PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

ZYLAMENE SR 800 mg modified-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 800 mg mesalazine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablets.

Reddish brown coloured, capsule-shaped, biconvex enteric-coated tablets imprinted with “435” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative colitis

ZYLAMENE SR 800 is used for the treatment and maintenance of remission in ulcerative colitis.

4.2 Posology and method of administration

Posology

Adults

Ulcerative colitis

Induction of remission: 2,4 g (three tablets) once daily or divided in 2 – 3 times daily. If required, the dose may be increased to 4,8 g (six tablets) divided in 2 – 3 times daily. 2,4 g may be taken once daily or in divided doses. Above 2,4 g should be taken in divided doses.

Maintenance of remission: 1,6 to 2,4 g (2 to 3 tablets) once daily or divided in 2 – 3 times daily.

The dose can be adjusted in accordance with the response to the treatment.

Mild acute disease: 2,4 g (three tablets) once daily or divided in 2 – 3 times daily, with concomitant corticosteroid therapy where clinically indicated.

Moderate acute disease: 2,4 g to 4,8 g (three to six tablets) divided in 2 – 3 times daily, with concomitant corticosteroid therapy where clinically indicated. 2,4 g may be taken once daily or in divided doses. Above 2,4 g should be taken in divided doses.

Maintenance therapy: 1,6 g to 2,4 g (two to three tablets) taken once daily or in divided doses. The maximum adult dose should not exceed six tablets a day and not exceed 3 tablets taken together at any one time.

Special populations

Elderly patients

The normal adult dosage may be used unless renal or liver function is severely impaired (see sections 4.3 and 4.4).

Paediatric population

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

Method of administration

The tablets should be swallowed whole with a glass of water one hour before food intake. They must not be chewed, crushed or broken before swallowing. If one or more doses have been missed, the next dose is to be taken as usual.

4.3 Contraindications

- Hypersensitivity to mesalazine or to any of the excipients listed in section 6.1.
- A history of sensitivity to salicylates or renal sensitivity to sulfasalazine.

- Severe renal impairment (GFR < 30 mL/min/1,73 m^2).
- Severe liver impairment.
- Gastric and duodenal ulcers.
- Bleeding tendency.

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 (dipsticks) should be determined prior to and during treatment, at the discretion of the treating medical practitioner. As a guideline, follow-up tests are recommended 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional signs appear, these tests should be performed immediately.

Elderly patients

Use in the elderly should be cautious and subject to patients having normal renal and hepatic function.

Intolerance

Discontinue treatment immediately if acute symptoms of intolerance occur including vomiting, cramps, abdominal pain, fever, severe headache or rash.

Mesalazine inhibits the thiopurine methyltransferase (TPMT) activity *in vitro* and may therefore impair the metabolism of azathioprine and 6-mercaptopurine (see section 4.5). Standard haematological indices (including the white cell count) should be monitored repeatedly in patients taking azathioprine, especially at the beginning of such combination therapy, whether or not ZYLAMENE SR 800 is prescribed.

Renal disorder

Mesalazine is excreted rapidly by the kidney, mainly as its metabolite, *N*-acetyl-5-aminosalicylic

acid. In rats, large doses of mesalazine injected intravenously produced tubular and glomerular toxicity. ZYLAMENE SR 800 should be used with extreme caution in patients with confirmed mild to moderate renal impairment (see section 4.3). Patients on ZYLAMENE SR 800 should have renal function monitored (with serum creatinine levels measured) prior to starting treatment. Renal function should then be monitored periodically during treatment, for example every 3 months for the first year, then 6 monthly for the next 4 years and annually thereafter, based on individual patient history. Medical practitioners should take into account risk factors such as prior and concomitant medications, duration and severity of disease and concurrent illnesses. Treatment with ZYLAMENE SR 800 should be discontinued if renal function deteriorates. If dehydration develops, normal electrolyte and fluid balance should be restored as soon as possible.

Blood dyscrasias

Serious blood dyscrasias (some with fatal outcome) have been reported very rarely with mesalazine, as in ZYLAMENE SR 800. Haematological investigations, including a complete blood count, may be performed prior to initiation and whilst on therapy, according to the medical practitioner’s judgement. Such tests should be done immediately if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Treatment should be stopped if there is suspicion or evidence of blood dyscrasia.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment, as in ZYLAMENE SR 800 (see section 4.8).

ZYLAMENE SR 800 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.

Liver impairment

There have been reports of increased liver enzyme levels in patients taking mesalazine, as in ZYLAMENE SR 800. Caution is advised if ZYLAMENE SR 800 is given to patients with liver impairment (see section 4.3).

Pulmonary disease

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with ZYLAMENE SR 800.

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported with mesalazine, as in ZYLAMENE SR 800. In case of previous mesalazine-induced cardiac hypersensitivity ZYLAMENE SR 800 must not be reintroduced. Caution should be used in patients with previous myo- or pericarditis of allergic background regardless of its origin.

Tablets in stool

There has been limited reports of intact tablets in the stool. What appear to be intact tablets may in some cases represent largely empty shells of the tablet coating. ZYLAMENE SR 800 tablets release their content in the lower gut even if the coating does not dissolve entirely. Once pH 7,0 is reached, cracks in the coating are sufficient for the release of mesalazine from the tablets. This process is irreversible from here on and mesalazine will therefore be released continuously, independent of intestinal pH. If tablets are observed in the stool repeatedly, the patient should consult his/her medical practitioner.

Children

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

Sodium

ZYLAMENE SR 800 contains less than 1 mmoL sodium (23 mg) per modified-release tablet, that is to say it is essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

ZYLAMENE SR 800 should not be given with lactulose or similar preparations, which lower stool pH and may prevent release of mesalazine.

Sulfasalazine decreases the absorption of digoxin. There are no data on interaction of digoxin with ZYLAMENE SR 800.

There is weak evidence that ZYLAMENE SR 800 might decrease the anticoagulant effect of warfarin; frequent international normalised ratio (INR) monitoring is advisable.

ZYLAMENE SR 800 can increase the immunosuppressive effects of azathioprine, 6 mercaptopurine or thioguanine. Life-threatening infection can occur. Patients should be closely observed for signs of infection and immunosuppression. Haematological parameters, such as leucocyte and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy.
If white blood cells are stable after 1 month, testing every 4 weeks for the following 12 weeks followed by 3 monthly monitoring intervals appears to be justified.

Concurrent use of other known nephrotoxic medicines, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and azathioprine, may increase the risk of renal reactions (see section 4.4).

The uricosuric activity of sulfinpyrazone and the diuretic effect of furosemide can be reduced.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

Mesalazine is known to cross the placental barrier, but the limited data available on its use in pregnant women do not allow accurate assessment of possible adverse effects.

ZYLAMENE SR 800 should therefore be used with caution during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Breastfeeding

Low concentrations of mesalazine and higher concentrations of its *N*-acetyl metabolite have been detected in human milk. While the clinical significance of this has not been determined, caution should be exercised when ZYLAMENE SR 800 is administered to a nursing woman.

Hypersensitivity reactions like diarrhoea cannot be excluded. Therefore, if the suckling neonate develops suspected adverse reactions, consideration should be given to discontinuation of breastfeeding or discontinuation of treatment of the mother.

4.7 Effects on ability to drive and use machines

ZYLAMENE SR 800 may influence on the ability to drive vehicles or operate machines.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent:	anaemia, eosinophilia (as part of an allergic reaction), altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia)
Frequency unknown:	bone marrow depression, blood disorder

Immune system disorders

Less frequent: hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis

Nervous system disorders

Frequent: headache

Less frequent: paraesthesia, tinnitus, dizziness, peripheral neuropathy, vertigo

Cardiac disorders

Less frequent: myocarditis, pericarditis

Respiratory, thoracic and mediastinal disorders

Less frequent: allergic and fibrotic lung reactions (including dyspnoea, bronchospasm cough, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), interstitial pneumonia, eosinophilic pneumonia, lung disorder

Frequency unknown: pleurisy pneumonia

Gastrointestinal disorders

Frequent: dyspepsia, nausea, vomiting, diarrhoea, abdominal pain

Less frequent: acute pancreatitis, flatulence, exacerbation of the symptoms of colitis

Hepatobiliary disorders

Less frequent: changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis, abnormal hepatic function, abnormal liver function tests

Frequency unknown: increased blood bilirubin

Skin and subcutaneous tissue disorders

Frequent: rash

Less frequent: pruritus, urticaria, photosensitivity*, alopecia, lupus erythematosus-like reactions, bullous skin reactions, erythema multiforme

Frequency unknown: Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal and connective tissue disorders

Frequent: myalgia, arthralgia

Frequency unknown: lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia

Renal and urinary disorders

Less frequent: impairment of renal function including acute and chronic interstitial nephritis, renal insufficiency, nephrotic syndrome and renal failure, which may be reversible on early withdrawal

Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

Reproductive system and breast disorders

Less frequent: oligospermia (reversible)

General disorders and administration site conditions

Less frequent: pyrexia, chest pain

Frequency unknown: intolerance to mesalazine with increased C-reactive protein and/or exacerbation of symptoms of underlying disease

Investigations

Frequency unknown: increased blood creatinine, amylase, red blood cell sedimentation rate, lipase and blood urea nitrogen (BUN), decreased weight and creatinine clearance.

Description of selected adverse reactions:

An unknown number of the above-mentioned undesirable effects are probably associated with the underlying inflammatory bowel disease (IBD) rather than ZYLAMENE SR 800 medicine. This holds true especially for gastrointestinal undesirable effects, arthralgia and alopecia.

**Photosensitivity:*

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

Paediatric population:

There is only limited safety experience with the use of ZYLAMENE SR 800 tablets in the paediatric population. It is expected that the target organs of possible adverse reactions in the paediatric population are the same as for adults (heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of ZYLAMENE SR 800 is important. It allows continued monitoring of the benefit/risk balance of ZYLAMENE SR 800. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdosage include that of salicylism: mixed acidosis-alkalosis, hyperventilation, pulmonary oedema, dehydration as a result of sweating and vomiting, and hypoglycaemia. There is no specific antidote for ZYLAMENE SR 800 overdose and treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 11.10 Medicines acting on gastrointestinal tract, others.

Pharmacotherapeutic group: Aminosalicylic acid and similar agents.

ATC code: A07EC02.

Mesalazine is thought to have a topical anti-inflammatory effect on the intestinal mucosa, where it has been shown to inhibit prostaglandin and leukotriene synthesis, release of reactive oxygen species and other actions.

5.2 Pharmacokinetic properties

ZYLAMENE SR 800 tablets are coated with an acrylic-based resin. Tablets coated with this specific resin have been shown to delay release of mesalazine until it reaches the terminal ileum and beyond.

Absorption

Based on cumulative urinary recovery of 5-aminosalicylic acid and its metabolite, *N*-acetyl-5-aminosalicylic acid (*N*-Ac-5-ASA), from single dose studies in healthy volunteers, approximately 20 % of the orally administered mesalazine in mesalazine 800 mg modified-release tablets is systemically absorbed, leaving the remainder available for local action and elimination in the faeces. Pharmacokinetics studies with mesalazine 800 mg modified-release tablets indicated that the t_{max} for mesalazine and its metabolite, *N*-Ac-5-ASA, is prolonged, reflecting the modified release characteristics, and ranged from 4 to 12 hours.

Distribution

The extent of systemic exposure to mesalazine, based on AUC and Ae %, following oral administration of mesalazine 800 mg modified-release tablets, is similar in fasted and fed subjects.

Large inter-subject variability in the plasma concentrations and terminal exponential half-lives ($t_{1/2}$) of mesalazine and *N*-Ac-5-ASA is seen following administration of mesalazine 800 mg modified-release tablets.

Biotransformation

The absorbed mesalazine is rapidly acetylated in the gut mucosal wall and by the liver to *N*-Ac-5-ASA, which is excreted mainly by the kidney.

Elimination

The mean $t_{1/2}$ for mesalazine and *N*-Ac-5-ASA are usually about 12 hours, but may vary from 2 to 15 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Colloidal silicon dioxide

Magnesium stearate (E572)

Microcrystalline cellulose [E460(i)]

Povidone

Sodium starch glycolate

Talc (E553b)

Coating:

Acetyl tributyl citrate

Iron oxide red (E172)

Methacrylic acid copolymer

Talc (E553b)

Titanium dioxide (E171)

Black ink:

Opacode Black [containing ammonium hydroxide (E527), black iron oxide (E172), propylene glycol (E1520), shellac (E904)].

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep in the original container until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

White HDPE bottle with a child-resistant closure containing 60 or 90 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park, Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBER

56/11.10/0648

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

19 March 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.