BENZTROP™

(BENZATROPINE MESILATE) TABLETS

1 NAME OF THE MEDICINE

Benzatropine mesilate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Benztrop tablet contains 2 mg of benzatropine mesilate.

Excipients with known effect: sugars (as lactose monohydrate).

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Benztrop 2 mg is a round, flat-faced white tablet, quarter-scored on one side and debossed with “PMS 2” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The treatment of all forms of parkinsonism. The treatment of extrapyramidal reactions (except tardive dyskinesia [see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use]) due to neuroleptic drugs.

4.2 DOSE AND METHOD OF ADMINISTRATION

Because Benztrop is cumulative in action, therapy should be initiated with a small dose which then can be increased gradually at five- or six-day intervals. Increases in dosage should be made in increments of 0.5 mg, to a maximum of 6 mg.

Some patients experience greatest relief when taking the entire dose at bedtime; others react more favourably to divided doses, two to four times a day.

The long duration of action of Benztrop makes it particularly suitable for administration at bedtime when the effects may persist throughout the night. Therefore, Benztrop enables the patient to turn in bed more easily and to rise in the morning.

When Benztrop is started, therapy with other agents in parkinsonism should not be terminated abruptly but reduced or discontinued gradually. Many patients obtain the greatest relief with a combination of Benztrop and other drugs.

Benztrop may be used concomitantly with SINEMET (carbidopa/levodopa, MSD), or with levodopa in which case periodic dosage adjustment may be required in order to maintain optimum response.

Arteriosclerotic, idiopathic and postencephalitic parkinsonism

The usual daily dose of Benztrop is 1 to 2 mg, with a range of 0.5 to 6 mg orally.

Dosage must be individualised. In determining the dosage, the age and weight of the patient and the type of parkinsonism must be taken into consideration. Older patients, thin patients and patients with arteriosclerotic parkinsonism generally cannot tolerate large doses. However, most patients with postencephalitic parkinsonism require and, indeed, tolerate fairly large doses. Patients with a poor mental outlook are usually poor candidates for therapy.

In arteriosclerosis and idiopathic parkinsonism, therapy may be initiated with a single daily dose of 0.5 mg to 1 mg at bedtime. This dosage will be adequate in some patients, whereas 4 mg to 6 mg a day may be required by others.

Therapy may be initiated in most patients with postencephalitic parkinsonism, with 2 mg a day in one or more doses. In highly sensitive individuals, therapy may be initiated with 0.5 mg at bedtime and increased as necessary.

Drug-induced parkinsonism

When treating extrapyramidal disorders due to central nervous system drugs such as phenothiazines or reserpine, a dosage of 1 to 4 mg once or twice a day is recommended. Dosage should be varied to suit the needs of the patient. Benztrop should be withdrawn to determine the continued need for medication after one or two weeks of administration. If parkinsonism recurs therapy with Benztrop can be reinstituted.

4.3 CONTRAINDICATIONS

Benztrop is contraindicated in children less than three years of age, and should be used with caution in older children because of the atropine-like side effects.

Benztrop is contraindicated in patients who are hypersensitive to any component in this product.

The use of Benztrop is contraindicated in the presence of narrow angle glaucoma.

Benztrop should not be used in patients with tardive dyskinesia as it can exacerbate this condition.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Benztrop has cumulative action. Patients with a tendency to tachycardia and patients with prostatic hypertrophy must be closely observed during treatment.

Benztrop may cause complaints of weakness and inability to move particular muscle groups in large doses. For example, if the neck has been rigid and suddenly relaxes, it may feel weak, causing some concern. In this event, dosage adjustment may be required.

With large doses or in susceptible patients, mental confusion and excitement may occur. Visual hallucinations have been reported occasionally. In the treatment of extrapyramidal symptoms due to central nervous system drugs, such as phenothiazines, in patients with mental disorders, occasionally there may be intensification of mental disorders with large doses. In such cases antiparkinsonian drugs can precipitate a toxic psychosis. Patients with mental disorders should be kept under careful observation, especially at the beginning of treatment or if dosage is increased.

Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy when these drugs have been discontinued. Antiparkinsonian agents usually do not alleviate their symptoms of tardive dyskinesia, and in some instances may aggravate or unmask such symptoms.

Benztrop is not recommended in tardive dyskinesia.

As Benztrop contains structural features of atropine, it may produce anhydrosis. Therefore, it should be given with caution during hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, the alcoholic, those who have central nervous system disease and those who do manual labour in a hot environment. When some disturbance of sweating already exists, anhydrosis may occur more readily. If there is evidence of anhydrosis, the possibility of hyperthermia should be considered. Dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhydrosis and fatal hyperthermia have occurred.

The physician should be aware of the possible occurrence of glaucoma. Although the drug does not appear to have any adverse effect on simple glaucoma, it should not be used in narrow-angle glaucoma. (See Section 4.3 Contraindications).

Dysuria may occur but rarely becomes a problem. Urinary retention has been reported with benzatropine.

Benztrop should be used with caution in patients with obstructive gastrointestinal disease as benzatropine may cause decreased motility and tone which may aggravate or precipitate obstruction.

Use in the elderly

No data available.

Paediatric use

See Section 4.3 Contraindications.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

When Benztrop is given concomitantly with anticholinergics or those with antidopaminergic activity, such as phenothiazines, haloperidol or other such drugs, patients should be advised to report fever, heat intolerance and gastrointestinal complaints promptly. Paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including Benztrop, in combination with phenothiazines and/or tricyclic antidepressants.

Alcohol and other CNS depressants, such as anxiolytics, sedatives and hypnotics, can increase the sedative effects of benzatropine.

Drugs that exert anticholinergic properties may pharmacodynamically oppose the effects of prokinetic agents such as cisapride or metoclopramide.

The doses of Benztrop and levodopa must be adjusted when the drugs are given simultaneously. Through its central anticholinergic actions Benztrop can potentiate the dopaminergic effects of levodopa. While some patients may benefit from this interaction, clinicians should be ready to decrease doses of levodopa if benzatropine is

added. The anticholinergic properties of Benztrop, by slowing gastrointestinal transit, may decrease levodopa bioavailability. However, this mechanism appears to be of modest clinical significance.

Anticholinergics can raise intragastric pH. This effect may interfere with the oral bioavailability of ketoconazole. Benztrop should be used cautiously in patients receiving ketoconazole.

Opiate agonists should be used cautiously with anticholinergics since additive depressive effects on GI motility or bladder function may be seen.

The muscarinic actions of drugs known as parasympathomimetics, including both direct cholinergic receptor agonists and cholinesterase inhibitors, can antagonise the anticholinergic actions of benzatropine. Benzatropine might also antagonise some of the effects of the parasympathomimetics.

Carbonic anhydrase inhibitors increase the alkalinity of the urine, thereby increasing the amount of nonionised drug available for renal tubular reabsorption.

Use with caution if Benztrop is administered with carbonic anhydrase inhibitors, which can decrease excretion and enhance the effects of Benztrop. Monitor for excessive anticholinergic adverse effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of benzatropine on fertility has not been investigated.

Use in pregnancy

Benztrop is Pregnancy Category B2 - *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

It is not known whether Benztrop can cause fetal harm when administered to a pregnant woman nor if it can affect reproductive capacity. The safe use of benzatropine in pregnancy has not been established.

Use in lactation

It is not known whether Benztrop is excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised if Benztrop is administered to a breastfeeding woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Benztrop may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions, most of which are anticholinergic or antihistaminic in nature, are listed below by body system in order of decreasing severity:

Cardiovascular: Tachycardia.

Digestive: Constipation, dry mouth, nausea, vomiting, paralytic ileus.

Reduce dosage or discontinue the drug temporarily if dry mouth is so severe that there is difficulty in swallowing or speaking, or loss of appetite and weight occur.

Slight reduction in dosage may control nausea and still give sufficient relief of symptoms. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Nervous system: Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations, exacerbation of pre-existing psychotic symptoms, nervousness, depression, listlessness, numbness of fingers.

Special senses: Dilated pupils, blurred vision.

Urogenital: Urinary retention, dysuria.

Metabolic / immune and skin: Occasionally, an allergic reaction, e.g. skin rash, develops. If this cannot be controlled by dosage reduction, the medication should be discontinued.

Other: Heat stroke, hyperthermia, fever.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Manifestations

As with any of those seen in atropine poisoning or antihistamine overdosage: CNS depression, preceded or followed by stimulation; confusion; nervousness; listlessness; intensification of mental symptoms or toxic psychosis in patients with mental illness being treated with phenothiazine derivatives; hallucinations (especially visual); dizziness; muscle weakness; ataxia; dry mouth; mydriasis; blurred vision; palpitations; tachycardia; nausea; vomiting; dysuria; numbness of fingers; dysphagia; allergic reactions, e.g. skin rash; headache; hot, dry, flushed skin, delirium; coma; shock; convulsions; respiratory arrest; anhydrosis; hyperthermia; glaucoma; constipation.

Treatment

Treatment is symptomatic and supportive.

Physostigmine salicylate, 1 to 2 mg subcutaneous or intravenous, will reverse symptoms of anticholinergic intoxication. A second injection may be given after two hours if required.

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Maintain respiration. A short-acting barbiturate may be used for CNS excitement, but with caution to avoid subsequent depression; supportive care for depression (avoid convulsant stimulants such as picrotoxin, pentylenetetrazole or bemegride); artificial respiration for severe respiratory depression; a local miotic for mydriasis and cycloplegia; ice bags or other cold applications

and alcohol sponges for hyperpyrexia, a vasopressor and fluids for circulatory collapse. Darken room for photophobia.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Benztrop is a centrally acting anticholinergic agent with antihistaminic properties resulting from the combination of the tropine portion of the atropine molecule and the benzohydryl portion of diphenhydramine. Animal studies have indicated that anticholinergic activity of benzatropine is approximately half that of atropine, while antihistaminic activity approaches that of pyrilamine. Its anticholinergic effects have been established as therapeutically significant in the management of parkinsonism. Benztrop antagonises the effect of acetylcholine, decreasing the imbalance between the neurotransmitters acetylcholine and dopamine, which may improve the symptoms of early Parkinson's disease.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Benztrop is administered orally. It is absorbed from the GI tract, crosses the blood-brain barrier, and may cross the placenta. After oral administration, a small part of the dose may pass through the GI tract unchanged into the faeces.

Distribution

Benzatropine binds extensively, approximately 95%, with serum proteins.

Metabolism

The metabolism of benzatropine is unknown.

Excretion

Most of the drug is excreted renally, both as parent drug and as metabolites.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Investigations of the genotoxic potential of benzatropine have not been performed.

Carcinogenicity

Investigations of the carcinogenic potential of benzatropine have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each Benztrop tablet contains the excipients pregelatinised maize starch 5 mg, lactose monohydrate 118.6 mg, microcrystalline cellulose 13.2 mg, and magnesium stearate 1.2 mg.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Supplied in bottles of 60 tablets.

Phebra product code: TAB005

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

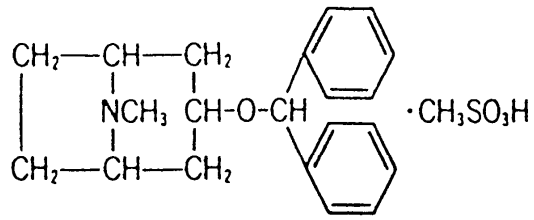
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Benzatropine mesilate is a synthetic compound resulting from the combination of the active portions of atropine and diphenhydramine. It is a crystalline white powder and very soluble in water.

The molecular weight of the compound is 403.5. The molecular formula is $C_{21}H_{25}NO.CH_4O_3S$.

Chemical structure



CAS number

132-17-2

[1] AUST R 83130

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - PRESCRIPTION ONLY MEDICINE

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15 Jul 2002

10 DATE OF REVISION

12 Feb 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformatted to align with new form with minor editorial changes
3	Minor editorial change
4.5	Minor typo correction.
4.9	Update of treatment section as per the TGA's recommendation
5	Minor editorial change
6.1	Added specific quantities per excipient as per ATRG summary. Minor editorial change
7	Minor formatting change

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