1. PRODUCT NAME

Benzatropine Injection (1 mg/mL), solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL of Benzatropine Injection contains 2 mg of benzatropine mesilate.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Benzatropine Injection is recommended for all forms of parkinsonism including arteriosclerotic, post- encephalitic, idiopathic, as well as medicine-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-medicine-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 medicines.

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.

Medicine-Induced Parkinsonism

When treating extrapyramidal disorders due to central nervous system medicines 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.

Special population

- Renal impairment: Benzatropine Injection should be used with caution in patients with renal impairment. Refer to section 4.4 Special warnings and precautions for use.
- Hepatic impairment: Benzatropine Injection should be used with caution in patients with hepatic impairment. Refer to section 4.4 Special warnings and precautions for use.

Paediatric population

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. Refer to section 4.3 Contraindications.

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 thisproduct.

Benzatropine Injection is contraindicated in patients with tardive dyskinesia, narrow angle glaucoma (Refer to

section 4.4 Special warnings and precautions for use), dementia or prostatism.

4.4 Special warnings and precautions for use

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

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 medicine 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 medicines, such as phenothiazines and reserpine, in patients with mental disorders, occasionally there may be intensification of mental disorders. In such cases antiparkinsonian medicines 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 medicines 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 medicines 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 medicine does not appear to have any adverse effect on simple glaucoma, Benzatropine Injection probably should not be used in narrow-angle glaucoma.

Benzatropine Injection should also be used with caution in patients with urinary retention, cardiovascular disease and hepatic or renal impairment.

Use in the elderly

No data available.

Pediatric use

See Section 4.3 Contraindications.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

When Benzatropine Injection is given concomitantly with phenothiazines, haloperidol or other medicines with anticholinergic or antidopaminergic activity, 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 medicines, including Benzatropine Injection, in combination with phenothiazines and/or tricyclic antidepressants.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

The effects of benzatropine on fertility have not been systematically studied. Men and women of childbearing potential must use effective contraception during treatment with Benzatropine Injection.

Use in Pregnancy

(Category B2)

It is not known whether Benzatropine Injection can cause fetal 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 medicine is excreted in human milk. Because many medicines 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 injection may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

4.8 Undesirable effects

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

Cardiovascular

Tachycardia.

Digestive

Constipation, dry mouth, nausea, 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 medicine 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, listlessness, numbness offingers.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/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 forphotophobia.

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

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

Benzatropine mesilate contains the tropine portion of the atropine molecule and the benzohydryl portion of diphenhydramine.

In laboratory animals, the antihistaminic activity and duration of action approachthose of pyrilamine maleate.

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

5.2 Pharmacokinetic properties

In a clinical study measuring serum levels of neuroleptics and anticholinergics via radioreceptor assay, the correlation between total daily dose of benzatropine and serum concentration was extremely poor (r = 0.0281). Serum concentrations varied nearly 100-fold with given doses between 2 and 6 mg/day. A markedly non-linear relationship between daily dose and serum anticholinergic agent levels was observed with an increasing oral dosage of benzatropine. In most cases, 2 mg increments in oral dose were associated with several-fold increases in the serum level of anticholinergic activity.

It has been reported that the duration of action for benzatropine may persist for up to 24 to 48 hours following a single 2 mg IM injection. Benzatropine binds extensively, approximately 95%, with serum proteins. Benzatropine crosses the blood-brain barrier.

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

None

6.3 Shelf life

36 months. The expiry date can be found on the packaging.

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 a clear, colourless solution, 2 mg in 2 mL glass vial.

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

Phebra product code: INJ197 2mL vial in cartons containing 5 vials.

INJ187 2 mL in cartons containing 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Proper safe handling and disposal should be observed by medical staff.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Phebra NZ Limited Auckland New

Zealand Telephone: 0508 743 272

9. DATE OF FIRST APPROVAL

03 Oct 2019

10. DATE OF REVISION OF THE TEXT

08 Apr 2021

SUMMARY TABLE OF CHANGES

Section (s) changed	Change(s)
4.4	*Use in elderly, Pediatric use and Effect on laboratory tests* sections have been added. More information for the users.
4.6	*Use in Pregnancy* section has been updated to add *Category B2* and to correct typographical error for *fetal*.
4.8	*Reporting suspected adverse reactions* subtitle has been added as per Datasheet template.
4.9	Treatment Section has been updated to include the following statement as per approved AU Product Information: *'For all overdoses, the mainstay of treatment is supportive and symptomatic care.'*
5.3	*Genotoxicity* and *Carcinogenicity* sections has been added in alignment with approved AU Product Information.
6.1	Section updated in alignment with approved AU Product Information.
6.3	Typographical correction. Shelf life has been updated from 24 to 36 months.
6.5	Section updated in alignment with approved AU Product Information.
9	Minor editorial change. Date format has been updated.
All	Version control added.