**TRIHEXYPHENIDYL HYDROCHLORIDE TABLETS, USP**

**DESCRIPTION**

Trihexyphenidyl HCl is a synthetic antispasmodic drug. It is designated chemically as α-Dihydroxy-α-phenyl-1-piperidinepropanol hydrochloride and its structural formula is as follows:

\[
\text{C}_{20}\text{H}_{31}\text{NO} \cdot \text{HCl}
\]

M.W. 337.93

Trihexyphenidyl HCl occurs as a white or creamy-white, almost odorless, crystalline powder. It is very slightly soluble in ether and benzene, slightly soluble in water and soluble in methanol.

Trihexyphenidyl Hydrochloride Tablets USP 2 mg and 5 mg contain the following inactive ingredients: magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

**CLINICAL PHARMACOLOGY**

Trihexyphenidyl HCl 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 itself and indirectly through an inhibitory effect upon the sympathetic nervous system. It also has a relaxing effect on smooth musculature; exerted both directly and indirectly through an inhibitory effect upon the sympathetic nervous system.

Trihexyphenidyl HCl is indicated as an adjunct in the treatment of all forms of parkinsonism (postencephalitic, arteriosclerotic, and idiopathic). It is often useful as adjuvant therapy when treating these forms of parkinsonism with levodopa.

Additionally, it is indicated for the control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoazepines, phenothiazines, thioxanthenes, and butyrophenones.

**CONTRAINDICATIONS**

Trihexyphenidyl HCl is contraindicated in patients with hypersensitivity to trihexyphenidyl and butyrophenones.

Nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes, trihexyphenidyl HCl is contraindicated in patients with hypersensitivity to trihexyphenidyl and butyrophenones.

**WARNINGS**

Patients to be treated with trihexyphenidyl HCl should have a gonioscope evaluation to assess the possibility of narrow angle glaucoma. Patients with narrow angle glaucoma should be administered with caution in hot weather, especially when given concomitantly with other antimuscarinic 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 heat 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 trihexyphenidyl. Clinical manifestations of NMS are hypotension, 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.

**PRECAUTIONS**

**General**

Patients with cardiac, liver, or kidney disorders, or with hypertension, should be closely monitored. Since trihexyphenidyl HCl has atropine-like properties, patients on long-term treatment should be carefully monitored for untoward reactions.

Since trihexyphenidyl HCl has parasympatholytic activity, it should be used with caution in patients with glaucoma, obstrusive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostate hypertrophy. Incipient glaucoma may be precipitated by parasympatholytic drugs such as trihexyphenidyl HCl.

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 trihexyphenidyl HCl may relieve some of these tardive dyskinesia symptoms. Tardive dyskinesia is recommended for use in patients with tardive dyskinesia unless they have concomitant Parkinson’s disease.

Patients with arteriosclerosis 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 DRUG ABUSE AND DEPENDENCE.)

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided (see DOSAGE AND ADMINISTRATION).

Information for Patients

Trihexyphenidyl HCl may impair mental and/or 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 trihexyphenidyl HCl 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 trihexyphenidyl HCl.

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

Patients should be advised to report the occurrence of GI problems, fever, or heat intolerance promptly since paralytic ileus, hyperthermia, or heat stroke may occur. If GI upset occurs, trihexyphenidyl HCl may be taken with food.

Patients should have close monitoring of intracranial pressure. (See WARNINGS.)

Drug Interactions

Cannabinoids, barbiturates, opiates, and alcohol may have additive effects with trihexyphenidyl HCl, and thus, an abuse potential exists.

Concurrent use of alcohol or other CNS depressants with trihexyphenidyl HCl may cause increased sedative effects.

Monoamine oxidase inhibitors and tricyclic antidepressants possessing significant anticholinergic activity may intensify the anticholinergic effects of antipsychotic agents because of the secondary anticholinergic activities of these medications.

Prophylactic administration of anticholinergic agents, such as trihexyphenidyl, as a prevention of drug-induced parkinsonism during neuroleptic therapy is not recommended. These drugs may increase the risk for the development of tardive dyskinesia during concomitant administration of anticholinergics and neuroleptics (see PRECAUTIONS, General).

The usual dose of either trihexyphenidyl or levodopa may need to be reduced during concomitant therapy, since concomitant administration may increase drug-induced involuntary movements (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies or adequate genotoxicity or fertility studies have been conducted for trihexyphenidyl HCl.

Pregnancy

TERATOCENIC EFFECTS PREGNANCY CATEGORY C

Animal reproduction studies to evaluate teratogenic and embryotoxic potential have not been conducted with trihexyphenidyl HCl. It is also not known whether trihexyphenidyl HCl can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Trihexyphenidyl HCl should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trihexyphenidyl HCl is administered to a nursing woman.

As with other anticholinergics, trihexyphenidyl may cause suppression of lactation. Therefore, trihexyphenidyl should only be used if the expected benefit to the mother outweighs the potential risk to the infant.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established. (See also ADVERSE REACTIONS.)

Geriatric Use
Sensitivity to the actions of parasympathomimetic drugs may increase with age, particularly over the age of 60; therefore, elderly patients generally should be started on low doses of trihexyphenidyl HCl and observed closely. Trihexyphenidyl HCl has been shown to cause some cognitive dysfunctions in the elderly, including confusion and memory impairment. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

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 trihexyphenidyl HCl 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 suppurative 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 trihexyphenidyl HCl.

Potential side effects associated with the use of any atropine-like drugs, including trihexyphenidyl HCl, include cognitive dysfunction, memory impairment, constipation, dryness, urinary hesitancy or retention, tachycardia, dilatation of the pupil, increased intraocular pressure, chooreiform movements, weakness, vomiting, and headache. Exacerbation of parkinsonism with abrupt treatment withdrawal has been reported rarely. Neuroleptic malignant syndrome with abrupt treatment withdrawal has been reported (see WARNINGS, Neuroleptic Malignant Syndrome).

The occurrence of angle-closure glaucoma in patients receiving trihexyphenidyl HCl 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, psychoses, forgetfulness, weight loss, restlessness, chorea, and sleep alterations.

DRUG ABUSE AND DEPENDENCE

Although trihexyphenidyl HCl is not classified as a controlled substance, the possibility of abuse should be borne in mind due to its stimulant and euphoriant properties.

OVERDOSAGE

The mean oral LD50 of trihexyphenidyl HCl has been reported to be 365 mg/kg (range, 325 to 410 mg/kg) in mice and 1660 mg/kg (1420 to 1940 mg/kg) in rats. At a dose of 40 mg/kg, dogs have exhibited enuresis, restlessness followed by dryness, 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 trihexyphenidyl HCl overdoses taken in conjunction with other CNS-depressant agents have been reported or in patients with a compromised respiratory condition. Trihexyphenidyl blood concentrations associated with the fatalities ranged from 0.03 to 0.80 mg/l.

Signs and Symptoms

Overdosis with trihexyphenidyl HCl produces typical central symptoms of atropine intoxication (the central anticholinergic syndrome). Correct diagnosis depends upon recognition of the peripheral signs of parasympathetic blockade, including dilated and sluggish pupils; warm, dry skin; facial flushing; decreased secretion of the mouth, pharynx, nose, and bronchi; mydriasis; decreased intraocular pressure; tachycardia; cardiac accelerated responses; urinary retention; and changes in mental status. The characteristic 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 barbiturate may be administered if CNS excitation is observed. Phenothiazines are contraindicated because the toxicity may be intensified when given with atropine-like drugs.

Signs and Symptoms associated with the fatalities ranged from 0.03 to 0.80 mg/l. The size and frequency of the trihexyphenidyl HCl dose needed to control extrapyramidal manifestations such as delusions, hallucinations, and paranoia, all of which may occur with any of the atropine-like drugs, have been reported rarely with trihexyphenidyl HCl.

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided. Abrupt withdrawal of treatment may result in neuroleptic malignant syndrome (NMS) (see WARNINGS).

Idiopathic Parkinsonism

As initial therapy for parkinsonism, 1 mg of trihexyphenidyl HCl in tablet 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 to 10 mg 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 postencephalitic group, may require a total daily dose of 12 to 15 mg.

Drug-Induced Parkinsonism

The size and frequency of the trihexyphenidyl HCl dose needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thiothixene, and butyrophenechines, 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 with as little as 1 mg 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 while instituting trihexyphenidyl HCl therapy and then adjusting the dosage of both drugs until the desired atactic effect is retained without onset of extrapyramidal reactions.

It is sometimes possible to maintain the patient on a reduced trihexyphenidyl HCl 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 trihexyphenidyl HCl therapy was discontinued.

Concomitant Use with Levodopa

When trihexyphenidyl HCl 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. An trihexyphenidyl HCl dosage of 3 to 6 mg daily, in divided doses, is usually adequate.

Concomitant Use with Other Parasympathetic Inhibitors

Trihexyphenidyl 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 trihexyphenidyl HCl is increased.

HOW SUPPLIED

Trihexyphenidyl Hydrochloride Tablets, USP 2 mg are white colored, round debossed with N, T on either side of the score line and ‘2’ on the other side.

Trihexyphenidyl Hydrochloride Tablets, USP 5 mg are white colored, round debossed with N, T on either side of the score line.

Trihexyphenidyl Hydrochloride Tablets, USP 2 mg are available in Bottle of 100 tablets (NDC 16571-160-10)

Trihexyphenidyl Hydrochloride Tablets, USP 5 mg are available in Bottle of 100 tablets (NDC 16571-161-10)

Trihexyphenidyl Hydrochloride Tablets, USP 2 mg are available in Bottle of 100 tablets (NDC 16571-160-11)

Trihexyphenidyl Hydrochloride Tablets, USP 5 mg are available in Bottle of 100 tablets (NDC 16571-161-10)

Dispense in a tight container with child-resistant closure. Store at 20°-25°C (68°-77°F). (See USP controlled room temperature.)

Manufactured by: NATCO PHARMA LIMITED
Kothur-509 228, A.P. India.

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TRIHEXYPHENIDYL HYDROCHLORIDE TABLETS, USP

Open Size: 160 x 265 mm

Folding: 27 x 27 mm

Date/08/12/2010

Version: 02

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