

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40251

DRAFT FINAL PRINTED LABELING

Trihexyphenidyl Hydrochloride

Elixir, USP

2 mg per 5 mL

SEP 27 1999

Rx Only

Code 734A00
Rev. 10/98

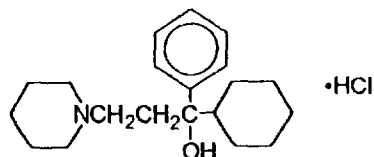
DESCRIPTION:

Trihexyphenidyl Hydrochloride Elixir, for oral administration, is a synthetic antispasmodic drug.

Each 5 mL contains 2 mg trihexyphenidyl hydrochloride and alcohol 5% in a clear, colorless, lime-peppermint flavored preparation. In addition, it contains the following inactive ingredients: Citric Acid, Flavoring, Methylparaben, Propylparaben and Sorbitol Solution.

Trihexyphenidyl Hydrochloride is a white or slightly off-white, crystalline powder, having not more than a very faint odor.

Trihexyphenidyl Hydrochloride is the substituted piperidine salt, (+)-1-(1-cyclohexyl-1-phenyl-1-piperidyl)propanol hydrochloride. It has the following structural formula:



$C_{20}H_{31}NO$ HCl

M.W. 337.94

The pH range of Trihexyphenidyl Hydrochloride Elixir USP is between 2.0 and 3.0.

CLINICAL PHARMACOLOGY:

Trihexyphenidyl 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 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.

INDICATIONS AND USAGE:

Trihexyphenidyl Hydrochloride Elixir 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 dibenzoxazepines, phenothiazines, thioxanthenes and butyrophenones.

WARNINGS:

Patients to be treated with trihexyphenidyl should have a gonioscope evaluation and close monitoring of intraocular pressures at regular periodic intervals.

PRECAUTIONS:

Although trihexyphenidyl is not contraindicated for patients with cardiac, liver, or kidney disorders, or with hypertension, such patients should be maintained under close observation.

Since the use of trihexyphenidyl may in some cases continue indefinitely and since it has atropine-like properties, patients should be subjected to constant and careful long-term observation to avoid allergic and other untoward reactions. In as much as trihexyphenidyl possesses some parasympatholytic activity, it 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. Geriatric patients, particularly over the age of 60, frequently develop increased sensitivity to the actions of drugs of this type, and hence, require strict dosage regulation. Incipient glaucoma may be precipitated by parasympatholytic drugs such as trihexyphenidyl.*

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 may relieve some of these parkinsonism symptoms.

ADVERSE REACTIONS:

Minor side effects, such as dryness of the mouth, blurring of 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 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 and hallucinations, plus one doubtful case of paranoia all of which may occur with any of the atropine-like drugs, have been reported rarely with trihexyphenidyl.

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.

Potential side effects associated with the use of any atropine-like drugs include constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular tension, weakness, vomiting and headache.

The occurrence of angle-closure glaucoma due to long-term treatment with trihexyphenidyl has been reported.

DOSAGE AND ADMINISTRATION:

Dosage should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age. Whether trihexyphenidyl may best be given before or after meals should be determined by the way the patient reacts. Postencephalitic 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. If trihexyphenidyl 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 induced can be allayed by mint candies, chewing gum or water.

Trihexyphenidyl in Idiopathic Parkinsonism:

As initial therapy for parkinsonism, 1 mg of trihexyphenidyl hydrochloride 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.

Trihexyphenidyl in Drug-Induced Parkinsonism:

The size and frequency of dose of trihexyphenidyl hydrochloride needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thioxanthenes and butyrophenones, 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 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 on instituting trihexyphenidyl therapy and then adjusting 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 trihexyphenidyl 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 therapy was discontinued.

Concomitant Use of Trihexyphenidyl with Levodopa:

When trihexyphenidyl 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. *Trihexyphenidyl hydrochloride dosage of 3 to 6 mg daily, in divided doses, is usually adequate.

Concomitant Use of Trihexyphenidyl Hydrochloride Elixir with Other Parasympathetic Inhibitors:

Trihexyphenidyl 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 is increased.

The total daily intake of trihexyphenidyl is tolerated best if divided up 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.

HOW SUPPLIED:

Trihexyphenidyl Hydrochloride Elixir, containing trihexyphenidyl hydrochloride 2 mg per 5 mL, is a clear, colorless, lime-peppermint flavored liquid supplied in 473 mL (16 fl oz) bottles, NDC 61748-054-36.

Dispense in a tight, light-resistant container with a child-resistant closure.

Store at controlled room temperature, 15 - 30 C (59 - 86 F). DO NOT FREEZE.

Distributed by:
VERSAPHARM, INCORPORATED
Marietta, GA 30065-1509

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Code 734A00

Rev. 10/98

NDC 61748-054-36

**Trihexyphenidyl
Hydrochloride Elixir USP
2 mg/5 mL**

Trihexyphenidyl HCl..... 2 mg
Alcohol 5 %



Lot:
Exp. Date:

PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure. This package not for household dispensing.
Store at controlled room temperature, 15°–30° C (59°–86° F).

Code 734A16

Rev. 04/98

P 27 1990

Usual Dosage: 3 to 5 teaspoonfuls (15 to 25 mL) daily for maintenance.

See package insert for complete prescribing information.

WARNING: Keep this and all medications out of the reach of children.

Manufactured by:
Mikart, Inc.
Atlanta, GA 30318

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Marietta, GA 30065