SUMMARY OF PRODUCT CHARACTERISTICS

Akineton® 4 mg

1. NAME OF THE MEDICINAL PRODUCT

Akineton® 4 mg - prolonged release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Biperiden Hydrochloride.
1 prolonged release tablet contains 4 mg Biperiden Hydrochloride equivalent to 3.6 mg Biperiden.

Excipient with known effect: Lactose monohydrate 252 mg and sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellowish, oblong prolonged release tablet scored on both sides.
The score line is not intended for breaking the prolonged release tablets.

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
Treatment with Akineton® is carried out incrementally as a rule. For this purpose, other
pharmaceutical forms are available. Before changing to the prolonged release tablets, the most
favourable dose must first be determined individually with Akineton® 2 mg fast release tablets,
depending upon the therapeutic effect and side-effects, respectively.

During the changeover, it should be remembered that 1 prolonged release tablet Akineton® 4 mg
contains twice the amount of active substance as 1 tablet Akineton® 2 mg.
When administering the prolonged release tablets, a lower dose than that established with Akineton®
2 mg tablets may possibly be sufficient. This is to be determined individually, according to the
therapeutic effect achieved and the respective side-effects.

Patients who e.g. previously received between ½ tablet Akineton® 2 mg 3 times daily and 1 tablet 2
times daily will now take 1 prolonged release tablet Akineton® 4 mg per day. Those who needed 1-2
tables Akineton® 2 mg 3 times daily will now receive 1-2 prolonged release tablets Akineton® 4 mg
per day.
It should be remembered that the change of dosage to the required amount of active substance when administering the prolonged release tablets should not be carried out abruptly, but most appropriately over a period of 10-20 days.

**Change of dosage from Akineton® 2 mg tablets to Akineton® 4 mg prolonged release tablets**

<table>
<thead>
<tr>
<th>Dosage Akineton® 2 mg tablets:</th>
<th>Change over to Akineton® 4 mg prolonged release tablets:</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ tablet 3x daily (equivalent to 3 mg Biperiden Hydrochloride)</td>
<td>1 prolonged release tablet 1x daily (equivalent to 4 mg Biperiden Hydrochloride)</td>
</tr>
<tr>
<td>1 tablet 2–3 x daily (equivalent to 4-6 mg Biperiden Hydrochloride)</td>
<td>1 prolonged release tablet 1x daily (equivalent to 4 mg Biperiden Hydrochloride)</td>
</tr>
<tr>
<td>2 tablets 2–3 x daily (equivalent to 8-12 mg Biperiden Hydrochloride)</td>
<td>2 prolonged release tablets daily (equivalent to 8 mg Biperiden Hydrochloride)</td>
</tr>
</tbody>
</table>

Akineton® 2 mg tablets and Akineton® 5mg ampoules are also available for treatment.

**Adults**

**Parkinson syndrome**

The average daily dose amounts to 1–2 prolonged release tablets Akineton® 4 mg (corresponding to 4–8 mg Biperiden Hydrochloride). Experience has shown that the total daily dose can be increased to a maximum of 3 prolonged release tablets Akineton® 4 mg (corresponding to 12 mg Biperiden Hydrochloride), if necessary.

**Drug-related extrapyramidal symptoms:**

For the treatment of drug-related extrapyramidal symptoms, 1 prolonged release tablet Akineton® 4 mg is administered daily concomitantly with the neuroleptic (corresponding to 4 mg Biperiden Hydrochloride). The required dosage can vary from 2 mg up to 6 mg Biperiden Hydrochloride per day, depending on the severity of symptoms. For cases in which a respectively lower or higher daily dosage than 4 mg Biperiden Hydrochloride is necessary, Akineton® 2 mg tablets are available.

**Children and adolescents (up to 18 years)**

The treatment of children and adolescents (up to 18 years) is not recommended since the experience with patients of this age group is limited and mainly related to short-time treatment in drug-induced dystonia (e.g. induced by neuroleptics or metoclopramide and analogous (see section 4.4).

**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**

Use in patients with impaired liver or renal function is not recommended, as no pharmacokinetic data is available.

**Remarks**

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

**Method of administration**

For an indicated dosage of one prolonged release tablet per day, this should be taken in the morning. If a dosage of two prolonged release tablets daily is indicated, it should be established on an individual basis whether the administration of
Akineton® 4 mg

a) One prolonged release tablet in the morning and one prolonged release tablet in the evening or
b) Two prolonged release tablets in the morning will lead to a better treatment result.

If in exceptional cases three prolonged release tablets have to be taken a day, a single dose of two tablets (corresponding to 8 mg Biperiden Hydrochloride) is not to be exceeded. The prolonged release tablets are to be taken without breaking, chewing and with a sufficient amount of liquid with or after meals. 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.

This medicine contains less than 1 mmol sodium (23 mg) per prolonged release tablet, that is to say essentially ‘sodium-free’

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 spasmyotics, 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 neuroleptics 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, anticholinergic 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 anticholinergic 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 M1).

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
After single oral administration of 4 mg Biperiden Hydrochloride (prolonged release tablets), the maximum plasma concentration of on average 1.1 (0.4-4.0) ng/ml is reached after an average 8 (2-24) h. After a seven day administration of 4 mg Biperiden Hydrochloride (prolonged release tablets) per day, the maximum plasma concentration of 1.2 (0.4-2.6) ng/ml is attained after an average 6 (4-12) 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 metabolism 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
Carnauba wax, docusate sodium, Yellow iron oxide (E 172), purified water, colloidal anhydrous silica, , hypromellose, hydroxypropylcellulose, lactose monohydrate, macrogol 400, macrogol 6000, Magnesium stearate, maize starch, microcrystalline cellulose, povidone (K-value 30), talc, titanium dioxide (E 171).

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/PVDC/Al-blistner pack with 30, 50, 60, 100 und 200 (5x40) prolonged release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER

Desma GmbH
Peter-Sander-Str. 41b
55252 Mainz-Kastel
Germany
Tel: +49 (0) 6134 21079 0
Fax: +49 (0) 6134 21079 24

8. MARKETING AUTHORISATION NUMBER

[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]