Sulfasalazin-Heyl®

1. NAME OF THE MEDICINAL PRODUCT

Sulfasalazin-Heyl

500 mg enteric coated tablets

2. QUALTITATIVE AND QUANTITATIVE COMPOSITION

Active pharmaceutical ingredient: sulfasalazine

1 enteric coated tablet contains 500 mg sulfasalazine

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, satin finished, oval, enteric coated film tablet of 15.4 to 16 mm in length

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of active rheumatoid arthritis (chronic polyarthritis) in adults
- Treatment of active juvenile idiopathic oligoarthritis (enthesitis-associated arthritis) in children from the age of six, who responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs) and/ or locale glucocorticoid injections
- Treatment of active juvenile idiopathic polyarthritis and polyarthritic spondylarthritis in children from the age of six (enthesitis-associated arthritis), who responded inadequately to non-steroidal anti- inflammatory drugs (NSAIDs)

4.2 Posology and method of administration

Posology

Active rheumatoid arthritis
Unless otherwise prescribed by the physician, Sulfasalazin-Heyl should be administered daily, initially in low doses and then gradually increased to the optimum dosage.

week	1	2	3	4*)
morning	-	1 enteric coated film tablet (500 mg sulfasalazine)	1 enteric coated film tablet (500 mg sulfasalazine)	2 enteric coated film tablets (1 000 mg sulfasalazine)
evening	1 enteric coated film tablet (500 mg sulfasalazine)	1 enteric coated film tablet (500 mg sulfasalazine)	2 enteric coated film tablets (1 000 mg sulfasalazine)	2 enteric coated film tablets (1 000 mg sulfasalazine)

*) and every further week

In patients who do not respond satisfactorily to 2 x 2 enteric coated film tablets (2 x 1 000 mg sulfasalazine) daily after 3 months, the daily dosage can be increased to 3 x 2 enteric coated film tablets (3 x 1 000 mg sulfasalazine). A dosage over 4 000 mg sulfasalazine should not be excessed.

Active juvenile idiopathic arthritis (children, six years of age and older)
The daily dosage should be 50 mg/kg body weight, divided into 2 single doses. The daily maximum dose is 2 g sulfasalazine. If no satisfactory effect occurs after 3 months, the daily dosage can be increased to 75 mg/kg body weight, maximum 3 g sulfasalazine per day.

To reduce possible gastrointestinal incompatibilities an upgrading therapy is recommended (starting with a quarter or a third of the maintenance dose), obtaining the maintenance dose after 4 weeks by weekly progression of the dose.

Method of administration

The enteric coated film tablets should be taken at least 1 hour prior to a mealtime with sufficient fluid and should be swallowed unbrokenly.

Experience has shown that clinical efficacy starts within 1 to 3 months of treatment. Additional treatment with analgesics or anti-inflammatory drugs may be necessary.

Sulfasalazin-Heyl is generally administered for long-term therapy. If it proves to be effective and well tolerated, it can be taken for many years.

Special patient groups

Senior patients:
No change of dosage is required. Due to possible undesirable effects senior patients should be monitored very thoroughly.

Reduced kidney function:
There is no reduced dosage required for patients suffering from slight to moderate limitation of renal function. However, Sulfasalazin-Heyl should be administered with special caution to this group of patients. (Patients with high grade renal insufficiency see section 4.3)

Reduced liver function (see section 5.2):
There is no reduced dosage required for patients suffering from slight to moderate limitation of liver function. However, Sulfasalazin-Heyl should be administered with special caution to this group of patients. (Patients with high grade liver function disorder see section 4.3)

Children and adolescents (younger than 6 years):
Sulfasalazin-Heyl should not be administered to children younger than 6 years. For treatment of children and adolescents see also section 4.3.

4.3 Contraindications

Sulfasalazin-Heyl may not be used in the presence of:
- hypersensitivity to the active substance, its metabolites or to any of the excipients listed in section 6.1;
- hypersensitivity to sulphonamides or salicylates;
- diseases of the blood forming system;
- acute intermittent porphyria;
- high grade liver insufficiency;
- high grade renal insufficiency;
- patients with glucose-6-phosphate dehydrogenase deficiency (risk of occurrence of haemolytic anaemia);
- pre-existing alteration of the haemogram like leukopenia or thrombocytopenia;
- ileus;
- Erythema exsudativum multiforme (even in anamnesis)

Concurrent therapy with methenamine is contraindicated.

Sulfasalazin-Heyl is not appropriate for treatment of systemic forms of juvenile idiopathic arthritis (JIA).

Sulfasalazin-Heyl should not be given to children younger than 6 years.

4.4 Special warnings and precautions for use

Sulfasalazine should be administered under medical supervision exclusively.

Severe, myelosuppression-associated infections have been reported, including sepsis and pneumonia. Patients who develop a new infection during treatment with sulfasalazine should be closely monitored. Sulfasalazine should be discontinued if a patient develops a severe infection. Caution should be exercised when considering the use of sulfasalazine in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infection.

Cases of life-threatening skin reactions (Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported in relation with application of Sulfasalazin-Heyl. Patients should be informed about the signs and symptoms of these severe side effects and they should be monitored closely regarding 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), therapy with Sulfasalazin-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 sulfasalazine the patient must never again be treated with sulfasalazine.

Checks and laboratory diagnostics
Complete blood counts, including differential white cell count and liver function tests, should be performed before starting treatment with sulfasalazine and every second week during the first three months of therapy. During the second three months, the same tests should be done once monthly and thereafter once every three months, and as clinically indicated.
Assessments of renal function (including urinanalysis) should be carried out in all patients at treatment initiation and at least once monthly during the first three months of therapy. Thereafter, further monitoring should be done according to clinical needs. Symptoms such as sore throat, fever, pallor, purpura or jaundice may be indications of myelosuppression, hemolysis or hepatotoxicity during therapy with sulfasalazine. In these cases, sulfasalazine therapy should be discontinued until the results of the blood tests are available.

Immunoglobulins may decrease on therapy with Sulfasalazin-Heyl and an increase in antinuclear antibodies (ANA) may occur. These changes can be due to illness. Their importance for the therapy is unclear. As a precaution, check of immunoglobulins and ANA is recommended at the beginning of treatment and at regular intervals.

Severe hypersensitivity reactions may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome (i.e., pseudomononucleosis), hematological abnormalities (including hematophagic histiocytosis), and/or pneumonitis including eosinophilic infiltration.

Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking various drugs including sulfasalazine. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not apparently evident. If such signs or symptoms are present, the patient should be evaluated immediately. Sulfasalazine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Women of child-bearing age
Sulfasalazine may cause or reinforce a deficiency of folic acid. Undersupply of folic acid during pregnancy has been associated with occurrence of neural tube defects (anencephaly, spina bifida).There is evidence that administration of sulfasalazine during the three month period before pregnancy increases the risk for neural tube defects for the unborn child. For women of child-bearing age without effective contraceptive measures supplementation with folic acid is recommended during therapy with sulfasalazine (see sections 4.5, 4.6, 4.8).

Male fertility
In men, application of sulfasalazine may lead to oligospermia with reversible impaired fertility. Spermatogenesis generally normalises within 2-3 months of withdrawal. There are no cases of teratogenic effects on the basis of reversible impaired fertility. The reduction of the quantity of sperm cells does not affect sexual potency.

Paediatric population
Only specialists having adequate experience in diagnosis and treatment of the respective rheumatoid disease should initiate and monitor therapy with Sulfasalazin-Heyl in children.

Sulfasalazin-Heyl should be administered with precaution to
- patients tending to hypersensitivity reactions (allergic predisposition) or bronchial asthma;
- patients with slight liver or renal insufficiency or with identified hypersensitivity to sulfonyl urea.

Sufficient hydration must be supplied for all patients (even for the dazed ones).

In slow acetylators the sulfapyridine concentrations can reach toxic levels. Therefore, the determination of the acetylator phenotype is recommended during the initial treating stage with sulfasalazine, in the event of side effects it should always be performed. It is also helpful to establish the phenotype for cases in which several substances administered simultaneously need to be acetylated and the rheumatoid arthritis is combined with Sjögren's and/or other overlap syndromes. This is also helpful prior to beginning the therapy in high-risk patients (age, body weight, concomitant diseases).

4.5 Interaction with other medicinal products and other forms of interaction

The intake of sulfasalazine together with other medical products may lead to interactions caused by the active substance itself or by its main metabolites. Concurrent intake of antibiotics, iron and calcium, folic acid and medicinal products with strong protein binding results in the most clinically relevant pharmacokinetic interactions.

Folic acid
During therapy with sulfasalazine folic acid levels may decrease, presumably due to an inhibition of absorption. This can result in a deficiency of folic acid respectively enhance an existing deficiency caused by underlying illness or pregnancy (see sections 4.4, 4.6 and 4.8).

Iron
Sulfasalazine and iron form chelates. This results in reduced absorption of sulfasalazine, but not of its metabolite sulfapyridine.

Calcium
Under concurrent calcium gluconate therapy delayed absorption of sulfasalazine has been reported.

Digoxine
Inhibition of absorption of digoxine during intake of sulfasalazine was reported in isolated cases.

Antibiotics
Concurrent administration of antibiotics (demonstrated for ampicillin, neomycin, rifampicin and ethambutol) can reduce the effectiveness of sulfasalazine because the partial bacterial cleavage is reduced due to a disturbance of the intestinal microflora.

Anion exchanger resins
Anion exchanger resins such as colestipol and cholestyramine bind both sulfasalazine and its metabolites in the intestines.

Anticoagulants
The cleavage of oral anticoagulants such as phenprocoumone or dicumarol by the liver can be affected. Concurrent intake requires special precaution and continuous monitoring of the coagulation status.

Medicinal products with high protein binding
Simultaneous administration of methotrexate, phenylbutazone, sulfinpyrazone or other medical active substances with high protein binding may augment the effectiveness of these drugs.

Medicinal products with haematotoxic effect
Leukopenia, anaemia and/or thrombocytopenia may occur more frequent and more intensive. Concurrent intake of sulfasalazine and other possible haematotoxic drugs (e.g. etanercept) requires a close monitoring.

Ciclosporine
Combined application may result in reduced levels of cyclosporine. Presumably the induction of cytochrome P450 is the reason. Control and adaptation of dosage can be necessary.

Typhus live vaccine
A decreased immune reaction after administration of typhus live vaccine is possible. Therefore, an interval of at least 24 hours is recommended between the intake of sulfasalazine and the application of typhus live vaccine.

Hepatotoxic drugs
During concurrent intake of sulfasalazine and other hepatotoxic drugs liver function must be monitored thoroughly.

Sulfonylurea
When sulfonylurea is administered simultaneously their blood sugar decreasing effect can be intensified.

Methenamine
Due to a possible formation of crystalluria sulfasalazine must not be administered in combination with methenamine containing compounds (see section 4.3).

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result were observed in patients exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal experimental examinations of limited extent do not suggest damaging effects regarding pregnancy or embryo-foetal development (see section 5.3).

Therapy with sulfasalazine may result in a deficiency of folic acid or reinforce an existing deficiency due to an underlying disease or pregnancy (see sections 4.4, 4.5 and 5.8). Since deficiency of folic acid at the period of conception or during the first trimester of pregnancy is associated with an increased risk for neural tube defects (e.g. spina bifida) a supplemented administration of folic acid during sulfasalazine therapy for women of child-bearing age and in the first trimester of pregnancy is recommended.

There have been case reports of neural tube defects (NTDs) in infants born to mothers who were exposed to sulfasalazine during pregnancy, but the role of sulfasalazine in these defects has not been studied.

Sulfasalazin-Heyl should be prescribed with precaution to pregnant women, especially if they belong to the slow acetylator phenotype.

Lactation
Sulfasalazine and sulfapyridine are found in low concentration in breast milk. Caution should be exercised, especially when breastfeeding premature infants and those with G-6-PDH deficiency. There are reports of bloody stools or diarrhoea in human milk fed infants of mothers taking sulfasalazine. In cases where the outcome was reported, bloody stools or diarrhea resolved in the infant after discontinuation of sulfasalazine in the mother or discontinuation of breastfeeding. Sulfasalazin-Heyl should only be prescribed with precaution to breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Reactivity can be restricted in some patients. Patients suffering from vertigo or central nervous dysfunctions undergoing therapy with sulfasalazine should not drive, use potentially dangerous machines or do other activities, that could become dangerous because of restricted reactivity.

This is especially applied to concurrence with alcohol.

4.8 Undesirable effects

In single cases it can be difficult to diagnose undesirable effects because some of the undesirable reactions of sulfasalazine therapy can be signs of the disease as well. As a precaution the occurrence should always be reported to the treating doctor since only he is able to assess the signs correctly.

Many of the side effects are dose-dependent and can be alleviated or avoided by reducing the dose.

Slow acetylators may show an increased level of active ingredient. Therefore it is recommended to determine the acetylator phenotype if side effects occur.

The following categories are used as a base for frequency specification 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)

The following undesirable effects may occur:

Infections and infestations

Rare:	pseudomembranous colitis

Blood and lymphatic system disorders

Common:	folic acid deficiency anaemia (megaloblastosis and macrocytosis), leukopenia
Uncommon:	pancytopenia, haemolytic anaemia, methaemoglobinaemia, thrombocytopenia
Rare:	agranulocytosis, aplastic anaemia, myelosuppression, plasmocytosis, eosinophilia
Very rare:	myelodysplastic syndrome
Not known:	pseudomononucleosis

The possible life-threatening agranulocytosis becomes manifest in severe general disorder, associated with fever, shivering, palpitation, sore throat and swallow pain as well as painful stomatitis and inflammation of the nasopharyngeal zone plus in the anal and genital area. In these cases Sulfasalazin-Heyl has to be withdrawn **immediately**. Sulfasalazin-Heyl should not be taken again after these disorders have abated.

Immune system disorders

Uncommon:	induction of auto-antibodies, hypogammaglobulinaemia, lupus erythematodes syndrome
Rare:	DRESS syndrome (skin reaction with eosinophilia and systemic symptoms, partly reactions similar to mononucleosis infectiosa or serum sickness), anaphylaxis

Metabolism and nutrition disorders

Common:	appetite lost
Not known:	folate deficiency

Psychiatric disorders

Uncommon:	depression
Very rare:	psychosis

Nervous system disorders

Very common:	headaches
Common:	vertigo, taste disturbance
Uncommon:	paraesthesias, altered smell sensation
Rare:	taste metallic
Very rare:	central and peripheral neuropathy, transverse myelitis, aseptic meningitis
Not known:	encephalopathies

Eye disorders

Uncommon:	allergic conjunctivitis
Rare:	xanthochromia of the eyes
Very rare:	xanthochromia of contact lenses

Ear and labyrinth disorders

Uncommon:	tinnitus

Heart diseases

Uncommon:	palpitations, tachycardia
Very rare:	pericarditis, myocarditis

Vascular diseases

Uncommon:	hypertension
Very rare:	Raynaud syndrome
Not known:	pallor

Respiratory, thoracic and mediastinal disorders

Common:	cough
Uncommon:	bronchial asthma, dyspnoea
Rare:	fibrosing alveolitis, eosinophilic pneumonia
Very rare:	bronchiolitis obliterans
Not known:	interstitial lung disease, eosinophilic infiltration, oropharyngeal pain

Gastrointestinal disorders

Very common:	nausea, abdominal pain, appetite lost, dyspepsia, stomach discomfort
Common:	vomiting, diarrhoea, abdominal pain
Uncommon:	flatulence
Rare:	pancreatitis, stomatitis
Very rare:	exacerbation of remitting ulcerous colitis

Hepatobiliary disorders

Common:	raised levels of liver enzymes
Uncommon:	jaundice
Rare:	hepatitis
Very rare:	fulminant hepatitis (with potentially fatal consequences)
Not known:	hepatic failure, cholestatic hepatitis, cholestasis

Skin and subcutaneous tissue disorders

Common:	pruritus, exanthema, purpura
Uncommon:	urticaria, Quincke's oedema, photo sensibility, enanthema, alopecia
Rare:	cyanosis, yellow-orange discoloration of the skin, exfoliative dermatitis
Very rare:	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see section 4.4)
Not known:	acute generalized exanthematous pustulosis, erythema, dermatitis lichenoid

Musculoskeletal and connective tissue disorders

Common:	arthralgia
Uncommon:	muscular weakness
Rare:	myalgia
Not known:	Sjogren's syndrome

Renal and urinary disorders

Common:	proteinuria
Rare:	haematuria, crystalluria, yellow-orange discoloration of the urine
Very rare:	acute interstitial nephritis, nephrotic syndrome
Not known:	nephrolithiasis

Reproductive system and breast disorders

Very common:	in men: reversibel oligospermia, temporary impaired fertility

Congenital, familial and genetic disorders

Rare:	acute episodes of porphyria

General disorders and administration site conditions

Very common:	fatigue
Common:	fever, sleepiness, giddiness, disturbances of concentration, sleeplessness
Uncommon:	face oedema, debilitiy
Not known:	yellow-orange discoloration of body fluids

Investigations

Rare:	nuclear antibody (ANA) increased

In general the undesirable effects can be subdivided into 2 groups:

The first group is dose-dependent, depending on the the acetylator phenotype and mostly unpredictable. This group includes undesirable effects like nausea and vomiting, headaches, haemolytic anaemia and methaemoglobinaemia.
In case of dose-dependent undesirable effects treatment with Sulfasalzin-Heyl can be continued after an interruption of 1 week, starting with small doses and increasing slowly under clinical supervision.

The second group is composed of hypersensitivity reactions which are unpredictable and occur in the majority of the cases at an early stage of the treatment. This group includes undesirable effects like skin rash, aplastic anaemia, disturbances of liver and lung function as well as auto immune haemolysis.
In cases of hypersensitivity reactions treatment with Sulfasalazin-Heyl should be stopped immediately.

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

Phenomena of intoxications
There is evidence that incidence and severity of intoxications due to overdose are explained directly by sulfapyridine concentration in the serum. Symptoms of overdose can be: nausea, vomiting, gastric disorders and abdominal pain. In progressed cases symptoms of the central nervous system like giddiness, convulsions et cetera may occur. Sulfapyridine concentrations in the serum can be utilized to control the course after overdose.

Treatment of intoxication
In case of overdose gastric lavage is recommended after intake of the filmtablets within up to 2.5 hours. Digestion accelerating agents may eventually reduce absorption of sulfasalazine if the intake of the filmtablets is dated back longer than 2.5 hours. Sulfasalazin-Heyl and its metabolites are dialyzable. In cases of severe intoxication or hypersensitivity reactions treatment with Sulfasalazin-Heyl should be terminated immediately.

Methaemoglobinaemia can be antagonized by administration of toluidine blue (2 to 4 mg/kg body weight i.v). or methylene blue (1 to 2 mg/kg body weight i.v.).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	Specific antirheumatic
ATC-Code:	M01CX02

Sulfasalazine (salazosulfapyridine, 5[4-(2-pyridylsulfamoyl)phenylazo]salicylic acid, SASP) is an azo compound of the sulfonamide sulfapyridine and 5-aminosalicylic acid (5-ASA). Although the pharmacokinetic properties of the substance are for the most part known and its clinical efficacy in the treatment of chronic rheumatoid arthritis has been proven, some points concerning its actual mechanism of action remain unclear.

In the treatment of chronic rheumatoid arthritis, sulfasalazine can be assigned to the class of basis therapeutic agents. A major factor in the action of sulfasalazine appears to be its effects on leukotrien synthesis, the metabolism of arachidonic acid and lipoxygenation at the site of the inflammatory process. What part the substance's antimicrobial action plays in its efficacy is as yet unknown. The possibility of a modulating effect on the immune system is also under discussion.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, approximately 20 % of sulfasalazine is absorbed from the small intestine.

Distribution
Maximum plasma concentration is reached after 3 to 6 hours. The average half-life following a single dose is 5.7 hours, following repeated intake 7.6 hours. Protein binding is more than 95 %.

Biotransformation and elimination
A smaller amount of the absorbed substance is excreted with the urine, the rest enters the small intestine via bile again (enterohepatic circulation). Serum level falls to a very low concentration within 2 days after intake. The biggest amount of the administered sulfasalazine dose reaches the large intestine and is split by enterobacteria into its metabolites sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is absorbed, partly acetylated, hydroxylated and glucuronylated. For the most part sulfapyridine is excreted renal, then. Not acetylated sulfapyridine is bound to serum albumin and reaches its maximum plasma concentration after 12 hours. After 3 days there is no more sulfapyridine detectable in the serum. Following intake of a single dose of 2 g sulfasalazine about 80 % (70-90 %) of the dose is detectable in the urine as intact molecule and sulfapyridine metabolites. According to their genetic predisposition, slow

acetylators develop higher serum concentrations of free sulfapyridine, therefore exhibiting rather undesirable effects.

The absorbed amount of 5-aminosalicylic acid is excreted with the urine quickly, primarily as acetyl-5-aminosalicylic acid. A bigger amount is excreted via faeces.

Bioavailability

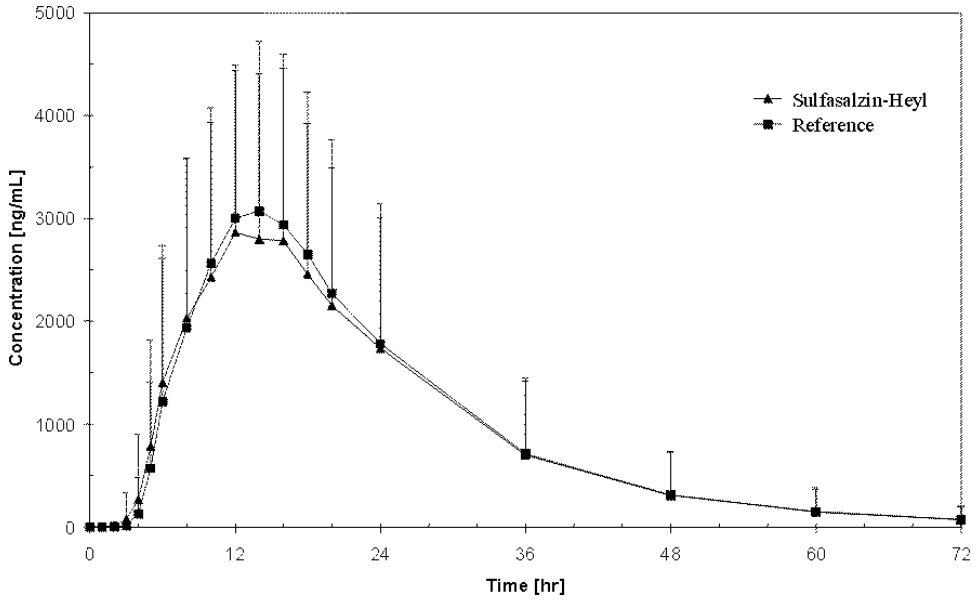
Determination of bioavailability is possible via serum sulfapyridine values. However, as it is not yet clear whether the sulfasalazine effect is due to the whole molecule or the metabolites, it has no relevance to the use of sulfasalazine. It is known that with higher levels of sulfapyridine the side effect rate increases. In general, however, it is sufficient to orient the dose at the occurrence of side effects, because the serum levels, in which side effects are noticeable, can be individually very different.

A bioavailability study (cross-over, single dose, 1000 mg sulfasalazine oral per application) conducted with 24 subjects in 2003 and compared to a reference preparation showed the following pharmacokinetic parameters for sulfasalazine and the metabolites sulfapyridine and N-acetyl-sulfapyridine:

			Sulfasalazin -Heyl	**Reference preparation**
Sulfapyridine	maximum plasma concentration C_{max}	[µg/ml]	3.4 ± 1.7	3.6 ± 1.7
	time of maximum plasma concentration t_{max}	[h]	12.5 ± 3.7	12.3 ± 2.8
	area under the concentration/time curve AUC	[µg/ml/h]	67.0 ± 43.5	68.8 ± 44.4
N-acetyl-sulfapyridine	maximum plasma concentration C_{max}	[µg/ml]	2.3 ± 1.3	2.5 ± 1.6
	time of maximum plasma concentration t_{max}	[h]	16.6 ± 4.0	16.3 ± 4.0
	area under the concentration/time curve AUC	[µg/ml/h]	51.3 ± 25.9	53.9 ± 30.4
Sulfasalazine	maximum plasma concentration C_{max}	[µg/ml]	5.8 ± 6.1	6.0 ± 5.5
	time of maximum plasma concentration t_{max}	[h]	5.4 ± 1.8	5.7 ± 1.3
	area under the concentration/time curve AUC	[µg/ml/h]	45.6 ± 50.0	44.3 ± 42.2

Sulfasalazine is a pro-drug. The bioavailability assessment was based on the active metabolite sulfapyridine.

Mean plasma level curves of sulfapyridine of compared to a reference preparation in a concentration time diagram:



5.3 Preclinical safety data

Chronic toxicity
In chronic toxicity studies conducted with dogs (250 mg and 500 mg/kg body weight) over a period of 6 months, a slight enlargement of the thyroid gland was observed. Minor changes in the testicular epithelium were only determined at doses of 500 mg/kg. Comparable results have been found in rats (6 months studies).

Reproductive toxicity
Studies in rats revealed a reversible impairment of the male fertility. Following daily administration of 500 mg/kg body weight over a defined period, intake of the drug was interrupted for 10 days (new spermiogenetic cycle). Fertility and general virility normalised afterwards.

Teratological studies in rats showed no undesirable effects following oral administration of 500 mg/kg body weight. The harmless dose regarding an effect on the pre- and postnatal development was 200 mg/kg body weight, respectively.

Mutagenicity and carcinogenicity
The available findings basing on *in vitro* and *in vivo* mutagenicity studies are ambiguous.
In biennial carcinogenicity studies in rats and mice an increased incidence of urinary bladder and kidney transitional cell papillomas and hepatocellular adenomas/carcinomas was observed after treatment with sulfasalazine. The current epidemiological data do not indicate a tumorigenic potential of sulfasalazine in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium; crospovidone; macrogol 6000; magnesium stearate; sodium citrate 2 H_2O; methacrylic acid-ethyl acrylate copolymer (1:1); povidone; propylene glycol: silica, colloidal anhydrous; stearic acid; talc; titanium dioxide; water, purified.

6.2 Incompatibilites

None known so far.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

White plastic bottle with 100 enteric coated filmtablets N2
White plastic bottle with 300 enteric coated filmtablets N3

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

16573.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 13.10.1993
Date of latest renewal: 25.06.2001

10. DATE OF REVISION OF THE TEXT

December 2018

11. PRESCRIPTION STATE

By prescription only