BENZATROPINE INJECTION

(BENZATROPINE MESILATE)

1 NAME OF THE MEDICINE

Benzatropine mesilate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Benzatropine Injection is available as 2 mg in 2 mL vials.

Benzatropine Injection contains benzatropine mesilate as the active ingredient.

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

3 PHARMACEUTICAL FORM

Benzatropine Injection, 2 mg in 2 mL, clear, colourless, particle free solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Benzatropine Injection is recommended for all forms of parkinsonism - including arteriosclerotic, post-encephalitic, idiopathic, as well as drug-induced extrapyramidal disorders (except tardive dyskinesia). It can be effective at any stage of the disease, even when a patient has become bedridden. Benzatropine Injection often is helpful in patients who have become unresponsive to other agents. Benzatropine Injection is a powerful anticholinergic agent which is mainly effective in relieving tremor and rigidity. Therapy is directed toward control of disturbing symptoms to permit the patient maximum integration of function with minimum discomfort.

In non-drug-induced parkinsonism, partial control of symptoms is usually achieved.

4.2 DOSE AND METHOD OF ADMINISTRATION

Benzatropine Injection is available as an injection for intravenous and intramuscular use. Each millilitre of the injection contains:

Benzatropine mesilate	1.0 mg
Sodium chloride	9.0 mg
Water for injections q.s	1.0 mL

Because Benzatropine Injection 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.

The injection is especially useful for psychotic patients with acute dystonic reactions or other reactions that make oral medication difficult or impossible.

There is no significant difference in the onset of effect following intravenous or intramuscular injection. Improvement is noticeable within a few minutes after injection.

In emergency situations, when the patient's condition is alarming, administration of 1 to 2 mL of Benzatropine Injection will provide quick relief. If the signs of parkinsonism begin to return, the dose can be repeated.

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 Benzatropine Injection makes it particularly suitable for administration at bedtime when the effects may persist throughout the night. Consequently, Benzatropine Injection enables the patient to turn in bed more easily and to rise in the morning.

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

Benzatropine Injection may be used concomitantly with combinations of carbidopa/ levodopa, 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 Benzatropine Injection is 1 to 2 mg, with a range of 0.5 to 6 mg parenterally.

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.

In postencephalitic parkinsonism, therapy may be initiated in most patients 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. After one or two weeks of administration, Benzatropine Injection should be withdrawn to determine the continued need for medication.

If parkinsonism recurs, therapy with Benzatropine Injection can be reinstituted.

Usually the injection of 1 to 2 mL of Benzatropine Injection quickly relieves acute dystonic reactions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

4.3 CONTRAINDICATIONS

Because of the atropine-like side effects, Benzatropine Injection is contraindicated in children under three years of age, and should be used with caution in older children.

Benzatropine Injection is contraindicated in patients who are hypersensitive to any component of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When Benzatropine Injection is given concomitantly with phenothiazines, haloperidol, or other drugs with anticholinergic or antidopaminergic activity, patients should be advised to report gastrointestinal complaints, fever or heat intolerance promptly. Paralytic ileus, hyperthermia and heat stroke, all of which have sometimes been fatal, have occurred in patients taking anticholinergic-type antiparkinsonism drugs, including Benzatropine Injection, in combination with phenothiazines and/or tricyclic antidepressants.

Dysuria may occur, but rarely becomes a problem. Urinary retention has been reported with Benzatropine Injection.

Since benzatropine mesilate has cumulative action, continued supervision is advisable. Patients with a tendency to tachycardia and patients with prostatic hypertrophy, should be closely observed during treatment.

In large doses, the drug may cause complaints of weakness and inability to move particular muscle groups. 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.

Mental confusion and excitement may occur with large doses, or in susceptible patients. Visual hallucinations have been reported occasionally. Furthermore, in the treatment of extrapyramidal symptoms due to central nervous system drugs, such as phenothiazines and reserpine, in patients with mental disorders, occasionally there may be intensification of mental disorders. 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. Benzatropine Injection is not recommended in tardive dyskinesia.

Since benzatropine mesilate contains structural features of atropine, it may produce anhydrosis. For this reason, 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.

Anhydrosis may occur more readily when some disturbance of sweating already exists. 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, Benzatropine Injection probably should not be used in narrow-angle glaucoma.

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

Antipsychotic drugs such as phenothiazines or haloperidol; tricyclic antidepressants (see Special warnings and precautions for use).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

(Category B2)

It is not known whether Benzatropine Injection can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Benzatropine Injection should be given to a pregnant woman only if clearly needed.

Use in lactation

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 Benzatropine Injection is administered to a nursing mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Benzatropine mesilate 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, paralytic ileus, vomiting.

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

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, listless-ness, numbness of fingers.

Special senses

Blurred vision, dilated pupils.

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

Heatstroke, 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:

- (Australia) http://www.tga.gov.au/reporting-problems ,
- (New Zealand) https://nzphvc.otago.ac.nz/reporting/ or
- (Singapore) https://www.hsa.gov.sg/adverse-events/healthcare-professionals'-guide-to-adverse-events-reporting .

4.9 OVERDOSE

Symptoms

May be 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 or reserpine; 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.

The oral LD50 in the mouse is 94 mg/kg. The intravenous LD50 in the mouse is 24 mg/kg.

Treatment

For all overdoses, the mainstay of treatment is supportive and symptomatic care. Physostigmine salicylate, 1 to 2 mg s.c. or i.v., will reverse symptoms of anticholinergic intoxication. A second injection may be given after two hours if required. Otherwise treatment is symptomatic and supportive. 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.

In Australia, for information on the management of overdose, contact the Poisons Information Centre on 131126.

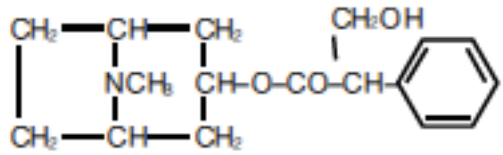
In New Zealand, for advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

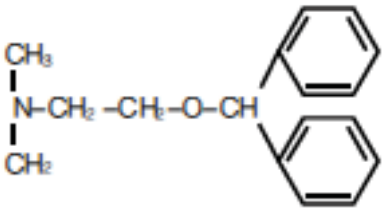
5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

If the formula for benzatropine mesilate is compared with that of atropine:



and that of diphenhydramine:



it can be seen that benzatropine contains the tropine portion of the atropine molecule and the benzohydryl portion of diphenhydramine.

Benzatropine possesses both anticholinergic and antihistaminic effects, although only the former have been established as therapeutically significant in the management of parkinsonism.

In laboratory animals the antihistaminic activity and duration of action approach those of pyrilamine maleate.

In the isolated guinea pig ileum, the anticholinergic activity of this drug is about equal to that of atropine; however, when administered orally to unanaesthetised cats, benzatropine is only about half as active as atropine.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

No data available.

Distribution

No data available.

Metabolism

No data available.

Excretion

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each Benzatropine Injection contains:

Sodium chloride	18.0 mg
Water for injections q.s	2.0 mL

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

The expiry date can be found on the packaging.

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Protect from light. Do not freeze. Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Benzatropine Injection is supplied as 2 mg / 2 mL glass vials.

Phebra product code: INJ197 2 mL vial supplied in a carton containing 5 vials

INJ187 2 mL vial supplied in a carton containing 10 vials

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

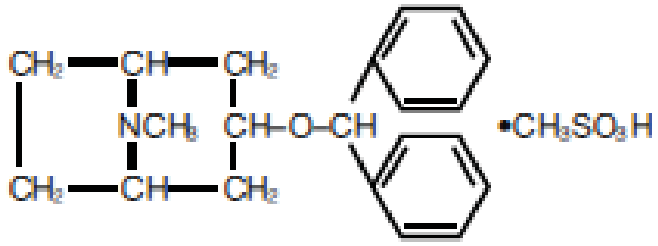
Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Benzatropine mesilate is a synthetic compound resulting from the combination of the active portions of atropine and diphenhydramine.

Benzatropine mesilate is a crystalline white powder and is very soluble in water.

Chemical structure



CAS number

132-17-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

[1] AUST R 276242

8 MANUFACTURER / DISTRIBUTOR

Manufactured by Phebra[2] Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

Distributed in New Zealand by Phebra NZ Limited
Telephone: +64 0508 743 272

Distributed in Singapore by Novem Healthcare Pte Ltd., 23 New Industrial Road, #03-08 Solstice Business Center, Singapore 536209
Telephone: +65 64433673

9 DATE OF FIRST APPROVAL

18 Jul 2017 (Australia)

10 DATE OF REVISION

26 Apr 2021

[2] Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	PI reformatted to align with new form
4.2	Included '*Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration' as* per HSA-Singapore's request.
4.4	Information from section 4.5 has been moved as first paragraph and '*Dysuria may occur, but rarely becomes a problem. Urinary retention has been reported with Benzatropine Injection'* was added as per HSA-Singapore's request.
4.5	Updated as per HSA (Singapore's) request. Most of the information was moved to section 4.4
4.8	Included '*paralytic ileus'* reaction under the 'Digestive' section as per HSA-Singapore's request. Added New Zealand and Singapore website reference, where Healthcare professionals are asked to report any suspected adverse reactions as this is a harmonized packaging component for AU-SG-NZ.
4.9	Minor editorial changes. Added *'In New Zealand, for advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).*
6.3	Minor editorial change
6.6	Minor editorial change
8	Section title has been amended from 'Sponsor' to 'Manufacturer/Distributor'. Added 'Manufacturer by' for Phebra and included Distributor details for New Zealand and Singapore.
9	Added '(Australia)'
10	Accordingly updated.