

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AKINETON® Tablets

AKINETON® Injection

COMPOSITION

Each tablet contains 2 mg biperiden hydrochloride.

Each ampoule contains 5 mg/ml biperiden lactate.

Excipients (Tablets):

Calcium hydrogen phosphate dihydrate, copovidone (copolyvidone), lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, potato starch, talc.

Contains sugar: lactose monohydrate.

Excipients (solution for Injection):

Lactic acid, sodium hydroxide, water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 5.4.1. Anti-parkinsonism preparations.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Biperiden is an anticholinergic medicine that exhibits effects on the central nervous system (CNS), binding competitively to peripheral and central muscarinic receptors with a high affinity to M1 receptor subtype in the frontal cerebral cortex.

Pharmacokinetic properties

Absorption:

Following an oral dose of biperiden 4 mg, peak levels were observed after 1,4 hours. The bioavailability of orally administered biperiden hydrochloride is 33 %.

Plasma concentration:

Peak plasma concentrations of approximately $4,1 \pm 0,9$ ng/ml are reached in approximately 1,5 hours. The oral plasma clearance rate is about 146 L/hour. The plasma concentration curve is biphasic after the intravenous injection of 4 mg biperiden lactate (equivalent to 3,1 mg biperiden) with an initial half-life of 1,5 hours and a terminal half-life of 24 hours. Plasma clearance is $11,6 \pm 0,8$ ml min⁻¹ kg⁻¹ in healthy young volunteers.

Distribution:

Volume of distribution of biperiden is $24 \pm 4,1$ L/kg. Biperiden binds extensively to plasma proteins.

Elimination:

After oral administration, the elimination half-life is 21 hours. Unchanged biperiden is not detected in urine.

Special Populations:

Renal and hepatic impairment:

There are no pharmacokinetic data available for the use of AKINETON in patients with liver or kidney impairment.

Elderly patients:

Elderly patients are more sensitive to the anticholinergic action of biperiden due to physiological and pathophysiological changes that often accompany the aging process.

INDICATIONS

AKINETON is indicated for:

- Parkinsonism;
- drug-induced extrapyramidal symptoms

CONTRAINDICATIONS

AKINETON is contraindicated in:

- Patients with hypersensitivity to the active ingredient or to any of the excipients in AKINETON (See COMPOSITION);
- narrow angle glaucoma;
- mechanical stenosis or obstruction (ileus) in the gastro-intestinal tract;
- megacolon;
- patients with cerebral impairment crisis (See WARNINGS and SPECIAL PRECAUTIONS);

- pregnancy and lactation (See PREGNANCY and LACTATION);
- myasthenia gravis.

WARNINGS AND SPECIAL PRECAUTIONS

- Patients with central nervous system impairment may have an increased risk of side effects of AKINETON.
- Feeling of unrest, confusion, or conditions similar to psychoses, are symptoms of overdosage which in patients with low tolerance, such as patients with cerebral arteriosclerosis, may occur even with doses falling into the therapeutic range; similar symptoms occur if AKINETON is given together with antidepressants or neuroleptics (See SIDE EFFECTS).
- In patients with prostatic enlargement, AKINETON may cause urinary retention.
- AKINETON should be used with caution in patients diagnosed with lower urinary tract symptoms (LUTS) or benign prostatic hypertrophy obstruction (BPH) due to the possible development of acute urinary retention, voiding difficulty, and other anticholinergic side effects.
- AKINETON should be administered with caution in conditions which may be associated with tachycardia or in patients who show an increased tendency to convulsions.
- The consumption of alcohol should be avoided under AKINETON therapy (See INTERACTIONS).
- Following parenteral administration, severe blood pressure decrease and severe bradycardia may occur especially if the injection is too rapid (See Dosage and Directions).
- AKINETON should not be used in patients with myasthenia gravis.
- Impaired memory, as well as lack of concentration and euphoria frequently occur in patients taking AKINETON (see SIDE EFFECTS).
- Tolerance, withdrawal and relapse are consistent with AKINETON dependence due to long-term use of anticholinergics.
- They may cause dependency.

Effects on ability to drive and use machines:

AKINETON may impair the patient's speed of reaction. Since adverse reactions such as tiredness, dizziness, drowsiness, delirium, hallucination, anxiety, agitation, euphoric mood, confusional state, accommodation disorders, mydriasis, photophobia, and narrow-angle glaucoma may occur in patients receiving AKINETON, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous

machinery or perform any tasks that requires coherent concentration especially if used with other medicines that affect the central nervous system or alcohol (See SIDE EFFECTS).

In these situations, impaired decision making could lead to accidents.

Withdrawal symptoms:

Upon cessation of treatment or reduction of the dose, insomnia develops. Abrupt cessation can lead to the following withdrawal symptoms: nausea, sweating, and urinary urgency (See SIDE EFFECTS).

INTERACTIONS

After additional administrations of AKINETON concomitantly with other anti-parkinsonism medicines, quinidine or tricyclic antidepressants, a possible intensification of vegetative or central effects as described above is observed; the AKINETON dose should in this case be reduced or discontinued. The effects of alcohol are intensified during treatment with AKINETON (See WARNINGS and SPECIAL PRECAUTIONS).

PREGNANCY AND LACTATION

The safety and efficacy of AKINETON in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Parkinsonism:

Tablets: Gradually increase from 1 mg ($\frac{1}{2}$ a tablet) twice daily up to the individually adjusted optimal dose which generally ranges between 1 mg ($\frac{1}{2}$ a tablet) to 4 mg (2 tablets) three to four times daily.

Ampoules: In severe cases 10 to 20 mg (=2 to 4 ml) intramuscularly or slowly intravenously administered, over the duration of the day.

Drug-induced extrapyramidal symptoms:

Adults: Take orally, concomitant with the neuroleptic medicines, 1 mg ($\frac{1}{2}$ a tablet) to 4 mg (2 tablets) one to four times daily, increased as required, to maximum of 18 mg (9 tablets) daily.

Children aged between 3-15 years receive 1 mg ($\frac{1}{2}$ a tablet) to 2 mg (1 tablet) three times daily.

The parental dose for adults is 2,5 to 5 mg (0,5 to 1 ml) given intramuscularly or slowly intravenously. The suggested dose for children up to 1 year of age is 1 mg, up to 6 years 2 mg, and up to 10 years 3 mg, given slowly intravenously. Dependent on individual reactivity, extrapyramidal symptoms may disappear already in the course of injection. In this case the injection should be stopped immediately. If required, injection of a dose

appropriate to the child's age can be repeated after 30 minutes.

SIDE-EFFECTS

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as: *Very common* $\geq 1/10$; *Common* $\geq 1/100$, $< 1/10$; *Uncommon* $\geq 1/1\ 000$, $< 1/100$;

Rare $\geq 1/10\ 000$, $< 1/1\ 000$; *Very rare* $< 1/10\ 000$, including isolated reports.

System Organ Class	Frequency grouping
Psychiatric disorders	<i>Frequent:</i> Delirium, hallucination, insomnia.
	<i>Frequency unknown:</i> Anxiety, agitation, euphoric mood, depersonalisation, derealisation and confusional state.
	Restlessness, or conditions similar to psychotic disorder, are symptoms of overdosage which in patients with low tolerance, such as patients with cerebral arteriosclerosis, may occur even with doses falling into the therapeutic range; similar symptoms occur if AKINETON is given together with antidepressants or neuroleptics in high doses (See WARNINGS and SPECIAL PRECAUTIONS).
Nervous system disorders	<i>Frequent:</i> Headache, tardive dyskinesia, ataxia, and speech disorder, memory impairment, impaired cognitive function.
	<i>Frequency unknown:</i> Dizziness, drowsiness and convulsions.
Eye disorders	<i>Frequency unknown:</i> Accommodation disorders, blurred vision, mydriasis, photophobia, and narrow-angle glaucoma.
Ear and labyrinth disorders	<i>Frequency unknown:</i> Vertigo.
Cardiac disorders	<i>Less frequent:</i> Bradycardia.
	<i>Frequency unknown:</i> Tachycardia.
Vascular disorders	<i>Frequency unknown:</i> Hypotension
Gastrointestinal disorders	<i>Frequent:</i> Constipation, obstipation, abdominal discomfort, nausea, gastric disorder.
	<i>Frequency unknown:</i> Dry mouth.
Skin and subcutaneous tissue disorders	<i>Frequency unknown:</i> Hypohidrosis.
Renal and urinary disorders	<i>Less frequent:</i> Urinary retention
General disorders and administrative site conditions	<i>Frequency unknown:</i> Fatigue, fever, hot skin

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

The picture of intoxication is essentially the same as that of atropine intoxication with peripheral anticholinergic symptoms (such as wide, sluggish pupils, dilated pupils, slowing of movements, reddening of face, dryness of mucous membranes, flushing, rise in heart rate, atony of bowels and bladder, increased temperature, especially

in children) and disorders of the central nervous system (such as excitation, confusion, clouding of consciousness, agitation, delirium, mental fog and/or hallucinations). In case of massive intoxication there is a risk of circulatory failure and central respiratory paralysis.

Treatment

Acetylcholinesterase inhibitors may be used as antidotes, especially physostigmine, which passes the blood brain barrier, and also influences the centrally induced symptoms.

IDENTIFICATION

Tablet: Scored, almost white tablet marked with a double score line on one side.

Ampoules: Clear, colourless solution in colourless ampoule.

PRESENTATION

AKINETON 50's: Blister packs with 10 tablets per blister and 5 blisters per pack.

AKINETON Injection: 5 colourless type I glass ampoules, 1 ml each.

STORAGE INSTRUCTIONS

Store at or below 25 °C, in a cool, dry place.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REFERENCE NUMBER

AKINETON® Tablets: B1042 (Act 101/1965)

AKINETON® Injection: B1039 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

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AKINETON Tablets NAMIBIA: NS2 Reg. No.: 14/5.4.1/0195	AKINETON Injection NAMIBIA: NS2 Reg. No.: 14/5.4.1/0196	AKINETON Tablets BOTSWANA: S2 Reg. No.: B9305380	AKINETON Injection BOTSWANA: S2 Reg. No.: BOT1803351
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