Summary of Product Characteristics/SmPC

1. NAME OF THE MEDICINAL PRODUCT

Kaliumbromid DESITIN 850 mg Tabletten
Active substance: potassium bromide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 850 mg of potassium bromide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White tablet with score line. The tablet can be divided into equal doses.

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 (e.g. Dravet Syndrome). Kaliumbromid DESITIN 850 mg Tabletten 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 Kaliumbromid DESITIN 850 mg Tabletten.

Kaliumbromid DESITIN 850 mg Tabletten is not effective in the treatment of absences, myo- clonic or tonic seizures; seizure provocation is possible in these cases.

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

4.2 Posology and method of administration

Posology

Treatment with Kaliumbromid DESITIN 850 mg Tabletten 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 recommended starting or maintenance dose (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 Kaliumbromid DESITIN 850 mg Tabletten, 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 tablets of Kaliumbromid DESITIN 850 mg Tabletten 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 Kaliumbromid DESITIN 850 mg Tabletten may be continued in the adult patient.

NOTES: During an infection children will be given only half of the usually administered dose to prevent substance accumulation and consecutive undesirable effects.

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

Method of administration

Tablets of Kaliumbromid DESITIN 850 mg Tabletten should be taken 2-3 times daily after the meals with a lot of fluid (approx. 100 to 150 ml). Kaliumbromid DESITIN 850 mg Tabletten tablets are divisible. 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 Kaliumbromid DESITIN 850 mg Tabletten. 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 dose based on body weight. 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

Kaliumbromid DESITIN 850 mg Tabletten must not be given to patients with

- Hypersensitivity to potassium bromide or to any of the excipients listed in section 6.1,
- known bromide intolerance,
- renal insufficiency.

Use in pregnancy and lactation is contraindicated (see section 4.6 “Pregnancy and lactation”)

Kaliumbromid DESITIN 850 mg Tabletten should not be given in case of
- bronchial asthma
- hypoalimentation or nutrition disorders.

4.4 Special warnings and precautions for use

Patients with potassium-restricted diets should take this medicinal product with care (see section 4.2 “Posology and method of administration”). Due to its potassium bromide content, hyperpotassemia with gastric complaints and diarrhea are possible.

Suicidal ideation and behaviour have been reported in patients treated with anti- epileptic agents in several indications. A meta-analysis of randomised placebo- controlled trials of antiepiletic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Kaliumbromid DESITIN 850 mg Tabletten.
Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Prior to initiation of Kaliumbromid DESITIN 850 mg Tabletten, standard parameters of renal function have to be determined and electrolyte disturbances have to be excluded.

During treatment with Kaliumbromid DESITIN 850 mg Tabletten 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, the treating physician may have to adjust the dose.

During treatment with Kaliumbromid DESITIN 850 mg Tabletten 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.

The use of potassium bromide may cause falsely high values in the laboratory diagnostic determination of serum chloride concentration (pseudohyperchloremia).

1 tablet contains 7.13 mmol (278.6 mg) of potassium. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

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 Fertility, pregnancy and lactation

Administration of Kaliumbromid DESITIN 850 mg Tabletten 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, even when administered correctly, Kaliumbromid DESITIN 850 mg Tabletten 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

Adverse reactions frequency is defined using the following convention:

Very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1 000 to < 1/100)
rare (≥ 1/10 000 to < 1/1 000)
very rare (< 1/10 000)
not known (cannot be estimated from the available data).

Nervous system disorders

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 4.9 “Overdose”).

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

Eye disorders
Conjunctivitis with lacrimation.

Respiratory , thoracic and mediastinal disorders
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 disorders
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 subcutaneous tissue disorders
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 Kaliumbromid DESITIN 850 mg Tabletten results in fast clearing of symptoms, though scars (bromoderma tuberosum) may remain. Re-exposition results in reappearance of these symptoms of bromide intolerance.

Musculoskeletal and connective tissue disorders
Very rare: Bromide induced arthritis.

General disorders and administration site conditions
Weight reduction, polydipsia
A case of bromide induced hypothyroidism has been reported.

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 to the *Bundesinstitut für Arzneimittel und Medizinprodukte* (Federal Institute for Drugs and Medical Devices), *Abt. Pharmakovigilanz* (Department of Pharmacovigilance), Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

Symptoms of overdose
In case of Kaliumbromid DESITIN 850 mg Tabletten 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 oedema with papillary stasis and high cerebrospinal pressure, delirium, aggression and psychosis.

Treatment of overdose
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 Kaliumbromid DESITIN 850 mg Tabletten, sodium chloride rich diet, much fluid orally.
- Moderate intoxication (oral feeding impossible, vital signs impaired): Interruption of treatment with Kaliumbromid DESITIN 850 mg Tabletten, 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

Pharmacotherapeutic group: Other antiepileptics

ATC code: N03AX21

Potassium bromide is a bitter tasting salt easy soluble in water. Only the bromide part is responsible for the pharmacologic 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 hydrate shell bromide, which is more lipophilic than chloride, 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 in-vitro 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 the related halogen 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 ions after oral application of sodium bromide (30 mg bromide/kg BW), which is comparable in this respect, 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 endocrine 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 carcinogenic 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 carcinogenic 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, newborns 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 acid (Ph.Eur.), highly dispersed silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Do not exceed the expiry date stated on the package.

6.4 Special precautions for storage

Store in the original package to protect from moisture.
Do not store above 25°C.

6.5 Nature and contents of container

Packs with 30 and 60 tablets in PVC/PVDC-aluminium foil blisters. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

DESITIN Arzneimittel GmbH
Weg beim Jäger 214, 22335 Hamburg
Telefon: (040) 5 91 01 525
Telefax: (040) 5 91 01 377

8. MARKETING AUTHORISATION NUMBER

Zul.-Nr.: 2201990.00.00

9. DATE OF RENEWAL OF THE AUTHORISATION /RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07. January 2019
Date of latest renewal: 22.05.2023

10. DATE OF REVISION OF THE TEXT

April 2024

11. LEGAL STATUS

Medicinal product subject to medical prescription