Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

DIBRO-BE mono

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 850 mg of potassium bromide. For excipients, see section 6.1.

3. PHARMCEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Generalised epilepsy of infancy with primary or secondary generalised tonic-clonic seizures and severe myoclonic syndromes of childhood. DIBRO-BE mono is indicated especially if other antiepileptic drugs are not or not sufficiently effective.

NOTE:

Due to its narrow therapeutic index it is recommended that only physicians experienced in treatment of epilepsy and use of bromide salts prescribe DIBRO-BE mono.

DIBRO-BE mono is not effective in the treatment of absences, myoclonic or tonic seizures; seizure provocation is possible in these cases.

For use in monotherapy experience regarding the efficacy of potassium bromide is insufficient.

4.2 Posology and method of administration

Posology

Treatment with DIBRO-BE mono can be started with the average maintenance dose. Further dose adjustments depend on the individual drug tolerance and the nature and severity of epilepsy.

Dose adjustments should be controlled for by serum concentration measurements. This is especially valid in patients with concomitant treatment with other antiepileptic drugs. In general, therapeutic serum concentrations of bromide should be in the range of 18.75 to 31.25 mmol/L (1.5 to 2.5 mg/ml) but not above 37.5 mmol/L (3.0 mg/ml) [x-ray-fluorescent analysis], or in the range of 12.5 to 21.75 mmol/L (1.0 to 1.75 mg/ml) but not above 25 mmol/L (2.0 mg/ml) [photometric analysis).

In individual patients the adequate dose of potassium bromide may differ considerably from the dose recommendations given in the table below (e.g. because of faster or slower substance elimination due to alterations in the sodium chloride balance).

Treatment is to be supervised by a physician experienced in epilepsy and treatment with bromide salts.

If a patient's medication is to be replaced by potassium bromide, the dose of the prior antiepileptic drug is to be reduced step by step, if possible under the conditions of hospitalisation.

The following dosage scheme is recommended for the treatment of generalised tonic-clonic seizures:

	BW in kg	Daily maintenance dose		Number of DIBRO-BE mono tablets, to be divided into 2-3 single doses**
		in mg/kg BW	in mg*	
Children				
[½ - 3 years]	7 - 15	50 - 70	350 - 1050	½ to 1½
[4 - 8 years]	16 - 28	40 - 60	640 - 1680	1 to 2
[9 - 15 years]	29 - 58	40 - 60	1160 - 3500	1½ to 4
Adults***		30 - 50	up to 4000	up to 4½

* Information on the daily dose given in mg are for orientation, only.
** Total dosage may be fitted to the calculated dose by alternated application of half tablets.
*** In case epilepsy is still present after the patient is grown up, application of DIBRO-BE mono may be continued in the adult patient.

NOTE:

During an infection children will be given only half dose to prevent substance culmulation and consecutive undesirable effects.

A maximum daily dose of 4000 mg must not be exceeded since side effects are likely to occur frequently in higher doses.

In case of potassium-free or -restricted diet:

1 tablet contains 278.6 mg of potassium.

Method of administration

DIBRO-BE mono tablets should be taken 2-3 times daily after the meals with a lot of fluid (approx. 100 to 150 ml). DIBRO-BE mono tablets are breakable. It is possible to degrade the tablets in lukewarm water or tea while gently stirring.

In principle, antiepileptic treatment is a long-term therapy. In an individual patient a physician experienced in epilepsy and bromide therapy should decide on initiation, duration and discontinuation of DIBRO-BE mono. In general, dose reductions and discontinuation of medication shall be considered after 2 to 3 years of treatment at the earliest. Withdrawal of the substance should follow a stepwise dose reduction.

Children may outgrow the initially calculated dose. The dosage should be adjusted in correspondence with the body weight development rather than according to age. In any case, EEG-recordings shall not worsen.

4.3 Contraindications

DIBRO-BE mono must not be given to patients with

- known bromide intolerance
- renal insufficiency.

DIBRO-BE mono should not be given in case of

- bronchial asthma
- hypoalimentation or nutrition disorders.

4.4 Special warnings and special precautions for use

Special warnings

Patients with potassium-restricted diets should take DIBRO-BE mono with care (see section 4.2 "POSOLOGY"). Due to its potassium content, hyperpotassemia with gastric complaints and diarrhea are possible.

Special precautions for use

Prior to initiation of DIBRO-BE mono, standard parameters of renal function have to be determined and electrolyte disturbances have to be excluded.

During treatment with DIBRO-BE mono sodium chloride intake should be normal and fluid consumption should be sufficient. In case of severe emesis, diarrhea or severe loss of fluid due to increased sweating, adverse effects of potassium bromide are more likely. In these cases it may be necessary to adjust the bromide dose.

During treatment with DIBRO-BE mono serum concentrations have to be determined in regular intervals: In the first 3 months of treatment at least every 4 weeks, afterwards every 3 months. In this context it has to be kept in mind that different methods of determination yield different results: Results of photometric determination are approximately 1/3 below the results of x-ray/fluorescent analysis.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacological interactions with other antiepileptic drugs do not occur. However, concomitant medication with other sedative substances may enhance cerebral impairment.

Any changes in the sodium chloride balance will influence the body bromide concentrations since the concentration product of chloride and bromide is being held constant by the kidneys. Application of sodium chloride or diuretics reduces the bromide half-life. Bromide excretion induced by diuretics is dependent on the renal chloride elimination. Osmotic diuretics, for instance, reduce the half-life of bromide to approximately 37 hours, concomitant application of ethacrynic acid can further reduce bromide half-life to approximately 1.7 hours.

4.6 Pregnancy and lactation

Administration of DIBRO-BE mono is contraindicated in pregnancy and lactation since potassium bromide passes the placenta barrier and is excreted in the milk. Adverse effects on the fetus, newborn child or infant cannot be excluded. Therefore, patients beyond menarche are to be instructed to use effective means of contraception.

4.7 Effects on ability to drive and use machines

Depending on the individual bromide sensitivity and serum concentration, DIBRO-BE mono may impair the reactivity in such a way that the ability to drive and use machines is negatively influenced. This is especially true in connection with alcohol.

4.8 Undesirable effects

Central nervous system

The desired and undesired effects of potassium bromide lead to deceleration of cerebral processes in which there is a large inter-individual variance of bromide sensitivity.

- Low bromide concentrations (below 1.0 mg/ml, photometric analysis): In rare cases tiredness, prolonged reaction times, less spontaneous speech, headache.
- Intermediate bromide concentrations (1.0 – 1.5 mg/ml, photometric analysis): Increasing signs of deceleration of reaction times, concentration, minute motor activity, speech and thinking. Tiredness, increasing need for sleep, and headache are more frequent.
- High bromide concentrations (up to 2.25 mg/ml, photometric analysis): Tiredness, disturbed concentration, deceleration and speech disturbance. Possibly insisting headache. Signs of intoxication (bromism) are possible.
- Bromide concentrations above 2.25 – 2.5 mg/ml (photometric analysis): Bromide intoxication, bromism (see section 2.9 “OVERDOSE”).

  NOTE:

  Even in case of adequate dose determination cumulation and signs of a chronic relative intoxication (bromism) can occur when intercurrent diseases induce fluid depletion.

Respiratory tract

- Potassium bromide increases the secretion of serous and mucous glands: Serous rhinitis, myxorrhea, bronchitis, sinusitis and exacerbation of bronchial asthma can occur. This is especially true in patients with allergic diathesis.

Gastrointestinal tract

- Due to the drug’s high osmolarity and potassium content large single doses can induce an unpleasant feeling of fullness, gastric pain and vomiting. These effects can be controlled for by taking the drug with a lot of fluid after the meals and splitting of the total daily dose into 2-3 portions given across the day.

- Rare: Coated tongue, bad breath, aphtha, obstipation or diarrhea.
- Very rare: Gastritis, ulcer (including perforation); pancreatitis.

  NOTE:

  In patients with intermediate or high bromide serum concentrations disturbed appetite can induce a subacutely progressing bromide intoxication due to reduced sodium chloride intake.

Skin and appendages

- Very common: Papulopustular skin alterations (bromide acne) in approximately 25% of the patients treated (partially independent of dose). Severe course may necessitate withdrawal of treatment.
- Rare: Bromoderma tuberosum (granulating, tumorous skin alteration) or halogen panniculitis (necrotizing inflammation of the subcutaneous adipose tissue, initially possibly picturing an erythema nodosum; perhaps in the course of a systemic bromide intolerance with fever, signs of inflammation, diarrhea) as cutaneous, probably bromide allergic phenomena. Withdrawal of DIBRO-BE mono results in fast clearing of symptoms, though scars (bromoderma tuberosum) may remain. Re-exposition results in reappearance of these symptoms of bromide intolerance.

Body as a whole

- Weight reduction, polydipsia
- A case of bromide induced hypothyroidism has been reported.

Musculoskeletal system

- Very rare: Bromide induced arthritis.

Special senses

- Conjunctivitis with lacrimation.

4.9 Overdose

In case of DIBRO-BE mono overdose signs and symptoms listed in section 4.8 “UNDESIRABLE EFFECTS” can occur in greater severity.

Acute overdose will usually lead to nausea and vomiting. In a single case, occurrence of epidermal necrolysis was reported.

Bromide serum concentrations above 2.0 – 2.5 mg/ml can result in bromism with disturbed vigilance reaching from somnolence to coma, cachexia and exsiccosis as well as diverse neurological disturbances such as missing or pathological reflexes, cloni, tremor, ataxia, sensory abnormalities, pareses, pupil abnormalities, slurred speech, brain edema with papillary stasis and high cerebrospinal pressure, delirium, aggressivity and psychosis.

A specific antidote is not known. Therapeutic measures in case of overdose aim towards faster elimination of bromide:

- Minor intoxication (oral feeding possible, vital signs unimpaired): Interruption of treatment with DIBRO-BE mono, sodium chloride rich diet, much fluid orally.
- Moderate intoxication (oral feeding impossible, vital signs impaired): Interruption of treatment with DIBRO-BE mono, intravenous infusions with isotonic sodium chloride, enteral tube feeding, monitoring.
- Severe intoxication (coma, psychosis): Forced diuresis under intensive care, in special cases hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Potassium bromide is bitter tasting salt easy soluble in water. Only the bromide part is responsible for the pharmacodynamic properties of the drug. In animal studies increasing bromide concentrations resulted in an elevation of the convulsion threshold. In high dosages it was not any longer possible to induce epileptic seizures by electric stimulation.

The exact mechanism by which bromide produces anticonvulsant effects is still unknown. Recent study results indicate that bromide stabilises nerve membrane excitability in a dose-dependent manner. Due to its smaller hydrated diameter bromide enters the nerve cell through chloride channels more easily than chloride and inhibits the spread of epileptic potentials by membrane hyperpolarisation. Findings suggest that bromide enhances GABA-activated currents and elicits a larger anion influx which is followed by the generation of a larger inhibitory postsynaptic potential. In further experiments with cultivated rat neurons bromide suppressed late recurrent discharges induced by low magnesium concentrations as a model of pharmacoresistant epilepsy.

5.2 Pharmacokinetic properties

Potassium bromide is rapidly and completely absorbed from the upper gastrointestinal tract. Maximum serum concentrations are reached after approximately 3 hours. Like chloride bromide is distributed into all body fluids. The concentration product of bromide and chloride is being held constant by the kidneys. Addition of one factor reduces the concentration of the other.

The absolute bioavailability of bromide after oral application of sodium bromide (30 mg bromide/kg BW) reached a mean of 96% (range: 75% to 118%) in a study with 7 subjects.

Bromides are not metabolised and thus are excreted unchanged. They do not undergo any protein or fat binding. Elimination is almost exclusively renal. Small amounts are excreted with sweat, tears and other body fluids. The daily excretion rate amounts to 5% of the total volume with a total body clearance of 26±1.7 ml/kg per day. Due to slow elimination and rapid and complete absorption bromides tend to accumulate. Human elimination half-life is approximately 12 days after oral administration. Adults reach steady state serum concentrations of bromide after 30-40 days on average, in children an unstable steady state can be achieved after 3 to 4 weeks.

With a daily bromide application of 5 g concentrations of 0.25 to 1 mmol/L are excreated in the milk.

5.3 Preclinical safety data

Acute toxicity

See section 4.9 “OVERDOSE”.

Chronic toxicity

A chronic toxicity study with diets containing 500 ppm potassium bromide for a period of up to 2 years did not show any treatment related findings in male and female Fischer (F344) rats. In another experiment alterations of the endocrine system were observed in rats after feeding sodium bromide in large quantities. The predominant finding was a suppressed function of the thyroid gland with reduced thyroxine concentrations in serum and in the thyroid gland. However, in a human pharmacodynamic study 4 mg of sodium bromide/kg BW daily for 12 weeks did not yield any alterations. Only after 9 mg/kg BW daily increases within the normal ranges of the serum concentrations of thyroxine and triiodothyronine were measured.

Mutagenic and oncogenic potential

Micronucleus assays in mice did not reveal any mutagenic potential of potassium bromide in doses up to 500 mg/kg BW. A carcinogenicity study with diets containing 500 ppm potassium bromide for a period of up to 2 years did not show any treatment related findings in male and female Fischer (F344) rats. On this basis a definite assessment of the mutagenic and oncogenic potential of bromide is not possible, though.

Reproduction toxicity

Potassium bromide crosses the placenta and is excreted in the milk. Results of animal studies and systematic observations in humans allowing a sufficient evaluation of the safety of potassium bromide in pregnancy and lactation are not available. In single cases, new-borns showed malformations and signs of bromism after their mothers had taken bromine-containing drugs or were exposed to bromine-containing chemicals in pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone, cellulose microcrystalline, povidone K 25, stearic palmitic acid, highly dispersed silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Protect from moisture

6.5 Nature and contents of container

One pack contains 60 tablets

6.6 Instructions for use and handling and disposal

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

7. MARKETING AUTHORISATION HOLDER

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