

Data Sheet

COGENTIN[®]

Solution for Injection

Benzotropine mesylate 1 mg/mL

Presentation

COGENTIN injection is a clear solution free of extraneous matter contained in a glass ampoule (2 mL benzotropine mesylate per ampoule, 1 mg/mL).

Therapeutic Class

Antiparkinson agent.

Indications

COGENTIN is recommended for all forms of parkinsonism including arteriosclerotic, postencephalitic, 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.

COGENTIN often is helpful in patients who have become unresponsive to other agents. COGENTIN 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.

Dosage and Administration

COGENTIN is available as a sterile injection for intravenous and intramuscular use. Each millilitre of the injection contains:

Benzotropine mesylate	1.0 mg
Sodium chloride	9.0 mg
Water for injection q.s.	1.0 mL

Because COGENTIN 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. There is no significant difference in onset of effect following intravenous or intramuscular injection. Improvement sometimes 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 COGENTIN injection usually 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 COGENTIN makes it particularly suitable for administration at bedtime when the effects may persist throughout the night. Consequently, COGENTIN enables the patient to turn in bed more easily and to rise in the morning.

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

COGENTIN 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 dosage of COGENTIN is 1 to 2 mg, with a range of 0.5 to 6 mg.

Dosage must be individualised. In determining the dosage, the age and weight of the patient and 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 usually are poor candidates for therapy.

In arteriosclerotic 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, COGENTIN should be withdrawn to determine the continued need for medication. If parkinsonism recurs, therapy with COGENTIN can be reinstated.

Usually the injection of 1 to 2 mL of COGENTIN quickly relieves acute dystonic reactions, after which benztrapine tablets, 1 to 2 mg twice a day, usually prevent recurrence.

Contraindications

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

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

COGENTIN is contraindicated in patients with tardive dyskinesia, narrow angle glaucoma (see Warnings and Precautions), dementia or prostatism.

Warnings and Precautions

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

Since benzotropine mesylate has cumulative action, continued supervision is advisable. Patients with a tendency to tachycardia and patients with prostatic hypertrophy should be observed closely 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. Antiparkinsonism agents usually do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate or unmask such symptoms. COGENTIN is not recommended in tardive dyskinesia (see Contraindications).

Since benzotropine mesylate contains structural features of atropine, it may produce anhidrosis. 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. 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 at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhidrosis 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, COGENTIN probably should not be used in narrow-angle glaucoma (see Contraindications).

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

Use in Pregnancy

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

Nursing Mothers

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 COGENTIN is administered to a nursing mother.

Paediatric Use

See Contraindications.

Animal Toxicology

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

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 agent is about equal to that of atropine; however, when administered orally to unanaesthetised cats, benztropine is only about half as active as atropine.

Adverse Effects

Adverse effects, 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.

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 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: Heat stroke, hyperthermia, fever.

Interactions

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

Overdosage

Manifestations

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; anhidrosis; hyperthermia; glaucoma; constipation.

Treatment of Overdosage

Physostigmine salicylate, 1 to 2 mg SC or IV, will reverse symptoms of anti-cholinergic intoxication. A second injection may be given after 2 hours if required. Otherwise treatment is symptomatic and supportive. Induce emesis or perform gastric lavage (contraindicated in precomatose, convulsive, or psychotic states). 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, pentylenetetrazol, 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.

Actions

Benztropine mesylate is a synthetic compound containing structural features found in both atropine and diphenhydramine.

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

In a clinical study measuring serum levels of neuroleptics and anticholinergics via radioreceptor assay, the correlation between total daily dose of benztropine 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 benztropine. 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 benztropine may persist for up to 24 to 48 hours following a single 2 mg IM injection. Benztropine binds extensively, approximately 95%, with serum proteins. Benztropine crosses the blood-brain barrier.

Pharmacokinetics

Absorption/Metabolism

Data on Absorption/Metabolism are not available.

Excretion - Milk

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 COGENTIN is administered to a nursing mother.

Placental Transfer

It is not known whether benztropine mesylate passes the placental barrier.

Pharmaceutical Precautions and Storage Conditions

Protect from light. Protect product from freezing. Store below 30°C.

Medicine Classification

Prescription Medicine

Package Quantities

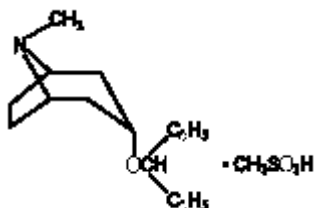
COGENTIN injection is available in 2 mL ampoules (1 mg/mL).

Further Information

Chemistry

Benztropine mesylate is a synthetic compound containing structural features found in atropine and diphenhydramine.

It is designated chemically as 8-azabicyclo [3.2.1] octane, 3-(diphenylmethoxy)-, endo, methanesulfonate. Its empirical formula is $C_{21}H_{25}NO \cdot CH_4O_3S$, and its structural formula is:



Benztropine mesylate is a crystalline white powder, very soluble in water, and has a molecular weight of 403.54.

Benztropine mesylate contains the tropine portion of the atropine molecule and the benzohydryl portion of diphenhydramine.

Ingredients

Active ingredient:

- benztropine mesylate 1 mg per mL

Inactive ingredients:

- sodium chloride
 - water for injection
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Date of Preparation

11 August 2010