ECG abnormal, hypotension, migraine, ventricular extrasystoles. Rare: Angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, extrasystoles, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache.
CNS:

Frequent: CNS stimulation, concentration impaired, depression, emotional lability, vertigo. Infrequent: Akinesia, alcohol abuse, amnesia, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction, thinking abnormal. Rare: Abnormal EEG, abnormal gait, antisocial reaction, choreoathetosis, circumoral paresthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome.

GI:

Frequent: Nausea and vomiting. Infrequent: Bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, vomiting and diarrhea, rectal hemorrhage. Rare: Aphthous stomatitis, bloody diarrhea, bulimia, colitis,
duodenitis, esophagitis, fecal impaction, fecal incontinence, gastritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries.

**Genitourinary:**

**Hematologic:**
Infrequent: Anemia, leukopenia, lymphadenopathy, purpura, WBC abnormality. Rare: Eosinophilia, iron deficiency anemia, leukocytosis, lymphedema, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia.

**Special Senses:**
Infrequent: Abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus. Rare: Amblyopia, cataract specified, conjunctival edema, corneal lesion, corneal ulcer, exophthalmos, eye hemorrhage,
glaucoma, hyperacusis, otitis externa, photophobia, retinal hemorrhage, taste loss.

**Respiratory:** Frequent: Cough increased, rhinitis. Infrequent: Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis. Rare: Hiccup, lung fibrosis, sputum increased, voice alteration.

**Overdose**

Overdose attempts have been reported with paroxetine; up to 850 mg alone and in combination with other agents. In cases where paroxetine was used alone, no deaths have occurred and recovery was medically uneventful.

Symptoms of overdosage with paroxetine include nausea, vomiting, tremor, dilated pupils, dry mouth and irritability. There are no reports of ECG abnormalities, coma or convulsions following overdosage with paroxetine alone.

No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant.

The stomach should be emptied either by the induction of emesis, lavage or both. Following evacuation, 20 to 30 g of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. Supportive care with frequent monitoring of vital signs and careful observation is indicated.

**Drug Interactions**

MAOIs, Phenobarbital, theophylline, 5HT1 agonists (e.g., sumatriptan), phenytoin, lithium, anticoagulants (increased bleeding), procyclidine, cimetidine,
St. John's Wort, drugs highly bound to plasma protein, drugs affecting liver enzymes. Avoid concurrent use of paroxetine and tryptophan

Dosage:

**Usual Adult Dose:**

The administration of 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 Adjustments:**

Based on pharmacokinetic parameters, steady-state paroxetine plasma levels are achieved over a 7 to 14 days interval. Hence, dosage adjustments in 10 mg increments should be made at 1 to 2 week intervals or according to clinician's judgment.

**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. Paroxetine should be administered once daily in the morning and may be taken with or without food. The tablet should be swallowed rather than chewed.

**Maintenance:**

During long-term therapy, the dosage should be maintained at the lowest effective level.

**Geriatriecs:**

A lower dosage may be considered for elderly and/or debilitated patients. Increases in dose may be made if indicated up to a maximum of 40 mg daily.
Children:
The use of paroxetine in children under 18 years of age is not recommended as safety and efficacy have not been established in this population.

Renal/Hepatic Impairment:
Paroxetine should be used with caution in patients with renal or hepatic impairment. Dosage should be restricted to the lower end of the range in patients with clinically significant renal or hepatic impairment (see Precautions).
1.0: Analytical method development and validation for Paroxetine hydrochloride in bulk drug and tablet dosage form

Materials:
The paroxetine reference substance (assigned purity 99.8%) and coated tablets containing paroxetine was manufactured by Glaxo smithkline pharmaceutical Ltd, Mumbai. Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine: 10 mg–yellow (scored); 20 mg–pink (scored); 30 mg–blue, 40 mg–green The tablets where claimed to contain the following inactive agents dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and one or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

Instrumentation and conditions
Spectral and absorbance measurements were made with a JASCO 7800 UV-VIS and INTRALAB 5100 detector with 10 mm quartz cells.

Methods:
1.1: Determination of $\lambda_{\text{max}}$ for Paroxetine hydrochloride:
Paroxetine was found to be freely soluble in methanol.
For the determination of $\lambda_{\text{max}}$ an accurately weighed amount (50 mg) of Paroxetine was quantitatively transferred into a 25-ml calibrated flask and dissolved in 20 ml methanol, made volume with the same solvent to obtain a stock solution of 2 mg/ mL. This solution was further diluted to get a stock solution of 1 µg/ml and then scanned at all wavelengths to determine the absorption maxima of paroxetine.
1.2: Preparation of Calibration curve:

1.2.1: Determination of absorbance at Concentration range of 10\(\mu\)g/mL to 100 \(\mu\)g/mL.

For the determination of the range at which Paroxetine hydrochloride obeys beer lamberts law, initially solution of paroxetine hydrochloride was prepared in the range of 10\(\mu\)g/mL to 100 \(\mu\)g/mL. The absorption of all these solution was determined at 294 nm.

1.2.2: Determination of absorbance at Concentration range of to 1 \(\mu\)g/mL to 10\(\mu\)g/mL

The different concentration of paroxetine hydrochloride reference standard equivalent to paroxetine (200 \(\mu\)g/mL) were prepared by accurately weighing 22.15 mg paroxetine hydrochloride reference substance (equivalent to 20 mg of paroxetine) into 100 mL volumetric flask. From this solution working standard solution of concentration of 1 to 10 \(\mu\)g /ml of paroxetine, were prepared by dilution with methanol. The absorption of all these solutions was determined at 294 nm.

1.3: Assay of paroxetine in tablets

Twenty tablets were weighed to obtain the average tablet weight. The tablets were ground up and powdered tablets equivalent to 100 mg of paroxetine was transferred to a 500 mL volumetric flask; 250 mL methanol were added and the flask was shaken for 20 minutes by mechanical shaker followed by addition of methanol to volume (final concentration of 0.2 mg/mL). The contents of the flask were mixed well and filtered using whatman filter of 0.45 microns. Aliquots of 5 mL of this solution were transferred to a 200 mL volumetric flask and methanol was added to volume to give an estimated concentration of 5 \(\mu\)g/mL. This solution was prepared six times and the absorbance of each solution was determined at 294 nm and the concentration of drug in sample solution was determined from calibration curve.
1.4: Method validation

1.4.1: Calibration and sensitivity

Calibration curve for the determination of Paroxetine was constructed by plotting the absorbance’s as a function of the corresponding concentrations.

1.4.2: Precision

The precision of the assay, as well linearity of the calibration curve, were determined. The precision of the proposed method was determined by analyzing 5 replicate samples of standard paroxetine solution at one concentration level. Having established the quantitative relationships between the parameters studied, and knowing the predictive performance of their association model, a linear simple regression by the least square method was applied.

1.4.3: Accuracy and interference liabilities

Before proceeding with the analysis of paroxetine in its tablets, interference liabilities were carried out to explore the effect of common excipients that might be added during tablets formulation. Samples were prepared by mixing known amount (10 mg) of paroxetine with various amounts of the common excipients: starch, glucose, lactose, acacia, talc, and magnesium stearate. These laboratory-prepared samples were analyzed by the proposed method applying the general recommended procedure. The statistical accuracy was determined by adding known amount of paroxetine reference standard to the samples at the beginning of the process.

1.4.4: Recovery studies

The recovery studies were carried out at three different concentration levels of reference standard, respectively, R1, R2, R3 and R4. The percentage recovery for added paroxetine hydrochloride was calculated using the equation proposed by Association of Analytical Communities.
1.4.5: Ruggedness

Ruggedness was tested by applying the proposed methods to the assays of Paroxetine using the same operational conditions but using two different instruments at two different laboratories and different elapsed time.