Akineton® 2 mg

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Akineton® 2 mg - tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Biperiden Hydrochloride.
1 tablet contains 2 mg Biperiden Hydrochloride equivalent to 1.8 mg Biperiden.

Excipient with known effect: Lactose monohydrate 38 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, biplanar tablet, cross-scored on one side.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- All forms of parkinsonism,
- Drug-induced extrapyramidal symptoms excito-motor phenomena, parkinsonoid, akinesia, rigidity, akathisia, acute dystonia.

4.2 Posology and method of administration

Biperiden has to be dosed individually.
Treatment should begin with the lowest dose and then be increased to the most favourable dose for the patient.

Posology

Adults

Parkinson syndrome
Initially 2 times ½ tablet (2 mg Biperiden hydrochloride/day) distributed over the day. The dose can be increased daily by 2 mg. As maintenance dose, 3–4 times daily ½–2 tablets (corresponding to 3–16 mg/day) are administered. The maximum daily dose amounts to 16 mg Biperiden hydrochloride (corresponding to 8 tablets/day).

Drug-related extrapyramidal symptoms:
For the treatment of drug-related extrapyramidal symptoms, ½–1 tablet is administered 2–3 times daily concomitantly with the neuroleptic (corresponding to 2–6 mg Biperiden hydrochloride/day), depending on the severity of the symptoms.

Children and adolescents (up to 18 years)

For the treatment of drug-induced extrapyramidal symptoms, children from 3 to 15 years receive 1–3 times daily 1/2–1 tablet (equivalent to 1–6 mg biperiden hydrochloride/ day).

Older patients
Caution with dosing is necessary! The lowest possible dose should be used initially and the dose should then be slowly increased, depending on the response of the patient (see also section 5.2).

Patients with impaired liver or renal function
No pharmacokinetic data is available in patients with impaired liver or renal function. For this reason, caution is necessary when dosing. Start with the lowest possible dose and, depending upon the response of the patient, the dose should be increased slowly.

Remarks
In patients requiring a quick onset of action, an injection solution is available.

Method of administration

The total daily dose should be divided into several single administrations and taken uniformly distributed over the day.
The tablets can be divided into two equal doses and should be taken with sufficient liquid preferably during or after a meal.
Undesired effects on the gastro-intestinal tract can be avoided by taking the tablets immediately after meals.

Duration of treatment

The duration of treatment depends on the type and extent of the disease and can range from short-term administration to long-term medication.
Treatment with this medication should not be discontinued abruptly, but in steps.

4.3 Contraindications

Akineton® should not be used in case of:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- untreated narrow angle glaucoma
- mechanical stenoses in the gastro-intestinal tract
- Megacolon
- Ileus

4.4 Special warnings and precautions for use

Anti-cholinergic drugs, such as Biperiden, with a central mode of action can lead to an increased tendency to cerebral seizures. In patients with an increased tendency to convulsions, Akineton® is to be dosed carefully (see side-effects).

In the case of urinary retention, patients should empty the bladder before taking the respective dose of Biperiden.
Biperiden can lead sporadically to difficulties in micturition, in particular in patients with prostate hypertrophy, more seldom to urinary retention.

The intraocular pressure should be controlled regularly (see side-effects). Caution should also be taken in cases of existing glaucoma.

Akineton® may only be used with particular caution in patients with Myasthenia gravis.

In patients who suffer from diseases which can lead to tachycardia, Akineton® should be used with caution.

If marked dryness of the mouth occurs, this can be improved by frequently drinking small amounts of liquid or by chewing sugar-free chewing gum.

Precautions in specific patient groups
In **older patients,** in particular those with cerebro-organic symptoms, careful dosing is necessary. Older patients, especially those with organo-cerebral changes of a vascular or degenerative nature, frequently show an increased sensitivity towards therapeutic doses of the active substance.

Experience with Biperiden in **children and adolescents up to 18 years of age** is limited and extends primarily to the use for a limited period of time in cases of drug-induced dystonia (e.g. due to neuroleptics or metoclopramide and analogous compounds), which can arise as side-effects or symptoms of an intoxication.

Patients during **pregnancy and lactation period** see section 4.6.
Impaired memory may arise while taking Biperiden (see also section 4.8 Side-effects).

Special remarks:
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Reports of misuse and dependency upon taking Biperiden have been reported in isolated cases, due to occasionally observed mood-enhancing and euphoric effects.

Other than in the case of vital complications, abrupt discontinuation of the drug is to be avoided due to the danger of excessive counter-regulation.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other anti-cholinergic drugs, e.g. psycho-pharmaceuticals, antihistamines, anti-Parkinson drugs and spasmolytics, can lead to an increase in central and peripheral side-effects.
Taking quinidine concomitantly can lead to an enhancement of anti-cholinergic cardio-vascular effects (in particular to AV-conduction).
Levodopa and the concomitant administration of Akineton® can enhance dyskinesia. Generalised choreiform disturbances of movement have been observed with the concomitant use of Biperiden and Levodopa/Carbidopa preparations in patients with Parkinson's disease.
Tardive dyskinesia induced by neuoleptics may be enhanced by Akineton®. Occasionally, Parkinson symptoms in existing delayed dyskinesia may be so serious, that anti-cholinergic treatment becomes necessary.
An increase in the effects of alcohol under Akineton® may occur (avoid alcohol).
The effect of metoclopramide and compounds with similar effects on the gastro-intestinal tract is antagonised by anti-cholinergic drugs such as Akineton®.
Anti-cholinergics can increase the central-nervous side-effects of pethidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Akineton® should be administered during pregnancy only after a careful risk-benefit analysis, as no experience is available with its use in pregnancy.

Breastfeeding
Anti-cholinergic drugs can inhibit lactation. Due to the chemical structure of the active substance, it can be assumed that Biperiden passes into breast milk. For this reason, weaning is recommended.

Fertility
No data are available on the effects of Akineton® on fertility.

4.7 Effects on ability to drive and use machines

Due to central nervous and peripheral side-effects, such as e.g. tiredness, dizziness and drowsiness, even when used correctly this drug can also change the ability to react to such an extent that – independent of the limitation due to the underlying disease to be treated – the ability to actively participate in road traffic or operate electrically or motor-driven tools and machines is further impaired. This is particularly true with the concomitant use of other centrally active drugs, anticholingeric drugs and especially in connection with alcohol.

4.8 Undesirable effects

4.8.a Summary of the safety profile

Side-effects may occur particularly at the beginning of treatment and if the dosage is increased too quickly.
Central excitation effects are frequently seen in patients with symptoms of a cerebral deficiency and can necessitate a decrease in the dosage.

4.8.b Structured list of adverse reactions

The following frequencies are used as the basis in the evaluation of side-effects:

Very common	($\geq$ 1/10)
Common	($\geq$ 1/100 to < 1/10)
Uncommon	($\geq$ 1/1,000 to < 1/100)
Rare	($\geq$ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

Infections and infestations
Not known: Parotitis.

Immune system disorders
Very rare: Hypersensitivity.

Psychiatric disorders
Rare: In higher doses excitement, agitation, fear, confusion, delirious syndromes, hallucinations, sleeplessness.
Very rare: Nervousness, euphoria.

Nervous system disorders
Rare: Fatigue, dizziness and disturbance of memory.
Very rare: Headache, dyskinesia, ataxia and speaking disorder, increased disposition to cerebral seizures and convulsions.

Eye disorders
Very rare: Disturbance of accommodation, mydriasis, photosensitivity. Closed-angle glaucoma might occur (controlling of intraocular pressure).

Cardiac disorders
Rare: Tachycardia.
Very rare: Bradycardia.

Gastrointestinal disorders
Rare: Dryness of mouth, nausea, gastric disorder.
Very rare: Constipation

Skin and subcutaneous tissue disorders
Very rare: Reduced perspiration, allergic rash.

Musculoskeletal and connective tissue disorders
Rare: Muscle twitching.

Renal and urinary disorders
Very rare: Voiding disorders, especially in patients with prostate adenoma (dose reduction), more seldom: urinary retention.

General disorders and administration site conditions
Rare: Drowsiness.

4.8.c Description of selected adverse reactions

There have been reports of temporarily reduced REM sleep (sleeping phase with rapid eye movements), characterised by an increase in the time needed to reach this stage and a percentage decrease in the length of this phase in the total sleep.

4.8.d Paediatric population

The safety profile in the Paediatric population is similar to that in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose
Symptoms of an intoxication resemble in principle that of atropine poisoning with peripheral anti-cholinergic symptoms (wide, slow-reacting pupils; dryness of the membranes; redness of the face; increased cardiac rate; intestinal and bladder atony; raised temperature) and central nervous disturbances (such as excitation, delirium, confusion, clouding of consciousness and/or hallucinations). In severe intoxications, there is a risk of circulatory collapse and central respiratory paralysis.

Therapeutic measures in overdose
Acetylcholinesterase inhibitors, particularly physostigmine, which can pass into the cerebrospinal fluid, are recommended as antidotes, which can also influence centrally triggered symptoms (and/or physostigmine salicylate, in case of a positive physostigmine test). If necessary, support of the

cardiovascular and respiratory functions (artificial respiration with oxygen), heat dissipation in case of febrile temperatures and the application of a bladder catheter should be used, depending on the type of symptoms.
Furthermore, gastric lavage or measures which reduce the absorption from the gastro-intestinal tract may be undertaken, if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-parkinson drugs, anticholinergic agents, biperiden,
ATC code: N04AA02.

Biperiden is a predominantly centrally acting anti-cholinergic. It has a peripheral effect, which is low in comparison to atropine. Biperiden binds competitively to peripheral and central muscarinic receptors (primarily M_1).
In animal experiments, Biperiden influences parkinson-like conditions (tremor, rigor), which are caused by centrally acting cholinergics.
Akineton® thus influences conditions, which are accompanied by cholinergic hyperactivity in the CNS: for example, Parkinson's syndrome as extra-pyramidal dopamine deficiency syndrome as a consequence of neuronal degeneration, as well as other symptoms triggered by neuroleptics, which can likewise be attributed to a disturbance of dopaminergic neurotransmission in the basal ganglia. The balance of dopaminergic and cholinergic functions is thereby impaired. The relative cholinergic over-activity can be therapeutically suppressed by anti-cholinergic drugs, such as Akineton®.

5.2 Pharmacokinetic properties

Absorption
Biperiden hydrochloride is quickly absorbed after 4 mg are taken orally with a lag-time of 27min. The maximum plasma concentration of 4-7 ng/ml is attained after 1-2 h.

Bioavailability
The bioavailability of orally administered Biperiden Hydrochloride is about 30%.

Distribution
The plasma protein binding of Biperiden amounts to about 95%. An apparent distribution volume of 24 ± 4.1 l/kg was determined for Biperiden. Biperiden is easily accessible to the tissue with a half-life time of tissue distribution of 0.6 h and a ratio of the total distribution volume to central distribution volume of 9.6.
Details on the placenta passage of Biperiden are not available.

Biotransformation
Biperiden is virtually fully metabolised - unchanged Biperiden has not been detected in the urine. The main metabolite of Biperiden occurs by hydroxylation at the bicycloheptane ring (60%), in addition an additional hydroxylation at the piperidine ring (40%) partially takes place.
The numerous metabolites (as hydroxylation products and their conjugates) are eliminated 50:50 via the urine and faeces, respectively.

Elimination
The terminal plasma elimination half-life after single oral administration of Biperiden Hydrochloride in young, healthy volunteers is 11-24 h, the plasma clearance is about 146 l/kg. At steady-state, a plasma elimination half-life of 25 ± 9 h was measured.

Older patients:

Bioavailability
As liver weight, blood flow and liver enzyme activity can decrease with age, a lower metabolisation rate of Biperiden in the liver can be assumed in older patients and thus an increased bioavailability and lower elimination rate in comparison to younger patients. In a comparative study, older patients showed 3-5-fold higher AUC values and 2-fold longer elimination half-lives than younger volunteers.

Elimination
A terminal elimination half-life of 30 ± 6 h was determined after single oral administration in older patients. The elimination half-life time at a steady-state was 39 ± 12 h.

Pharmacokinetic data for patients with impaired liver and renal function are unknown.

5.3 Preclinical safety data

Chronic toxicity
Investigations on the chronic toxicity in rats and dogs gave no indication of organ toxicity.

Mutagenic and tumourigenic potential
In-vivo and in-vitro investigations with Biperiden gave no indication for a mutagenic or clastogenic effect. Long-term studies in animals regarding the tumourigenic potential of Biperiden are not available.

Reproduction toxicity
Biperiden has been insufficiently tested for its reproduction toxicological characteristics in animals. No investigations are available on the effects on fertility, foetal and postnatal development. Embryo toxicity studies have given no indications of a teratogenic potential or other embryotoxic characteristics in the therapeutic dosage range.

No experience is available in humans on the safety of application during pregnancy and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate, copovidone, purified water, potato starch, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

This drug should no longer be used after the expiry date.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Al-blister pack with 30, 50, 60, 100 and 200 (5x40) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation:>
<Date of latest renewal:>

[To be completed nationally**]**

10. DATE OF REVISION OF THE TEXT

[To be completed nationally**]**