SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

PENTASA 500 mg controlled-release tablets

2. Qualitative and quantitative composition

Each tablet contains 500 mg mesalazine.

For the full list of excipients see section 6.1.

3. Pharmaceutical form

Controlled-release tablet

Light grey to light brown, spotted, round tablet with break notch.
Stamp: *PENTASA* on one side, *500 mg* on the other side.

4. Clinical particulars

4.1 Therapeutic indications

- Acute treatment of ulcerative colitis as well as treatment for avoidance of recurrence.
- Treatment for symptomatic recovery in patients with active Crohn's disease.

4.2 Posology and method of administration

If not prescribed otherwise, the following general dosing recommendations apply:

Ulcerative colitis:

Adults:
Acute therapy: individual dose up to 4 g mesalazine daily, divided into 2 single doses, i.e. 2 times daily up to 4 PENTASA 500 mg controlled-release tablets.

Maintenance therapy: recommended dose 1.5 g mesalazine daily, divided into 2 – 3 single doses, e.g. 3 times daily 1 PENTASA 500 mg controlled-release tablet.

Children and adolescents:
There are only limited data on the effect in children (6 – 18 years).

Children from the age of 6 years:
Acute therapy:
The dose should be determined on an individual basis, initially with 30 – 50 mg/kg body weight/day, divided into single doses.
Maximum dose: 75 mg/kg body weight/day, in single doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance therapy:
The dose should be determined on an individual basis, initially with 15 – 30 mg/kg body weight/day, divided into single doses. The total dose should not exceed 1.5 g/day (recommended adult dose).

Crohn's disease:

Adults:
Acute therapy: up to 4 g mesalazine daily, divided into 2 – 3 single doses, e.g. 2 times daily 2 – 4 PENTASA 500 mg controlled-release tablets each or 3 times daily 2 – 3 controlled-release tablets each (30 - 50 mg/kg body weight/day)

Children and adolescents:
There are only limited data on the effect in children (6 – 18 years).

Children from the age of 6 years:
Acute therapy:
The dose should be determined on an individual basis, initially with 30 – 50 mg/kg body weight/day, divided into single doses.
Maximum dose: 75 mg/kg body weight/day, in single doses. The total dose should not exceed 4 g/day (maximum adult dose).

It is usually recommended that children with a body weight of up to 40 kg should receive half the dose given to adults and children above 40 kg should receive the normal adult dose.

Take the controlled-release tablets without chewing, preferably between meals, with sufficient fluid or put them into water or fruit juice, stir and drink.

The duration of administration is up to the discretion of the treating physician. It depends on the course of the disease. PENTASA 500 mg controlled-release tablets are suitable for long-term use.

4.3 Contraindications

- Hypersensitivity to mesalazine, salicylates or to any of the excipients listed in section 6.1.

- Severe liver and renal impairment

4.4 Special warnings and precautions for use

Caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates). In these patients, treatment with PENTASA 500 mg controlled-release tablets should only be commenced under careful medical supervision.

In case of acute symptoms of intolerance, i.e. abdominal cramps, abdominal pain, fever, severe headache and rash, the treatment should be discontinued immediately.

Caution is recommended in patients with impaired liver function. Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating physician.

The drug is not recommended for use in patients with impaired renal function and in patients with haemorrhagic diathesis. The renal function should be regularly monitored (e.g. serum creatinine), especially during the initial phase of treatment. Urinary status (dip sticks) should be determined prior to and during treatment at the discretion of the treating physician. Mesalazine induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. The concurrent use of other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions.

Caution is recommended in patients with active peptic ulcer.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment.

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely. Serious blood dyscrasias have been reported very rarely with mesalazine (see section 4.5). Blood tests for differential blood counts is recommended prior to and during treatment, at the discretion of the treating physician. Treatment should be discontinued on suspicion or evidence of these adverse reactions.

Follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional symptoms occur, these tests should be performed immediately.

4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed. Combination therapy with PENTASA and azathioprine or 6-mercaptopurine or thioguanine have shown a higher frequency of myelosuppressive effects, and an interaction cannot be ruled out, however, the mechanism behind the interaction is not established. Regular monitoring of white blood cells is recommended and the dosage regimen of thiopurine should be adjusted accordingly.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

PENTASA 500 mg controlled-release tablets should not be used during pregnancy and lactation except when the potential benefits of the treatment outweigh the possible hazards in the opinion of the physician.

Pregnancy:

Mesalazine is known to cross the placental barrier. Data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on the pregnancy or on the health of the foetus/new-born child. To date no other relevant epidemiologic data are available. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Blood disorders (leucopenia, thrombocytopenia and anemia) have been reported in new-borns of mothers being treated with PENTASA.

In one single case after long-term use of a high dose of mesalazine (2-4g, orally) during pregnancy, renal failure in a neonate was reported.

Lactation:
Mesalazine is excreted in breast milk. The mesalazine-concentration in breast milk is lower than in maternal blood, whereas the metabolite acetyl mesalazine appears in similar or increased concentrations.

There is limited experience of the use of oral mesalazine in lactating women. No controlled studies with PENTASA during lactation have been carried out. Hypersensitivity reactions like diarrhea in the infant cannot be excluded. If the infant develops diarrhoea, breast-feeding should be discontinued.

Fertility:
Animal data on mesalazine show no effect on male and female fertility

4.7 Effects on ability to drive and use machines

PENTASA has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

The most frequent adverse reactions seen in clinical trials are diarrhea (3%), nausea (3%), abdominal pain (3%), headache (3%), vomiting (1 %) and rash (1 %). Occasionally, hypersensitivity reactions and drug fever may occur.

Frequency of side effects, based on clinical studies and experience after market introduction:

System organ classes	Common (≥ 1/100 bis <1/10)	Rare (≥ 1/10.000 bis <1/1.000)	Very rare (< 1/10.000)
Blood and lymphatic system disorders			Eosinophilia (as part of an allergic reaction) Altered blood counts (anemia, aplastic anemia, leucopenia (including granulocytopenia and neutropenia), thrombocytopenia, agranulocytosis, pancytopenia)

System organ classes	Common (≥ 1/100 bis <1/10)	Rare (≥ 1/10.000 bis <1/1.000)	Very rare (< 1/10.000)
Immune system disorders			Hypersensitivity reactions such as allergic exanthema Pancolitis
Nervous system disorders	Headache Dizziness		Peripheral neuropathy Benign intracranial hypertension in adolescents
Cardiac disorders		Myocarditis* Pericarditis*	Pericardial effusion
Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (including dyspnea, cough, bronchospasm, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis, pleurisy)
Gastrointestinal disorders	Diarrhea Abdominal pain Nausea Vomiting	Acute pancreatitis* Increased amylase (blood and/or urine) Flatulence	
Hepatobiliary disorders			Increased liver enzymes, cholestasis parameters and bilirubin, hepatoxicity (including hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)
Skin and subcutaneous tissue disorders	Rash (including urticaria and erythematous rash), Exanthema		Reversible alopecia Quincke´s-oedema

System organ classes	Common (≥ 1/100 bis <1/10)	Rare (≥ 1/10.000 bis <1/1.000)	Very rare (< 1/10.000)
Musculo-skeletal and connective tissue disorders			Myalgia Arthralgia Lupus erythematosus-like reactions
Renal and urinary disorders			Renal function impairment (including acute/chronic interstitial nephritis*, nephritic syndrome), (acute/chronic) renal insufficiency, discoloration of urine
Reproductive system and breast disorders			Oligospermia (reversible)
General disorders and administration site conditions			Drug fever

(*) The mechanism of mesalazin-induced myocarditis and pericarditis, pancreatitis, nephritis and hepatitis is unknown, but might be of allergic origin.

It is important to note that several of these disorders can also be attributed to the bowel disease itself.

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

Experience in animals:
Single oral doses of mesalazine of up to 5 g/kg in pigs and a single intravenous dose of mesalazine at 920 mg/kg in rats were not lethal.

Human experience:
There are rare data on overdosage (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive. There have been reports of patients taking oral daily doses of 8 grams for a month without any adverse events.

Management of overdose in human:
Symptomatic treatment at hospital. Close monitoring of renal function.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, aminosalicylic acid and similar agents
ATC code: A07 EC 02

Mesalazine is the active moiety of sulphasalazine which has already been used in the treatment of ulcerative colitis and Crohn's disease for a long time. Clinical examinations show that the therapeutic efficacy of both oral and rectal mesalazine is rather due to a local effect at the inflamed intestinal wall than to a systemic effect.
Increased leucocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B4 and increased free radical formation in the inflamed intestinal tissue are all present in patients with inflammatory bowel disease. Mesalazine has in-vitro and in-vivo pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leukotriene production and scavenge for free radicals. The mechanism of mesalazine, however, is still unknown.

The risk of colorectal cancer (CRC) is slightly increased in ulcerative colitis.
Observed effects of mesalazine in experimental models and patient biopsies support the role of mesalazine in prevention of colitis-associated CRC, with down regulation of both inflammation dependent and non-inflammation dependent signalling pathways involved in the development of colitis-associated CRC. However data from meta-analyses, including both referral and non-referral populations, provide inconsistent clinical information regarding the benefit of mesalazine in the carcinogenesis risk associated with ulcerative colitis.

5.2 Pharmacokinetic properties

General characteristics of the active substance:
The therapeutic efficacy of mesalazine is most probably due to the local contact of the active substance with the diseased area of the intestinal mucosa.

PENTASA controlled-release tablets consist of mesalazine microgranules coated with ethyl cellulose. After administration and decay of the tablets, mesalazine is continuously released in the gastrointestinal tract from the individual microgranules, independently of the pH value in the intestine.

The microgranules reach the duodenum within one hour following administration, independently from additional ingestion. The passage time through the small intestine is approximately 3 – 4 hours in healthy volunteers.

Absorption:
30 - 50 % of the oral dose is absorbed mainly in the small intestine. Mesalazine can be shown in the plasma already 15 minutes after administration.
Maximum plasma concentrations are reached 1-4 hours following administration. After a gradual deduction, mesalazine ceases to be detectable in the blood after 12

hours following administration. The plasma concentration curve for acetyl mesalazine runs similar, but the concentration is higher and elimination takes place more slowly.

The relation of acetyl mesalazine to mesalazine in the plasma is 3.5 following oral administration of a daily dose of 3 x 500 mg and 1.3 following 3 x 2 g, which can be related to a dose-dependent acetylation that is subject to a saturation mechanism.

The average steady-state plasma concentrations of mesalazine are 2 µmol/l for a daily dosage of 1.5 g, 8 µmol/l for 4g, and around 12 µmol/l for 6g. For acetyl mesalazine, the corresponding concentrations are at 6 µmol/l, 13 µmol/l and 16 µmol/l.

With oral administration, simultaneous ingestion does not have any influence on the transport and release of mesalazine but it reduces the systemic absorption.

Distribution:
Mesalazine and acetyl mesalazine do not cross the blood brain barrier. Protein binding of mesalazine is approximately 50% and of acetyl mesalazine about 80%.

Biotransformation:
Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl mesalazine (acetyl mesalazine). Some acetylation also occurs through the action of colonic bacteria. The acetylation seems to be independent of the acetylator phenotype of the patient.
Acetyl mesalazine is thought to be clinically as well as toxicologically inactive.

Elimination:
The plasma half-life of pure mesalazine following iv administration is approximately 40 minutes and for acetyl mesalazine approximately 70 minutes. Due to the continuous release of mesalazine in the entire gastrointestinal tract, the elimination half-life is not determinable after oral administration. The steady-state, however, is reached after a treatment period of 5 days with oral administration.
Both substances are excreted in urine and feces. The urinary excretion consists mainly of acetyl mesalazine.

Characteristics in patients:
The release of mesalazine at the intestinal mucosa after oral administration is only slightly influenced by pathophysiological changes like diarrhea and increased acidity in the intestine. In patients with impaired liver and kidney functions, the resultant decrease in the rate of elimination may constitute an increased risk of nephrotoxic adverse reactions.

5.3 Preclinical safety data

Definitive nephrotoxicity and possible gastrointestinal toxicity is demonstrated in all species examined. Nephrotoxicity is evident with doses 5-10 times those used in humans.

In animal studies, no significant toxicity has been observed in the gastrointestinal tract, in the liver or in the hemopoietic system.

In-vitro test systems and in-vivo studies showed no evidence of mutagenic effects. Studies on the tumorigenic potential carried out in rats showed no evidence of any substance-related increase in the incidence of tumors.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryo-foetal development, parturition or postnatal development.

6. Pharmaceutical particulars

6.1 List of excipients

Povidone K30, ethyl cellulose, magnesium stearate (Ph. Eur.), talcum, microcrystalline cellulose

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

OP with 100 controlled-release tablets with break notch
OP with 300 controlled-release tablets with break notch

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

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24109 Kiel

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8. Marketing authorisation number

2988/3195/NMR/2017

9. Date of first authorization/renewal of the authorisation

Mar 24, 2017

10. Date of revision of the text

October 2014

11. Prescription/pharmacy status

Prescription only