SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NORASA 500mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NORASA 500mg: One gastro-resistant tablet contains 500 mg Mesalazine

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

NORASA 500mg: Yellow, ochre, oblong tablet with a smooth surface

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate acute exacerbations of ulcerative colitis and for the maintenance of remission of ulcerative colitis.
4.2 Posology and method of administration

Adults and the elderly:
For the treatment of acute mild to moderate episodes of ulcerative colitis:
Depending on the clinical requirements in the individual case, one tablet of NORASA 500mg three times daily or two tablets of NORASA 500mg three times daily (equivalent to 1.5 – 3.0 g mesalazine daily).

For the maintenance of remission of ulcerative colitis:
One tablet of NORASA 500mg three times daily (equivalent to 1.5 g mesalazine daily)

Children and adolescents < 18 years
Clinical studies in children and adolescents below 18 years of age have not been carried out. Therefore, NORASA 500mg should not be administered to this age group.

The tablets should be swallowed whole and not chewed. The tablets should be taken with plenty of liquid.

Both in the treatment of acute inflammatory episodes and during long term treatment, NORASA 500mg should be used on a regular basis and consistently in order to achieve the desired therapeutic effects.

In general, an acute episode of ulcerative colitis subsides after 8 – 12 weeks; the dosage can then, in most patients, be reduced to the maintenance dose.

4.3 Contraindications

NORASA 500mg is contraindicated in cases of:

- Pre-existing hypersensitivity to salicylic acid and its derivatives or to any of the other constituents

- Severe impairment of hepatic and renal function

- Pre-existing gastric or duodenal ulcer
4.4 Special warnings and precautions for use

Blood tests (differential blood count; liver function parameters like ALT or AST; serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. As a guideline, controls are recommended 14 days after commencement of treatment, then a further two to three times at intervals of 4 weeks.

If the findings are normal, control examinations should be carried out every 3 months. If additional symptoms occur, control examinations should be performed immediately.

Caution is recommended in patients with impaired hepatic function.
NORASA 500mg is not recommended in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with NORASA 500mg.

Patients with a history of adverse drug reactions to preparations containing sulphasalazine should be kept under close medical surveillance on commencement of a course of treatment with NORASA 500mg. Should NORASA 500mg cause acute intolerability reactions such as cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

In rare cases NORASA 500mg may be excreted undissolved in stools of patients who have undergone a bowel resection or surgery in the ileocaecal area with removal of the ileocaecal valve. This phenomenon is caused by rapid bowel transit in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed.

Interactions may occur during treatment with NORASA 500mg and concomitant administration of the following medicinal products. Most of these possible interactions are based on theoretical reasons:
- Coumarin-type anticoagulants
  Possible potentiation of the anticoagulant effects (increasing the risk of gastrointestinal haemorrhage).

- Glucocorticoids
  Possible increase in undesirable gastric effects

- Sulphonylureas
  Possible increase in the blood glucose-lowering effects

- Methotrexate
  Possible increase in the toxic potential of methotrexate

- Probenecid/sulphinpyrazone
  Possible attenuation of the uricosuric effects

- Spironolactone/furosemide
  Possible attenuation of the diuretic effects

- Rifampicin
  Possible attenuation of the tuberculostatic effects

- Lactulose or similar preparations which lower stool pH
  Possible reduction of mesalazine release from the EC tablets due to decreased pH caused by bacterial metabolism.

In patients who are concomitantly treated with azathioprine or 6-mercaptourine, possible enhanced myelosuppressive effects of azathioprine or 6-mercaptopurine should be taken into account.

Concomitant use with other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions (see section 4.4).

4.6 Fertility, Pregnancy and lactation

There are no adequate data from the use of NORASA 500mg in pregnant women.

However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiological data are available. In one single case after long-term use of a high dose mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.
Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.

NORASA 500mg should only be used during pregnancy if the potential benefit outweighs the possible risk.

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. Only limited experience during lactation in woman is available to date. Hypersensitivity reactions like diarrhoea cannot be excluded. Therefore, NORASA 500mg should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the breast fed neonate develops diarrhoea, the breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

*Gastrointestinal disorders (rare, ≥1/10,000 - < 1/1,000):*
Abdominal pain, diarrhoea, flatulence, nausea, vomiting

*Nervous system disorders:*
Headache, dizziness (rare, ≥ 1/10,000 to < 1/1,000)
Peripheral neuropathy (very rare, < 0.01%)

*Renal disorders (very rare, < 1/10,000):*
Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency

*Immune system disorders (very rare, < 1/10,000):*
Hypersensitivity reactions, including allergic exanthema, drug fever, bronchospasm, peri- and myocarditis, acute pancreatitis, allergic alveolitis, lupus erythematosus syndrome, pancolitis.
**Musculoskeletal disorders (very rare, < 1/10,000):**
Myalgia, arthralgia.

**Blood and the lymphatic system disorders (very rare, < 1/10,000):**
Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia).

**Hepato-biliary disorders (very rare, < 1/10,000):**
Changes in hepatic function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis.

**Skin and appendages disorders (very rare, < 1/10,000):**
Alopecia

**Reproductive system disorders (very rare, < 1/10,000)**
Oligospermia (reversible)

### 4.9 Overdose

No cases of intoxication have been reported to date and no specific antidotes are known. If necessary, intravenous infusion of electrolytes (forced diuresis) should be considered in cases of overdose.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agent
ATC code: A07EC02

The mechanism of the anti-inflammatory action is unknown. The results of in vitro studies indicate that inhibition of lipoxigenase may play a role. Effects on prostaglandin concentrations in the intestinal mucosa have also been demonstrated.
Mesalazine (5-Aminosalicylic acid / 5-ASA) may also function as a free radical scavenger of reactive oxygen compounds.

Mesalazine, orally administered, acts predominantly locally at the gut mucosa and in the submucous tissue from the luminal side of the intestine. It is important, therefore, that mesalazine is available at the regions of inflammation. Systemic bioavailability / plasma concentrations of mesalazine therefore are of no relevance for therapeutic efficacy, but rather a factor for safety. The release of mesalazine from NORASA 500mg is pH dependent due to its Eudragit L/S tablet coating in order to achieve optimal availability.

5.2 Pharmacokinetic properties

General considerations regarding mesalazine

Mesalazine is therapeutically active within the lumen of the intestinal tract therefore the local availability of mesalazine, and not its systemic bioavailability, is relevant for the topical effect in the terminal ileum and colonic segments.

**Absorption:** Non-enteric coated mesalazine is rapidly and completely absorbed from the stomach and the upper intestine, but poorly from the large intestine. Variations in pH and transit time as well as differences in permeability within the gut can influence systemic absorption.

Food delays absorption and may influence both rate and extent of absorption. The gastroresistant and modified release characteristics of NORASA 500mg are designed to reduce systemic absorption.

Variations in plasma concentration can occur due to the physicochemical characteristics of the mesalazine molecule.

**Biotransformation:** Mesalazine is extensively metabolised, mainly to N-acetyl-mesalazine by the N-acetyl-transferase 1 (NAT 1) enzyme pre-systemically in intestinal epithelial cells and in the liver, and then excreted in the urine as a mixture of free mesalazine and N-acetyl-mesalazine. The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria.

The N-acetyl-mesalazine metabolite is inactive as an antiinflammatory agent. Protein binding of mesalazine and N-acetylmesalazine is 43% and 78%, respectively.

**Elimination:** Mesalazine and its metabolite N-acetyl-mesalazine are eliminated via the faeces (major part), renally (varies between 20 and 50%, dependent on kind of application, pharmaceutical preparation and route of mesalazine release, respectively), and biliary (minor part). Renal excretion predominantly occurs as N-acetyl-mesalazine. About 1% of total administered mesalazine dose is excreted into the breast milk mainly as N-acetyl-mesalazine.
NORASA 500mg gastro-resistant tablets specific

**Local availability in the GI tract**: A combined pharmacoscintigraphic/pharmacokinetic study showed that mesalazine is released after approximately 5-6 hours in the ileo-caecal region/ascending colon. Since up to 20% of the dose is excreted in urine as cumulative amounts of mesalazine and N-acetyl-mesalazine, approximately 80% of the dose remains available in the lumen of the distal bowel.

5.3 **Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity (rat) or toxicity to reproduction. Kidney toxicity (renal papillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine. The clinical relevance of this finding is unknown.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Microcrystalline cellulose (E460), povidone, colloidal anhydrous silica, crospovidone, magnesium stearate (E 472B), hydroxypropylmethylcellulose (E464), methacrylic acid copolymer type A, methacrylic acid copolymer type B, polyethylene glycol, triethyl citrate, talc, titanium dioxide (E171), iron oxide yellow (E172)

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**
Five years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Orange PVC/PVDC/Al blister strips packed in cartons containing 30, 90 or 300 tablets.

6.6 Special precautions for disposal

Do not chew or crush tablets before swallowing.

7 MARKETING AUTHORISATION HOLDER

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