**Product information for health professionals**

## 1. Invented Name of the Medicinal Product

**PBENZ**

(Benzhexol Tablets BP 5 mg)

**Strength**

Benzhexol Hydrochloride BP ..... 5 mg

**Dosage Form**

Solid Dosage Form (Tablet)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Benzhexol Hydrochloride BP ..... 5 mg.
Excipients..... q.s.

**UNIT FORMULA**

| Sr. No. | Name of raw material | Label Claim (mg) | Overages (%) ** | Reference | Qty. /Tab(mg) | Qty./ Batch size (100000 tab) (kg) |
|---|---|---|---|---|---|---|
| **MIXING** | | | | | | |
| 1 | Trihexyphenidyl HCL | - | - | BP | 5.000 | 0.500 |
| 2 | Maize Starch | 142.00 | 5% | BP | 149.100 | 14.910 |
| 3 | Lactose | 50.00 | 6% | BP | 53.000 | 5.300 |
| 4 | Sodium Starch Glycolate | - | - | BP | 10.000 | 1.000 |
| 5 | Dibasic Calcium Phosphate | 74.00 | 6% | BP | 78.440 | 7.844 |
| **WET GRANULATION** | | | | | | |
| 6 | Maize Starch | - | - | BP | 12.000 | 1.200 |
| 7 | Sodium Benzoate | - | - | BP | 1.000 | 0.100 |
| 8 | Purified water@ | - | - | BP | Q.S. | 8 Liter |
| **LUBRICATION** | | | | | | |
| 9 | Magnesium stearate | - | - | BP | 5.000 | 0.500 |
| 10 | Purified talc | - | - | BP | 3.000 | 0.300 |
| 11 | Sodium Starch Glycolate | - | - | BP | 5.000 | 0.500 |
| 12 | Colloidal Anhydrous Silica | - | - | BP | 3.000 | 0.300 |
| **Total weight** | | | | | **310.0 mg** | **31.0 kg** |

## 3. PHARMACEUTICAL FORM

White colour round shaped flat uncoated tablet with embossing "PBENZ" & 5 with break line on side & plain on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This drug is indicated as an adjunct in the treatment of all forms of parkinsomism (postencephalitic, arteriosclerotic and idiopathic). It is often useful as adjuvant therapy when treating these forms of parkinsomism with levodopa. Additionally it is indicated for the control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes, and butyrophenones.

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Dosage should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age. Whether PBENZ may best be given before or after meals should be determined by the way the patient reacts. Post encephalitic patients who are usually more prone to excessive salivation, may prefer to take it after meals and may, in addition, require small amounts of atropine which, under such circumstances is sometimes an effective adjuvant. It PBENZ tends to dry the mouth excessively, it may be better to take it before meals, unless it causes nausea. If taken after meals .the thirst sometimes includes can be allayed by mint candies, chewing gum or water.

PBENZ in Idiopathic Parkinson ism.

As initial therapy for parkinsonism, 1 mg of Benzhexol HCl in tablet or elixir form may be administered the first day. The dose may then be increased by 2 mg increments at intervals of three to five days, until a total of 6 lo 10mg is given daily. The total daily dose will depend upon what is found to be the optimal level. Many patients derive maximum benefit from this daily total of 6 to 10 mg but some patients, chiefly those in the post encephalitic, group may require a total daily dose of 12 to 15mg.

Benzhexol HCl in Drug-induced Parkinsonism The size and frequency of dose of PBENZ needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines , thioxanthenes, and butyrosphenones must be determined empirically. The total daily dosage usually ranges between 5 and 15 mg although in some cases these reactions have been satisfactorily controlled on as little as 1mg daily. It may be advisable to commence therapy with a single 1 mg dose. If the extrapyramidal manifestations are not controlled in a few hours, the subsequent doses may be progressively increased until satisfactory

control is achieved. Satisfactory control may sometimes be more rapidly achieved by temporarily reducing the dosage of the tranquilizer on instituting Benzhexol HCl therapy and then ad1usting dosage of both drugs until the desired ataractic effect is retained without onset of extrapyramidal reactions.

It is sometimes possible to maintain the patient on a reduced PBENZ dosage after the reactions have remained under control for several days. Instances have been reported in which these reactions have remained in remission for long periods after PBENZ therapy was discontinued. Concomitant Use of PBENZ with Levodopa.

When PBENZ is used concomitantly with levodopa, the usual dose of each may need to be reduced. Careful adjustment is necessary, depending on side effects and degree of symptom control PBENZ dosage of 3 to 6 mg daily, in divided doses, is usually adequate.

Concomitant Use of Benzhexol HCl with Other Parasympathetic inhibitors

PBENZ TABLETS: Benzhexol HCl may be substituted in whole or in part for other parasympathetic inhibitors. The usual technique is partial substitution initially, with progressive reduction in the other medication as the dose of Benzhexol HCl is increased.

The total daily intake of PBENZ tablet is tolerated best if divided into 3 doses and taken at mealtimes. High doses (> 10 mg daily) may be divided into 4 parts, with 3 doses administered at mealtimes and the fourth at bedtime.

## 4.3 CONTRAINDICATIONS

PBENZ is contraindicated in patients with hypersensitivity to ingredients. PBENZ is also contraindicated in patients with narrow angle glaucoma. Blindness after long-term use due to narrow angle glaucoma has been reported.

## 4.4 WARNING AND PRECAUTIONS

Patients to be treated with PBENZ should have a Gonio scope evaluation prior to initiation of therapy and dose monitoring of intraocular pressures. The use of anticholinergic drugs may precipitate angle closure with an increase in intraocular pressure. If blurring of vision occurs during therapy, the possibility of narrow angle glaucoma should be considered. Blindness has been reported due to aggravation of narrow angle glaucoma.

PBENZ should be administered with caution in hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill. alcoholics, those who have central nervous system disease,

or those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased so that the ability to maintain body heal equilibrium via perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred with the use of anticholinergics under the conditions described above.

Neuroleptic Malignant Syndrome.

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with dose reduction or discontinuation of Benzhexol HCl Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias.) The diagnostic evaluation of patients with this syndrome is complicated in arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (eg. pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. General

Patients with cardiac, liver or kidney disorders or with hypertension, should be closely monitored.

Since PBENZ has atropine-like properties patients on long- term treatment should be carefully monitored for untoward reactions.

Since PBENZ has parasympatholytic activity, I should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy. Incipient glaucoma may be precipitated by parasympatholytic drugs such as PBENZ.

Tardive dyskinesia may appear in some patients on long-term therapy with antipsychotic drugs or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. However, parkinsonism and tardive dyskinesia often coexist in patients receiving chronic neuroleptic treatment, and anticholinergic therapy with PBENZ may relieve some of these parkinsonism symptoms. PBENZ is not recommended for use in patients with tardive dyskinesia unless they have concomitant parkinsonism disease.

Patients with arterioscierosis or with a history of idiosyncrasy to other drugs may exhibit reactions of mental confusion, agitation, disturbed behavior, or nausea and vomiting. Such patients should be allowed to develop a tolerance through the initial administration of a small dose and gradual increase in dose until an effective level is reached. If a severe reaction should occur, administration of the drug should be discontinued for a few days and then resumed at a lower dosage. Psychiatric disturbances can result from indiscriminate use (leading to overdosage) to sustain continued euphoria. (See DRUGS ABUSE AND DEPENDENCE) Abrupt withdrawal of

treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided.

Information for patients

PBENZ may impair mental and physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that PBENZ therapy does not adversely affect their ability to engage in such activities.

Because of increased sedative effects, patients should be cautioned to avoid the use of alcohol or other CNS depressants while taking PBENZ.

Since this medication may increase the susceptibility to heat stroke (gastrointestinal (GI) problems, fever, heat intolerance), use with caution during hot weather.

Patients should be advised to report the occurrence of GI problems, fever or heat intolerance promptly since paralyticileus, hyperthermia or heat stroke may occur. If GI upset occurs. PBENZ may be taken with food. Patients should have close monitoring of intraocular pressure.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Extra care should be taken when benzhexol HCl is given concomitantly with phenothiazines, clozapine, antihistamines, disopyramide, nefopam and amantadine because of the possibility of increased antimuscarinic side-effects.

Synergy has been reported between benzhexol HCl and tricyclic antidepressants, probably because of an additive effect at the receptor site. This can cause dry mouth, constipation and blurred vision. In the elderly, there is a danger of precipitating urinary retention, acute glaucoma or paralytic ileus.

Monoamine oxidase inhibitors can interact with concurrently administered anticholinergic agents including benzhexol HCl. This can cause dry mouth, blurred vision, urinary hesitancy, urinary retention and constipation.

In general, anticholinergic agents should be used with caution in patients who are receiving tricyclic antidepressants or monoamine oxidase inhibitors. In patients who are already on antidepressant therapy the dose of benzhexol HCl should be initially reduced and the patient reviewed regularly.

benzhexol HCl may be antagonistic with the actions of metoclopramide and domperidone on gastro-intestinal function.

The absorption of levodopa may possibly be reduced when used in conjunction with benzhexol

HCl.

benzhexol HCl may be antagonistic with the actions of parasympathomimetic.

## 4.6 PREGNANCY AND LACTATION

Pregnancy: There is inadequate information regarding the use of benzhexol HCl in pregnancy. Animal studies are insufficient with regard to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown. benzhexol HCl should not be used during pregnancy unless clearly necessary.

Lactation: It is unknown whether benzhexol HCl is excreted in human breast milk. The excretion of benzhexol HCl in milk has not been studies in animals. Infants may be very sensitive to the effects of antimuscarinic medications. Benzhexol HCl should not be used during breast-feeding.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Can cause blurring of vision, dizziness and mild nausea. Also, mental confusion in some cases.

## 4.8 UNDESIRABLE EFFECTS

Minor side effects, such as dryness of the mouth, blurred vision, dizziness, mild nausea or nervousness, will be experienced by 30 to 50 percent of all patients. These sensations, however, are much less troublesome with PBENZ than with belladonna alkaloids and are usually less disturbing than unalleviated parkinsonism. Such reactions tend to become less pronounced, and even to disappear, as treatment continues. Even before these reactions have remitted spontaneously, they may often be controlled by careful adjustment of dosage form, amount of drug or interval between doses. Isolated instances of supportive parotitis secondary to excessive dryness of the mouth, skin rashes, dilatation of the colon, paralytic ileus, and certain psychiatric manifestations such as delusions, hallucinations, and paranoia, all of which may occur with any of the atropine- like drugs, have been reported rarely with PBENZ. Potential side effects associated with the use of any atropine-like drugs,

Including PBENZ include cognitive dysfunctions, including confusion and memory impairment, constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular pressure, chloroform movements, weakness, vomiting and headache. Exacerbation of parkinsonism with abrupt treatment withdrawal has been reported. Neuroleptic malignant syndrome with abrupt treatment withdrawal has been reported .

The occurrence of angle-closure glaucoma in patients receiving Benzhexol HCl Hydrochloride has been reported(blindness has been reported in some cases). Paradoxical sinus bradycardia, dry skin and cycloplegia have been reported.

In addition to adverse events seen in adults, the following adverse events have been reported in the literature in pediatric patients hyperkinesia, psychosis, forgetfulness. weight loss, restlessness, chorea and sleep alterations.

## 4.9OVERDOSE

The mean oral LDSO of PBENZ has been reported to be 365 mg/kg (range, 325 lo410 mg/kg) in mice and 1660 mg/kg (1420101940 mg/kg) in rats. At a dose of 40 mg/kg, dogs have exhibited emesis, restlessness followed by drowsiness. equilibrium disturbances and mydriasis. In humans, doses up to 300 mg (5 mg/kg) have been ingested without fatalities or sequelae. However, rare cases of death associated with benzhexol HCl overdosage taken in con1unction with

other CNS. depressant agents have been reported or in patients with a compromised respiratory condition. Benzhexol HCl blood concentrations associated with the fatalities ranged from 0.03 to 0.80 mg/l.

### Signs and Symptoms

Overdosage with PBENZ produces typical central symptoms of atropine intoxication (the central anticholinergic syndrome). Correct diagnosis depends upon recognition of the peripheral signs of parasympathetic blockade, inducing dilated and sluggish pupils; warm, dry skin, facial flushing; decreased secretions of the mouth, pharynx, nose and bronchi; foul-smelling breath; elevated temperature, tachycardia, cardiac arrhythmias: decreased bowel sounds; and urinary retention. Neuropsychiatric signs such as delirium, disorientation, anxiety, hallucinations, illusions, confusion, incoherence, agitation, hyperactivity, ataxia, lip smacking and tasting movements, loss of memory, paranoia, combativeness, and seizures may be present. The condition can progress to stupor, coma, paralysis. cardiac and respiratory arrest, and death.

### Treatment

Treatment of acute overdose involves symptomatic and supportive therapy. Gastric lavage or other methods to limit absorption should be instituted. A small dose of diazepam or a short-acting barbrturate may be administered if CNS excitation is observed. Phenothiazines are contraindicated because the toxicity may be intensified due to their antimuscarinic action, causing coma. Respiratory support, artificial respiration or vasopressor agents may be necessary. Hyperpyrexia must be reversed, fluid volume replaced and acid balance maintained. Urinary catheterization may be necessary. It is not known PBENZ is dialyzable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Benzhexol HCl Hydrochloride is a tertiary amine antimuscarinic with actions similar to those of atropine. It also has a direct antispasmodic action on smooth muscle. The exact mechanism of action of Benzhexol HCl in parkinsonian syndrome may result from blockade of efferent impulses and from central inhibition of cerebral motor centers.

**ACTIONS**

PBENZ Benzhexol HCl Hydrochloride is the substituted piperidine salt, 3-(1-piperidine)-1-phenyl-cyclohexyl-1-propanol hydrochloride which exerts a direct

Inhibitory effect upon the parasympathetic nervous system. It also has a relaxing effect on smooth musculature, exerted both directly upon the muscle tissue self and indirectly through an inhibitory effect upon the parasympathetic nervous system. Its therapeutic properties are similar to those of atropine although undesirable side effects are ordinarily less frequent and severe than with the latter.

### 5.2 Pharmacokinetic properties

Exert an effect within 1 hour of a dose by mouth. Following oral administration of Benzhexol HCl there was an initial Benzhexol HCl Hydrochloride is well absorbed from the gastro-intestinal tract and has been stated to elimination phase with an estimated half-life of 5.33 hours followed by a terminal elimination phase with an estimated half-life of 32.7 hours.

### 5.3 Preclinical safety data

None stated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

| Excipients | Grade |
|---|---|
| Starch | BP |
| Lactose | BP |
| Dibasic Calcium Phosphate | BP |
| Sodium Benzoate | BP |
| Purified water | BP |
| Magnesium Stearate | BP |
| Talcum Powder | BP |
| Sodium Starch Glycolate | BP |
| Fumed Silica | BP |

**6.2 Incompatibilities:** Not applicable.

**6.3 Shelf life:** Three years.

**6.4 Special precautions for storage:** Store below 30°C.

**6.5 Nature and contents of container**

500 Tablets in HDPE Jar along with pack insert.

**6.6 Special precautions for disposal and other Special handling**

None

**7. Marketed by:**

**M/S. AQUATIX PHARMACEUTICALS LIMITED.**
No.7, Sapara Williams Street, Industrial
Estate, lkeja, Lagos, Nigeria.

**8. Manufactured by:**

**M/S. SWISS PHARMA PVT. LTD.**
G.I.D.C., PHASE IV,
VATAV, AHEMDABAD- 382 445.

**5. NAFDAC REGISTRATION NUMBER(S):** A4-1933