SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mecolzine 500 mg, gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Mecolzine 500 mg gastro-resistant tablets contains 500 mg mesalazine

Excipients with known effect:

Each tablet contains 2.13 mmols of Na (49 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets

Appearance: Oblong tablets of 17.9 mm of length and 8.3 mm of diameter, with homogeneous gastro-resistant orange coloured coating.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- For the treatment of acute episodes and prevention of further episodes (recurrence) of an inflammatory disease of the large intestine (colon), known by doctors as ulcerative colitis.
- For the treatment of acute episodes of Crohn's disease in adults (a chronic inflammatory bowel disease).

4.2 Posology and method of administration

Posology

Ulcerative colitis

Adults and elderly:

Depending upon the clinical requirements in individual cases, the following daily doses are recommended:

- For the treatment of acute episodes of ulcerative colitis: 1.5 g to 3.0 g mesalazine in three divided doses (1 or 2 tablets of Mecolzine 500 mg three times daily).
- For the prevention of recurrence/long term treatment of ulcerative colitis: 1.5 g mesalazine in three divided doses (1 tablet of Mecolzine 500 mg three times daily).

Paediatric population:

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

Children 6 years of age and older:

- For the treatment of acute episodes: to be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day. The total dose should not exceed the maximum adult dose. Do not crush, divide or chew the tablets.
- For the prevention of recurrence/long term treatment of ulcerative colitis: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed the recommended adult dose. Do not crush, divide or chew the tablets.
- 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.

Crohn's disease

Adults:

Depending upon the clinical requirements in individual cases, the following daily doses are recommended:

- For the treatment of acute episodes of Crohn's disease: 1.5 g to 4.0 g mesalazine in three divided doses (1 to 3 tablets of Mecolzine 500 mg three times daily).

Method of administration

Mecolzine 500 mg tablets should be taken in the morning, at midday and in the evening, 1 hour before meals. They should be swallowed whole, not chewed, and taken with plenty of fluid.

Treatment with Mecolzine 500 mg tablets should be administered regularly and consistently, both in the acute inflammatory stage and during maintenance therapy in order to achieve the desired therapeutic effect.

The duration of use is determined by the physician.

For maintenance of remission in ulcerative colitis, the dose can usually be reduced to 1.5 g mesalazine/day (adults and adolescents with a body weight over 40 kg) and 0.75 g mesalazine/day (children/adolescents).

4.3 Contraindications

Mecolzine 500 mg tablets are contraindicated in cases of

- Hypersensitivity to active substance salicylates or to any of the excipients listed in section 6.1.
- Severe impairment of hepatic or renal function.

4.4 Special warnings and precautions for use

Blood tests (differential blood count; liver function parameters such as 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, 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.

Caution is recommended in patients with impaired hepatic function.

Mecolzine 500 mg tablets should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

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

<u>Severe cutaneous adverse reactions</u>

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.

Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 Mecolzine 500 mg tablets. Should Mecolzine 500 mg tablets cause acute intolerance reactions

such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Note

In rare cases, in patients who have undergone bowel resection/bowel surgery in the ileocoecal region with removal of the ileocoecal valve, it has been observed that Mecolzine 500 mg tablets were excreted undissolved in the stool, due to an excessively rapid intestinal passage.

This medicinal product contains 49 mg sodium per tablet, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed.

In patients who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, 6-mercaptopurine or thioguanine should be taken into account.

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

4.6 Pregnancy and lactation, Fertility

Pregnancy

There are no adequate data on the use of Mecolzine 500 mg tablets in pregnant women. However, 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.

In one single case after long-term use of a high dose of 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.

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

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Mecolzine 500 mg tablets have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

System Organ Class	Frequency according to MedDRA convention				
	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				Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)	
Immune system disorders				Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Nervous system disorders	Headache		Dizziness	Peripheral neuropathy	
Cardiac disorders			Myocarditis, pericarditis		
Respiratory, thoracic and mediastinal				Allergic and fibrotic lung reactions (including dyspnoea,	

disorders				cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)	
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, vomiting, acute pancreatitis			
Hepatobiliary disorders			Cholestatic hepatitis	Hepatitis	
Skin and subcutaneous tissue disorders			Photo-sensitivity	Alopecia	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders			Arthralgia	Myalgia	
Renal and urinary disorders				Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	Nephrolithiasis*
Reproductive system and breast disorders				Oligospermia (reversible)	
General disorders			Asthenia, fatigue		
Investigations		Changes in liver function parameters (increase in transaminases and parameters of cholestasis), changes in pancreatic enzymes lipase and amylase increased),			

		eosinophil count increased			

* see section 4.4 for further information

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

Photosensitivity

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, Aminosalicylic acid and similar agents, ATC code: A07EC02.

Mechanism of action

The mechanism of the anti-inflammatory action is unknown. The results of in vitro studies indicate that inhibition of lipoxygenase 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 radical scavenger of reactive oxygen compounds.

Pharmacodynamic effects

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. In order to fulfil these criteria, Mecolzine 500 mg tablets are coated with Eudragit L and Eudragit S; they are thus gastro-resistant and release of mesalazine is pH-dependent.

5.2 PHARMACOKINETIC PROPERTIES

General considerations of mesalazine

Absorption

Mesalazine absorption is highest in proximal gut regions and lowest in distal gut areas.

Biotransformation

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and the liver to the pharmacologically inactive N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Protein binding of mesalazine and N-Ac-5-ASA is 43% and 78%, respectively.

Elimination

Mesalazine and its metabolite N-Ac-5-ASA 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-Ac-5-ASA.

About 1 % of total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

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

Mecolzine 500 mg tablets:

Sodium carbonate, anhydrous
Glycine
Povidone
microcrystalline cellulose
carboxymethyl sodium starch
colloidal silica oxide
calcium stearate

methacrylic acid polymer,
dibutyl sebacate
micronised talc
titanium dioxide (E-171)
polyethylenglycol 6000
yellow iron oxide (E-172)
red iron oxide (E-172)
isopropyl alcohol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Mecolzine 500 mg Tablets: 3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

An aluminium-aluminium heat-sealed blister containing 10 tablets

Package sizes: 30, 50 and 100 tablets per a cardboard box

7. MARKETING AUTHORIZATION HOLDER

Pacific Healthcare (Thailand) Co., Ltd.

1011 Supalai Grand Tower, Room No. 01, 29th Floor, Rama 3 Rd.,

Chongnonsee, Yannawa, Bangkok 10120, Thailand.

8. MARKETING AUTHORISATION NUMBER

Mecolzine 500 mg tablets: Reg No.

9. DATE OF THE FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION

Mecolzine 500 mg tablets:

10. DATE OF REVISION OF THE TEXT:

May, 2022