1. NAME OF THE MEDICINAL PRODUCT

Dimaval®

Solution for injection

Active substance: (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt 1H2O

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 H2O (DMPS sodium salt) corresponding to 250 mg (RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid, sodium salt.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection solution for intravenous or intramuscular application.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Unless otherwise prescribed, the usual dose for adults with acute poisoning is:

1st day: The content of 1 ampoule of Dimaval every three to four hours (corresponding to 1.5 – 2.0 g DMPS-Na daily)

2nd day: The content of 1 ampoule of Dimaval every four to six hours (corresponding to 1.0 – 1.5 g DMPS-Na daily)

3rd day: The content of 1 ampoule of Dimaval every six to eight hours (corresponding to 0.75 – 1.0 g DMPS-Na daily)

4th day: The content of 1 ampoule of Dimaval every eight to twelve hours (corresponding to 0.5 – 0.75 g DMPS-Na daily)

Subsequent days: Depending on the clinical condition, the content of one ampoule of Dimaval should be administered once to three times (corresponding to 0.25 – 0.75 g DMPS-Na per day) daily. As an alternative, the patient may be switched to the oral dosage form of DMPS-Na.

The solution for injection may be administered by 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 undesirable effects).

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 pharmaceutical by mouth.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of Dimaval.

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.

4.4 Special warnings and precautions for use

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.

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

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 injection or infusion solutions.

There were no reports on interactions when these substances are given separately.

If Dimaval and essential heavy metals 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 Pregnancy and lactation

There are not sufficient empirical data available on the application of Dimaval to pregnant women. Animal trials have not revealed any toxicity for the fetus or a teratogenic potential.

In principle, the drug should not be administered to pregnant women. 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 fetus is supplied with essential trace elements, for zinc deficiency caused by a chelating agent is known to be teratogenic.

Heavy metal contaminated mothers should not breast feed in general.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines 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)

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:

Cardiac disorders

Unknown

Especially if the preparation is injected 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, weakness.

Blood and lymphatic system disorders
Very rare
White cell count reduced up to 50 %.

Renal and urinary disorders
Very rare
Administration of DMPS causes mobilisation of mercury taken up in the body. This may trigger renal failure as a clinical symptom of mercury poisoning in cases.

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

Respiratory, thoracic and mediastinal disorders
Very rare
Stenocardia.

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

Very rare
Dysgeusia, unpleasant hydrogen-sulphide odour, loss of appetite.

General disorders and administration site conditions
Very rare
Pains in the injection area, abdominal complaints.

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

Very rare
An asthma attack can appear in asthma patients during or immediately after the injection.

Hepatobiliary disorders
Very rare
Increased levels of transaminases.

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

Therapy of overdose
DMPS can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Antidote for treatment of mercury intoxication.
ATC code: V03AB43

(RS)-2,3-Bis(sulfanyl)propane-1-sulfonic acid - previously known as (RS)-2,3-dimercapto-1-propanesulfonic 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 the elimination of heavy metals from space outside body cells, i.e. extracellular 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.

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
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.

DMPS is relatively rapidly eliminated. 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.

In 1991, pharmacokinetics was studied in five subjects following the i.v. injection of 3 mg per kg of body weight:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Blood</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg · h) /ml</td>
<td>55.20 ± 5.46</td>
<td>122.54 ± 27.53</td>
</tr>
<tr>
<td>Cmax µg/ml</td>
<td>17.70 ± 7.79</td>
<td>28.42 ± 2.17</td>
</tr>
<tr>
<td>t1/2α h</td>
<td>1.03 ± 0.23</td>
<td>1.06 ± 0.99</td>
</tr>
<tr>
<td>t1/2β h</td>
<td>15.99 ± 2.92</td>
<td>27.31 ± 8.99</td>
</tr>
<tr>
<td>Clearance ml/min</td>
<td>67.36 ± 11.63</td>
<td>30.34 ± 5.26</td>
</tr>
</tbody>
</table>

Average values and standard deviations

5.3 Preclinical safety data
Acute toxicity
The LD50 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.

Genotoxicity, carcinogenic potential
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.
Toxicity to reproduction
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 intra-arterial 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
Opened ampoules must not be stored; their contents must not be used but be discarded.

The shelf life is three years.

This pharmaceutical should not be used after the expiry date that is printed on the label and on the box.

6.4 Special precautions for storage
Keep out of the reach and sight of children!

Do not store above 25 °C!

6.5 Nature and contents of container
1 ampoule of 5 ml injection solution
5 ampoules of 5 ml injection solution each

6.6 Special precautions for disposal
No special requirements.