Dimaval® (DMPS) 100 mg Hartkapseln

1. NAME OF THE MEDICINAL PRODUCT

Dimaval (DMPS) 100 mg Hartkapseln

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 hard capsule contains 108.56 mg (RS)-2,3-bis(sulfanyl)propane-1-sulfonic acid, sodium salt 1 H_2O corresponding to 100 mg DMPS sodium salt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
Transparent hard capsule, 17.7 – 18.3 mm in length with white substance

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Clinically manifest, chronic and acute poisoning with mercury (inorganic and organic compounds, vapour and metallic mercury)
- Chronic poisoning with lead.

4.2 Posology and method of administration

Posology
The dosage depends basically on the type and severity of poisoning.

Adults receive for treatment of

- *acute poisoning*
  Initially a daily dose of 12 to 24 hard capsules Dimaval (DMPS) 100 mg Hartkapseln in single doses administered evenly over the day (e.g. 12 x 1 to 2 hard capsules per day).
- *chronic poisoning*
  3 to 4 hard capsules Dimaval (DMPS) 100 mg Hartkapseln daily. In severe chronic poisoning, the daily dose may be increased. The daily dose should be taken as individual doses of 1 to 2 capsules spread evenly throughout the day.

Method of administration
For oral use.
The capsules should be taken at least 1 hour prior to meals with liquid.

Duration of treatment
The duration of treatment depends on the clinical and laboratory findings (heavy metal excretion in the urine).

4.3 Contraindications

Hypersensitivity to the active substance, its salts or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In case of allergic reactions to DMPS therapy must be aborted. Otherwise a Stevens-Johnson's syndrome may occur.

Administration of Dimaval (DMPS) 100 mg Hartkapseln does not exclude the use of other measures for the treatment of poisoning (such as gastric lavage, dialysis, plasma exchange, etc.).

Monitoring of the urinary excretion of the toxic metal and of essential trace elements should be carried out regularly during long-term therapy.

4.5 Interactions with other medicinal products and other forms of interaction

Dimaval (DMPS) 100 mg Hartkapseln should not be taken simultaneously with mineral preparations. A possible DMPS-mineral chelate formation can lead to loss of effectivity of DMPS already in the intestines. For the same reason DMPS should be taken at least 1 hour prior to meals.

The simultaneous administration of charcoal and Dimaval (DMPS) 100 mg Hartkapseln should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy
DMPS did not show any teratogenic effects in animal experiments. Although adequate experience is not yet available in humans, pregnant women must not be generally excluded from DMPS therapy. The risk of poisoning and the risk of drug treatment should be carefully considered. In the case of treatment of pregnant women with DMPS, the mineral balance, especially of zinc, should be carefully monitored. It is known that zinc deficiency caused by chelating agents can have a teratogenic effect.

Breast-feeding
Heavy metal contaminated mothers should not breast feed in general.

Fertility
No data are available on the effect of Dimaval (DMPS) 100 mg Hartkapseln on male and female fertility.

4.7 Effects on ability to drive and use machines

No studies were performed investigating the effects on the ability to drive and to use heavy machinery.

4.8 Undesirable effects

The following frequency details are used as a base for the assessment of the side effects:

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)

Blood and lymphatic system disorders
Rare: Leukopenia

Immune system disorders
Uncommon: Shivering, fever or skin reactions, presumably of an allergic nature, such as itching or rash (exanthema, rash) which are generally reversible on withdrawal of the treatment.

Very rare: Severe allergic skin reactions (e.g. erythema exsudativum multiforme, Stevens-Johnson's syndrome)

Metabolism and nutrition disorders
Not known: Especially long-term use of Dimaval (DMPS) 100 mg Hartkapseln can influence the mineral balance, especially the elements zinc and copper.

Gastrointestinal disorders
Rare: Nausea

Hepatobiliary disorders
Very rare: Increased levels of transaminases

Renal und urinary disorders
Administration of DMPS causes mobilisation of mercury taken up in the body.
Very rare: as a result renal failure as clinical symptom of mercury poisoning

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 Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, Website: www.bfarm.de.

4.9 Overdose

Symptoms of overdose
Overdose after oral administration has not been observed yet. After intravenous administration symptoms such as drop in blood pressure, weakness or nausea may occur after overdose because of cardiovascular effects of DMPS.

Therapy of overdose
DMPS can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	Antidote for treatment of heavy metal intoxication
ATC-Code:	V03AB43 DMPS

Mechanism of action
(RS)-2,3-bis(sulfanyl)propane-1-sulfonic acid which is present in Dimaval (DMPS) 100 mg Hartkapseln as the sodium salt is a chelating agent from the group of vicinal dithiols. It forms stable complexes via the two neighbouring SH groups with various heavy metals and these are excreted predominantly via the kidneys in the urine. In this way, DMPS promotes the excretion especially of the heavy metals present in the extracellular space outside of the body cells, predominantly via the kidneys. DMPS and its heavy metal complexes are also dialysable.

The toxicity of heavy metals is, however, already reduced by complex formation because the heavy metals can no longer block the SH groups of vital enzymes.

There are indications that DMPS is also suitable for increasing heavy metal elimination in poisoning with
- arsenic (except for poisoning with arsine),
- copper,
- antimony,
- chromium,
- cobalt.

Pharmacodynamic effects
As a chelating agent DMPS can influence the balance of various essential minerals. Increased excretion in the urine has been observed especially for zinc and copper. In animal experiments, however, a reduction of the concentration in the plasma and organs could only be produced on long-term treatment at high doses. Normally, the trace elements present in the food are sufficient to compensate for increased excretion.

5.2 Pharmacokinetic properties

Distribution
After intravenous injection, DMPS achieves its highest dosage in the plasma and in the kidneys. Higher concentrations are also measured in the skin. In the other organs, especially the brain, there were only small quantities. Protein binding is about 90 %. Because of the rapid clearance, however, protein binding must only be very loose.

Elimination
In humans, about 50 % of the orally administered DMPS is detected in the urine. The highest DMPS concentration in the urine is achieved 2-3 h after oral administration.
DMPS is been eliminated relatively rapidly. Elimination takes place to about 90 % via the kidneys. After 24 hours, about 80 % of the administered dose is excreted (dog, monkey). The concentration decreases rapidly in both the plasma and the organs. Accumulation of the active ingredient after repeated administration does not take place.

Further information
Pharmacokinetic parameters were determined in five subjects following the i.v. injection of 3 mg/kg of body weight:

		Blood	Plasma
AUC	(µg · h)/ml	55.20 ± 5.46	122.54 ± 27.53
Cmax	µg/ml	17.70 ± 2.79	28.42 ± 2.17
$t_{½}\alpha$	h	1.03 ± 0.49	1.06 ± 0.23
$t_{½}ß$	h	15.99 ± 2.92	27.31 ± 8.99
Clearance	ml/min	67.38 ± 11.63	30.84 ± 5.26

Mean values and standard deviations

5.3 Preclinical safety data

Acute toxicity
The LD_{50} depends on the species and varies between 150 mg/kg BW (dog, cats, s.c.) and 2 000 mg/kg BW (mouse, s.c.). After administration of lethal doses, the animals died generally within one day of administration. Surviving animals recovered relatively quickly from the symptoms of poisoning.

At high doses i.v. DMPS exhibits cardiovascular effects. Studies in dogs showed a marked drop in blood pressure after injection of 15 mg to 150 mg/kg BW, which was reversible. At very high doses (300 mg/kg BW) the hypotensive effect was irreversible.

Subchronic toxicity
In animal experiments, there were no indications of heavy metal accumulation in the brain after administration of DMPS. Signs of kidney-damaging effects were not found. Investigations on the influence on the general behaviour did not show any persistent changes. The immune response was not modified. The i.v. administration of 30 mg DMPS (Na)/kg BW did not affect the rats' cardiovascular or respiratory functions.

Multiple i.v. or i.m. administrations did not lead to any visible reactions at the injection site. Local reactions occurred after paravenous or intra-arterial injections.

Chronic toxicity
Investigations on chronic toxicity of DMPS were carried out in rats and dogs. With the exception of lower serum levels of copper, neither histological changes in organs and tissues nor changes in the biochemical and histological parameters investigated were found even on daily intravenous administration of 15 mg DMPS/kg BW for 6 months in dogs.

Mutagenic and carcinogenic potential
DMPS at a dose of 0.004 - 2.5 µmol did not show any increase of mutation rate in the Ames test.

Reproductive toxicity
Investigations on the teratogenicity in rats and mice did not provide any evidence of changes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone, hypromellose, maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25 °C.

Keep the blister in the outer carton in order to protect from moisture.

6.5 Nature and contents of container

Original pack with 3 hard capsules in PVC/PVDC/aluminium blister
Original pack with 9 hard capsules in PVC/PVDC/aluminium blisters
Original pack with 20 hard capsules in PVC/PVDC/aluminium blisters

6.6 Special precautions for disposal of the product

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

6813507.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 October 1996
Date of latest renewal: 11 June 2008

10. DATE OF REVISION OF THE TEXT

December 2016

11. PRESCRIPTION STATE

By prescription only