Dimaval®

1. NAME OF THE MEDICINAL PRODUCT

Dimaval 250 mg DMPS-Na/5 ml Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule of 5 ml injection solution contains:
271.4 mg (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt 1 H_2O (DMPS sodium salt 1 H_2O) corresponding to 250 mg (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt (DMPS-Na)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute mercury poisoning (metallic, vapour, inorganic or organic compounds), if oral application or treatment by means of a gastric tube are not possible.

4.2 Posology and method of administration

Posology
The dose is always adjusted according to type and severity of poisoning.

Adults
Unless otherwise prescribed, the usual dose at acute poisoning is:

Day of treat-ment	Single dose		Dosing interval between single doses	Maximum daily dose	
	DMPS-Na	Number of ampoules		DMPS-Na	Number of ampoules
1	250 mg	1	3-4 hours	1 500-2 000 mg	6-8
2	250 mg	1	4-6 hours	1 000-1 500 mg	4-6
3	250 mg	1	6-8 hours	750-1 000 mg	3-4
4	250 mg	1	8-12 hours	500-750 mg	2-3

The content of one ampoule with 271.4 mg DMPS sodium salt monohydrate corresponds to 250 mg DMPS sodium salt (DMPS-Na).

Subsequent days: Depending on the clinical condition, the content of one ampoule of Dimaval should be administered once to three times daily (corresponding to 250 - 750 mg DMPS-Na per day). As an alternative, the patient may be switched to the oral pharmaceutical form of DMPS.

Method of administration
Intravenous or intramuscular application.
In the case of intravenous injection, Dimaval must be administered slowly, i.e. over a period of three to five minutes (see section 4.8).

The duration of treatment is dictated by the clinical and laboratory findings (heavy metal excretion in the urine).
However, the solution for injection should only be administered to patients who cannot take the oral pharmaceutical form.

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

If allergic reactions to DMPS appear the therapy must be aborted. Otherwise, the patients may develop a Stevens-Johnson syndrome.

Patients with renal insufficiency can only be treated with the drug if dialysis is performed concurrently.

A special caution is advisable at the application of the drug to patients with symptoms of allergic asthma.

Administration of Dimaval 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.

This medicinal product contains 27.4 mg sodium per ampoule, equivalent to 1.4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

The addition of other injection or infusion solutions may reduce the efficacy of the chelating agent. Consequently, the solution for injection must not be mixed with other solutions for injection or infusion. There were no reports on interactions when these substances are given separately.

If Dimaval and essential trace elements such as zinc and copper are applied concurrently, the pharmaceuticals may neutralize each other's efficacy. For this reason, it is advisable to perform any required substitution of trace elements at some later time.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt 1 H_2O in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Dimaval during pregnancy. However, if the application of Dimaval during pregnancy is necessary for vital reasons, the mineral balance, especially that of zinc and copper, must be monitored in order to ensure that the foetus is supplied with essential trace elements, for zinc deficiency caused by a chelating agent is known to be teratogenic.

Lactation
Heavy metal contaminated mothers should not breast feed in general.

Fertility
There are no data available on the effect of Dimaval on male and female fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use heavy machinery have been performed.

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)

Dependent on kind and severity of the illness, the necessary dosage and duration of the treatment -in individually different frequencies- the following undesirable effects can occur:

Blood and lymphatic system disorders
Very rare: white cell count reduced up to 50 %

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 (such as erythema exsudativum multiforme, Stevens-Johnson syndrome)
- asthma attack in asthma patients during or immediately after the injection

Metabolism and nutrition disorders
Very rare: unpleasant hydrogensulphide odour, dysgeusia, loss of appetite

Especially long-term use of Dimaval can influence the mineral balance, particularly the elements zinc and copper.

Cardiac disorders
Especially if Dimaval is injected too quickly, cardio-vascular reactions may occur, usually a short time after the injection (5 - 10 minutes). They become manifest as a drop in blood pressure, nausea, vertigo or weakness.

Respiratory, thoracic and mediastinal disorders
Very rare: stenocardia

Hepatobiliary disorders
Very rare: Increased levels of transaminases

Skin and subcutaneous tissue disorders
Uncommon: Skin reactions of an allergic nature

Renal and urinary disorders
Very rare Administration of DMPS causes mobilisation of mercury taken up in the body. In cases therefore, clinical symptoms of mercury poisoning may be triggered.

General disorders and administration site conditions
Very rare: pains in the injection area, abdominal complaints

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
Besides cardio-vascular reactions (see undesirable effects) overdosage of Dimaval may cause necroses in the injection place.

Treatment of overdose
DMPS can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmocotherapeutic group:	Antidote for treatment of mercury intoxication
ATC code:	V03AB43 DMPS

Mechanism of action
(RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid -previously known as (RS)-2,3-dimercapto-1-propanesulphonic acid (DMPS)-, which is contained in Dimaval in the form of a sodium salt, is a complexing agent from the group of vicinal dithiols. By means of the two adjacent SH-groups it forms stable complexes with various heavy metals. These are mainly excreted via the renal route with the urine. In this way DMPS stimulates especially the elimination of heavy metals from space outside body cells, i.e. extracelluar space. DMPS and its complexes with heavy metals are dialysable.

However, the toxicity of heavy metals is already reduced by complex formation, since heavy metals in the organism can no longer block the SH-groups in vital enzymes.

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
DMPS is 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 falls rapidly in both the plasma and organs. Accumulation of the active ingredient after repeated administration does not take place.

In rats with experimentally reduced kidney function higher plasma concentrations were found than in animals with normal kidney function. However, the concentration in the organs was nevertheless clearly lowered. Therefore, a secretion into the intestine and elimination with the faeces was assumed.

In patients with anuria DMPS can be removed by dialysis.

Further information
In 1991, pharmacokinetics was studied in five subjects following the i.v. injection of 3 mg per 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
$t_{½}\alpha$ **$t_{½}ß$**	h h	1.03 15.99	± 0.49 ± 2.92	1.06 27.31	± 0.23 ± 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.

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.

Mutagenicity / carcinogenicity
DMPS is examined for mutagenic properties insufficiently. DMPS at a dose of 0.004 - 2.5 µmol did not show any increase of mutation rate in the Ames test.

Reproductive toxicity
DMPS did not show any reference to reproduction toxicity in the animal experiments carried out. Studies to the teratogenicity at mice, rats and rabbits did not provide any references to changes.

Safety pharmacology
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 intraarterial injections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

The injection solution must not be mixed with other injection solutions.

The injection solution is sensitive to oxidants such as oxygen or iron(III) salts.

No essential heavy metals, for instance copper or zinc, may be added to the injection solution.

6.3 Shelf life

3 years

Opened ampoules must not be stored; their contents must not be used but discarded.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Packages with 1 ampoule containing 5 ml injection solution
Packages with 5 ampoules containing 5 ml injection solution each

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

25465.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 June1997
Date of latest renewal: 25 April 2003

10. DATE OF REVISION OF THE TEXT

April 2021

11. PRESCRIPTION STATE

By prescription only