Sulfadiazin-Heyl®

1. NAME OF THE MEDICINAL PRODUCT

Sulfadiazin-Heyl 500 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 500 mg sulfadiazine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, circular tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Toxoplasmosis (acute and recurrent form) in combination with pyrimethamine.

4.2 Posology and method of administration

Posology
Adults
Adults take 50 mg/kg body weight per day up to a maximum of 4.0 g (4 - 8 tablets) per day as the initial and maintenance dose.

Children over 2 months of age
Children over 2 months of age receive 50 -100 mg of sulfadiazine/kg body weight (max. 1.5 g per day). The initial dose for children over two months of age is ½ of the daily dose.

Method of administration
For oral use.
The total dosage is subdivided into 4 individual doses.

Tablets must be taken with sufficient liquid.

Care must be taken to ensure adequate fluid intake during treatment (in adults at least 1 200 ml urine excretion per day). If an adequate fluid intake cannot be achieved, then sodium hydrogen carbonate should be administered in order to reduce the risk of crystalluria.

4.3 Contraindications

- hypersensitivity to the active substance, sulfonamides or to any of the excipients listed in section 6.1.
- erythema exsudativum multiforme or DRESS-syndrome (also in the anamnesis),
- Stevens-Johnson syndrome or toxic epidermal necrolysis (also in the anamnesis),
- pathological changes in the haemogram with leukopenia and thrombopenia,
- congenital glucose-6-phosphate dehydrogenase deficiency of the erythrocytes,
- haemoglobin anomalies such as Hb Cologne and Hb Zurich,
- severe disorders of renal function (creatinine clearance less than 25 ml/min/1.73 m^2),
- severe liver damage or disorders of liver function (e.g. acute hepatitis),
- acute porphyria.

- during lactation in case of a premature baby.

4.4 Special warnings and precautions for use

Cases of life-threatening skin reaction (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported in association with the use of sulfadiazine. Patients should be informed about the signs and symptoms of these serious side-effects and closely monitored for the occurrence of skin reactions.

The risk of occurrence of SJS or TEN is highest in the first weeks of treatment. If signs or symptoms of SJS or TEN occur (e.g. a progressive skin rash, often with blisters or accompanied by mucosal lesions), treatment with Sulfadiazin-Heyl has to be stopped. The course of SJS and TEN is largely determined by early diagnosis and the immediate withdrawal of all suspicious drugs, i.e. early withdrawal improves the prognosis.
After occurrence of SJS or TEN in association with the use of sulfadiazine the patient must never again be treated with sulfadiazine.

The potentially life-threatening agranulocytosis manifests in a severe general feeling of being unwell, associated with fever, chills, palpitations, sore throat and swallowing problems as well as painful inflammations of the oral, nasal and pharyngeal mucosa and in the anal and genital area. In these cases therapy with Sulfadiazin-Heyl must be stopped **immediately**. When the symptoms have ceased Sulfadiazin-Heyl must not be re-used.
Immediate blood count checks must be carried out on the occurrence of sore throats, fever or flu-like symptoms during the therapy.

Special caution in the administration of Sulfadiazin-Heyl is necessary for patients with
- mild disorders of liver and renal function,
- disorders of the thyroid function,
- hypersensitivity to sulfonylurea antidiabetics and diuretics of the sulfonamide type.

Photosensitization may develop while taking sulfonamide-containing drugs. This should be considered with strong exposure to sun and UV light.

To avoid serious impairment of hematopoiesis, concurrent intake of folinic acid (in the form of calciumfolinat) is recommended during combination therapy of sulfadiazine and the folinic acid antagonist pyrimethamine.

Checks of urine and blood count should be carried out during therapy.

4.5 Interaction with other medicinal products and other forms of interaction

There are different types of interactions with other medicines. One possibility is the change of concentration of active substances due to competing reactions in plasma protein binding. This can lead to an increase of the effectiveness of other pharmacons (anticoagulants, oral antidiabetics of the sulfonylurea type, diphenylhydantoine, methotrexate, thiopental) or to an enhancement of the effectiveness of sulfonamides (probenecid, indometacin, phenylbutazone, salicylates, sulfinpyrazone).

Furthermore, a direct reaction with other active substances can take place. The sulfonamide will be absorbed to a lower extent at a simultaneous application of an antacid. The sulfonamide will be metabolized faster at application of paraldehyde. Together with hexamethylenetetramine (methenamine) there is a risk of a crystalluria. In combination with mandelic acid the risk of crystallisation is increased due to acidification of the urine.
Finally, the effectiveness of the sulfonamide can be changed due to competition reactions at the site of action. Antagonistic substances of similar structure (benzocaine, procaine, tetracaine) can reduce the effectiveness of the sulfonamide.

Amongst others, in vitro interactions are possible with: amiphenazole, chloramphenicol, chlorpromazine, gentamicin, hydralazine, insulin, kanamycin, lincomycin, methicillin, methyldopa, noradrenalin, procaine, prochlorperazine, promazine, promethazine, streptomycin, tetracyclines, vancomycin.

4.6 Fertility, pregnancy and lactation

Pregnancy
Sufficient experience about the use of Sulfadiazin-Heyl during pregnancy does not exist. Animal experimental studies have shown reproductive toxicity (see 5.3). Therefore, Sulfadiazin-Heyl shall not be used in the first trimester. Drugs with other active substances should be used for this period.

The administration of sulfonamides during pregnancy can increase the risk of a hyperbilirubinemia, particularly for premature infants. From the 2nd trimester a combination therapy with sulfadiazine, pyrimethamine and folinic acid may therefore be carried out only after a strict risk-benefit-assessment.

Breast-feeding
Sulfonamides pass into the mother's milk. Although several reports on undesirable effects of sulfonamides on infants exposed to their mother's milk exist, the amount taken in with the milk does not represent a particular risk for healthy babies very probably. On the other hand, newborn children with hyperbilirubinemia or glucose-6-phosphate-dehydrogenase deficiency of the erythrocytes should not be nursed during the medical treatment.

Sulfadiazin-Heyl is contraindicated for mothers of premature babies.

4.7 Effects on ability to drive and use machines

Very rarely, the intake of sulfadiazine leads to a transient myopia, so that the ability of the active participation in traffic or for operating heavy machinery could be influenced.

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
Very rare: blood count changes with thrombo- and leukocytopenia, agranulocytosis, eosinophilia, aplastic anaemia, acute haemolytic anaemia

Immune system disorders
Very rare: DRESS syndrome

Metabolism and nutrition disorders
Rare: folic acid deficiency with the symptoms anaemia and diarrhoea
Very rare: Hypoglycaemia

Eye disorders
Very rare: transient myopia

Gastrointestinal disorders
Uncommon: gastrointestinal symptoms such as nausea, vomiting, diarrhoea

Hepatobiliary disorders
Rare: cholestatic hepatosis
Very rare: focal or diffuse liver necrosis

Skin and subcutaneous tissue disorders
Uncommon: allergic reactions such as urticarial, erythematous, maculated and morbilliforme exanthemas, purpura, photo dermatosis, erythema nodosum, Lyell syndrome (epidermolysis acuta toxica), exfoliative dermatitis
Very rare: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4), petechial cutaneous haemorrhages,
cyanosis due to sulf- or methemoglobinaemia occurs at congenital glucose-6-phosphate-dehydrogenase deficiency of erythrocytes or at haemoglobin anomalies as Hb Cologne and Hb Zurich only

Renal and urinary disorders
Uncommon: crystalluria. Nephrolithiasis can lead to acute renal failure.
Very rare: interstitial nephritis

General disorders and administration site conditions
Uncommon: drug fever as well as headache and arthralgia

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 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
The symptoms of overdosage are crystalluria, oliguria, anuria, nausea, vomiting, diarrhoea, headaches and dizziness.

Treatment of overdose
Depending on the severity of the overdose the following measures have to be taken: Gastric lavage, acceleration of the renal excretion with a forced diuresis by increased fluid supply, haemodialysis, and administration of folic acid. In addition, blood count checks must be carried out.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bacteriostatic effective chemotherapeutic agent from the group of intermediately acting sulfonamides.
ATC code: J01EC02 Sulfadiazine

Mechanism of action
Sulfadiazine is a chemotherapeutic agent from the group of intermediately acting sulfonamides. The effect is bacteriostatic. The mechanism of action is based on the structural similarity of the sulfonamides to para-aminobenzoic acid and the thereby caused inhibition of the folic acid synthesis of the pathogens by a competitive blocking of the dihydropteroine acid synthetase.

Resistance data:
There are only a few studies on the resistance of toxoplasmosis. However, cases of therapy resistance are described. In current in-vitro experiments, most of the genotypically different strains

of Toxoplasma gondii responded to the application of sulfadiazine. Only 3 of the 17 types had an IC_{50} > 50 mg/l. There are, however, no references to mutations during the therapy which lead to a resistance or change of drug sensitivity.

5.2 Pharmacokinetic properties

Sulfadiazine is orally and parenterally applicable, sulfadiazine sodium only parenterally.

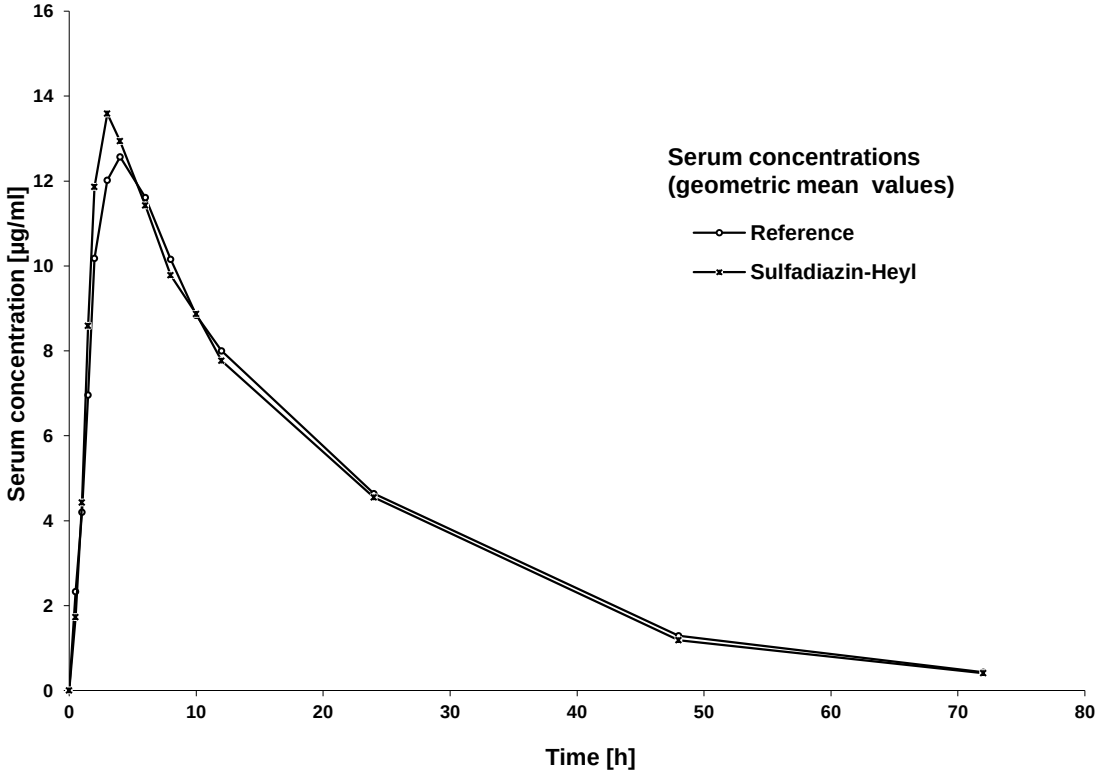
Absorption
After oral application sulfadiazine is resorbed quickly in the gastrointestinal tract.

Distribution
The plasma protein binding is approx. 55 % at a serum concentration of 100 µg/ml and normal plasma protein levels, margin of deviation is 20 - 55 %. Maximum blood levels are reached within 3 to 6 hours after an oral application. No data exist to the pharmacokinetics after intravenous and intramuscular application of sulfadiazine. The sulfadiazine concentrations in the liquor are about 50 % of the correspondent serum levels after an oral application.

Biotransformation/Elimination
The biological half-life varies between 8 and 16.8 hours. Sulfadiazine is metabolized in the liver by N-acetylation and glucuronidation. The acetylation degree is 15 %. The elimination is renally, mainly carried out via a glomerular filtration. At first quickly, then the excretion is more slowly carried out over a period of 2 - 3 days. 15 - 30 % of the substance are eliminated in the acetylated form. The renal clearance is 35 ml/minute. Alkalisation of the urine increases the solubility, since sulfonamides as weak acids are dissociating stronger in an alkaline medium. The substance is good dialysable as well at haemo- as at peritoneal dialysis.

Bioavailability
In 1996, a bioavailability study conducted with 16 subjects yielded in comparison with the reference preparation (stating the values as mean values):

	Reference	**Sulfadiazin-Heyl**
Maximum plasma concentration (C_{max}) [µg/ml]:	13.59	14.38
Time of maximum plasma concentration (t_{max}) [h]:	4.0	3.0
Area under the concentration/time curve $(AUC)_{\infty}$ [µg • h/ml]:	298.5	292.38



Mean plasma level curves compared to a reference preparation (suspension of the active pharmaceutical ingredient in water) in a concentration time diagram.

5.3 Preclinical safety data

Acute toxicity
The acute toxicity was checked on the mouse p.o., s.c. and i.p. and on the rat i.p. The LD_{50} was between 1.3 to 4 g/kg BW.

Subchronic toxicity
Examinations in different species of animals over 4 - 30 days showed moderate kidney toxicity. At very high doses it came to concrement formation, degeneration of the tubules, necroses and occasionally to directly inflammatory reactions in the kidney. In the mouse, very high blood level values led to a haemolytic anaemia.

Chronic toxicity
There are no examinations to the chronic toxicity (see section 4.8).

Mutagenic and tumor-generating potential
Sulfadiazine is not examined sufficiently regarding mutagenic effects. Previous tests did not suggest a mutagenic effect.
There are no long-term studies on a tumor-generating potential.

Reproductive toxicity
Sulfadiazine passes the placenta. On the due date, the concentration relationship in the maternal/foetal blood two to four hours after an oral application is at approx. 1.5.

The concentration in the maternal and foetal blood is the same approximately two hours after an intravenous application. The concentration in the amnion fluid corresponds to that in the maternal blood 6 to 8 hours after an intravenous application.

Results of animal experimental examinations: Among rats and rabbits, more cleft palates appeared after prenatal exposure of sulfadiazine/TMP.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium behenate; copovidone; crospovidone; maize starch; silica, colloidal anhydrous; talc

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 blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

Packages with 30 tablets in PVC/aluminium foil blisters
Packages with 100 tablets in PVC/aluminium foil blisters

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

6814197.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 1998
Date of latest renewal: 02 June 2008

10. DATE OF REVISION OF THE TEXT

December 2016

11. PRESCRIPTION STATE

By prescription only