SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

PENTASA Sachet 1000 mg prolonged release granules

PENTASA Xtend 2 g prolonged release granules

Mesalazine

2. Qualitative and quantitative composition

Each sachet PENTASA Sachet 1000 mg prolonged release granules contains 1 g mesalazine.
Each sachet PENTASA Xtend 2 g prolonged release granules contains 2 g mesalazine.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Prolonged release granules

White-grey to pale white-brown granules

4. Clinical particulars

4.1 Therapeutic indications

Mild to moderate ulcerative colitis

4.2 Posology and method of administration

Ulcerative colitis:

Adults
Active disease:
Individual dosage, up to 4 g mesalazine once daily or divided into 2-4 doses.

Maintenance treatment:
Individual dosage. Recommended dosage, 2 g mesalazine once daily.

Paediatric population
There is only limited documentation for an effect in children (age 6-18 years).

Children 6 years of age and older:
Active disease:
To be determined individually, starting with 30–50 mg/kg /day in divided doses.
Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance treatment:
To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

The granules must not be chewed. The contents of the sachet should be emptied onto the tongue and washed down with some water or orange juice.

4.3 Contraindications

Hypersensitivity to mesalazine, to any of the excipients or salicylates. Severe liver and/or 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 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.

As a guideline, 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 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Combination therapy with mesalazine and azathioprine or 6-mercaptopurine or thioguanine has shown a higher frequency of myelosuppressive effects. An interaction cannot be excluded, however, the mechanism of interaction is unknown. Regular monitoring of white blood cells is recommended and dosage of thiopurines should be adjusted accordingly.

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

4.6 Fertility, pregnancy and lactation

PENTASA prolonged release granules 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 fetus/newborn 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, embryo/foetal development, parturition or postnatal development. Blood disorders (leucopenia, thrombocytopenia and anaemia) have been reported in new-borns of mothers being treated with PENTASA prolonged release granules.

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. No controlled studies with PENTASA prolonged release granules during breast-feeding have been carried out. Only limited experience during lactation in women after oral application is available to date.
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 prolonged release granules 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 diarrhoea (3%), nausea (3%), abdominal pain (3%), headache (3%), vomiting (1%), and rash (1%).
Hypersensitivity reactions and drug fever may occasionally occur.

Frequency of adverse effects, based on clinical trials and reports from post-marketing

surveillance:

System organ class	Common (≥ 1/100 to <1/10)	Rare (≥ 1/10,000 to <1/1,000)	Very rare: (< 1/10,000)
Blood and lymphatic system disorders			Eosinophilia (as part of an allergic reaction)
			Altered blood counts (anaemia, aplastic anaemia, leukopenia (incl. granulocytopenia and neutropenia), thrombocytopenia, agranulocytosis, pancytopenia)
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*	Pericardial effusion
		Pericarditis*	
Respiratory, thoracic and mediastinal disorders			Allergic and fibrotic lung reactions (incl. dyspnoea, cough, bronchospasm, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, lung infiltration, pneumonitis, pleuritis)
Gastrointestinal disorders	Diarrhoea	Acute Pancreatitis*	
	Abdominal pain	Increased amylase values (blood and/or urine)	
	Nausea		
	Vomiting	Flatulence	
Hepato-biliary disorders			Increased liver enzymes, cholestasis parameters and bilirubin, hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic

		failure)
Skin and subcutaneous tissue disorders	Rash (incl. urticaria, erythematous rash)	Reversible alopecia Quincke's oedema
Musculoskeletal, connective tissue and bone disorders		Myalgia Arthralgia lupus erythematosus-like reactions
Renal and urinary disorders		Renal impairment (incl. acute/chronic interstitial nephritis*, nephrotic syndrome), (acute/chronic) renal insufficiency, urine discolouration
Reproductive system disorders		Oligospermia (reversible)
General disorders and administration site conditions		Drug fever

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

It is important to note that several of these disorders can also be attributed to the inflammatory 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: A single intravenous dose of mesalazine in rats of 920 mg/kg and single oral doses of mesalazine in pigs up to 5 g/kg were not lethal.

Human experience: There are rare data on overdose (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 daily oral doses of 8 g 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: A07E C02

Mesalazine is the active component of sulfasalazine, which has been used for a long time in the treatment of ulcerative colitis and Crohn's disease.
The therapeutic value of mesalazine appears to be due to local effect on the inflamed intestinal tissue, rather than to systemic effect.
Increased leukocyte 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 leukocyte chemotaxis, decrease cytokine and leukotriene production and scavenge for free radicals. The mechanism of action of mesalazine is, however, still not understood.

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:

PENTASA prolonged release granules consist of ethylcellulose coated microgranules of mesalazine. Following administration mesalazine is released continuously throughout the gastrointestinal tract in any enteral pH conditions. The microgranules enter the duodenum within an hour of administration, independent of food co-administration. The average small intestinal transit time is approximately 3-4 hours in healthy volunteers.

Metabolism: Mesalazine is metabolised into N-acetyl-mesalazine (acetyl-mesalazine) both pre-systemically by the intestinal mucosa and systemically in the liver. 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 believed to be clinically as well as toxicologically inactive.

Absorption: 30-50% of an oral dose is absorbed, predominantly from the small intestine. Maximum plasma concentrations are seen 1-4 hours post-dose. The plasma concentration of mesalazine decreases gradually and is no longer detectable 12 hours post-dose. The plasma concentration curve for acetyl-mesalazine follows the same pattern, but the concentration is generally higher and the elimination is slower.

The metabolic ratio of acetyl-mesalazine to mesalazine in plasma after oral administration ranges from 3.5 to 1.3 after daily doses of 500 mg x 3 and 2 g x 3, respectively, implying a dose-dependent acetylation which may be subject to saturation.

Mean steady-state plasma concentrations of mesalazine are approximately 2 µmol/l, 8 µmol/l and 12 µmol/l after 1.5 g, 4 g and 6 g daily dosages, respectively. For acetyl-mesalazine the corresponding concentrations are 6 µmol/l, 13 µmol/l and 16 µmol/l.
The transit and release of mesalazine after oral administration are independent of food co-administration, whereas the systemic absorption will be reduced.

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%.

Elimination: The plasma half-life following i.v. administration of mesalazine is approximately 40 minutes and for acetyl-mesalazine approximately 70 minutes. Due to the continuous release of mesalazine throughout the gastrointestinal tract, the elimination half-life cannot be determined after oral administration. Tests have shown that steady-state is reached after a treatment period of 5 days following oral administration.

Both mesalazine and acetyl-mesalazine are excreted with the urine and faeces. The urinary excretion consists mainly of acetyl-mesalazine.

Characteristics in patients:
The delivery of mesalazine to the intestinal mucosa after oral administration is only slightly affected by pathophysiologic changes such as diarrhoea and increased bowel acidity observed during active inflammatory bowel disease. A reduction in systemic absorption to 20-25% of the daily dose has been observed in patients with accelerated intestinal transit. Likewise, a corresponding increase in faecal excretion has been seen.

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, and nephrotoxicity is evident with doses 5–10 times those used in humans.

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

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

Ethylcellulose, povidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

The granules should be used immediately after first opening of the sachet.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium foil single dose container

Pack sizes:

PENTASA Sachet 1000 mg prolonged release granules:
1 x 50 sachets
2 x 50 or 1 x 100 sachets
3 x 50 or 1 x 150 sachets

PENTASA Xtend 2 g prolonged release granules:
1 x 60 sachets
1 x 120 sachets

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

FERRING GmbH
Wittland 11
D-24109 Kiel

Codistributor
FERRING Arzneimittel GmbH
Fabrikstraße 7
D-24103 Kiel
Tel: 0431 / 5852-0
Fax: 0431/ 5852-74

8. Marketing authorisation number

PENTASA Xtend 2 g prolonged release granules:
2987/3169/NMR/2017

9. Date of first authorisation/renewal of the authorisation

PENTASA Xtend 2 g prolonged release granules: Mar 24, 2017

10. Date of revision of the text

March 2015

11. Prescription status

Prescription only