PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

ZYLAMENE SR 1 200 prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 200 mg mesalazine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

Pale red-brown, oval-shaped, biconvex, bevelled, film-coated tablets debossed with ‘711’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults, including the elderly (> 65 years):

For induction of remission: 2,4 g to 4,8 g (two to four tablets) should be taken once daily. The highest dose of 4,8 g/day is recommended for patients not responding to lower doses of

ZYLAMENE SR. When using the highest dose (4,8 g/day), the effect of the treatment should be evaluated at 8 weeks.

For maintenance of remission: 2,4 g (two tablets) should be taken once daily.

Special populations

Hepatic or renal impairment:

Specific studies have not been performed to investigate ZYLAMENE SR in patients with hepatic or renal impairment (see sections 4.3 and 4.4).

Paediatric population

ZYLAMENE SR is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

Method of administration

ZYLAMENE SR is intended for once daily, oral administration. ZYLAMENE SR must not be crushed or chewed and should be swallowed whole, with or without food.

4.3 Contraindications

- History of hypersensitivity to salicylates (including mesalazine) or any of the excipients of ZYLAMENE SR (see section 6.1).
- Severe renal impairment (GFR < 30 mL/min/1,73 m^2) and/or severe hepatic impairment.

4.4 Special warnings and precautions for use

Use in the elderly should be with caution and is subject to patients having a normal renal function.

Reports of renal impairment, including minimal change nephropathy and acute/chronic interstitial

nephritis, have been associated with preparations containing mesalazine and pro-drugs of mesalazine. ZYLAMENE SR should be used with caution in patients with confirmed mild to moderate renal impairment. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and at least twice a year, while on treatment.

Patients with chronic lung function impairment, especially asthma, are at risk of hypersensitivity reactions and should be closely monitored.

Following mesalazine treatment, such as ZYLAMENE SR, serious blood dyscrasias have been reported. If the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat, haematological investigations should be performed. If there is suspicion of blood dyscrasia, treatment should be terminated (see sections 4.5 and 4.8).

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported. Caution should be used in prescribing ZYLAMENE SR to patients with conditions predisposing to the development of myo- or pericarditis. If such hypersensitivity reaction is suspected, products containing mesalazine must not be reintroduced.

Mesalazine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare-up of inflammatory bowel disease. Although the exact frequency of occurrence has not been determined, it has occurred in patients in controlled clinical trials of mesalazine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required and products containing mesalazine, as in ZYLAMENE SR, must not be reintroduced.

There have been reports of increased liver enzyme levels in patients taking preparations

containing mesalazine. Caution is recommended if ZYLAMENE SR is administered to patients with mild or moderate hepatic impairment.

Caution should be exercised when treating patients allergic to sulfasalazine due to the potential risk of cross sensitivity reactions between sulfasalazine and mesalazine.

Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of ZYLAMENE SR.

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

Porphyria:

Safety has not been established.

Sodium:

ZYLAMENE SR contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially sodium free.

4.5 Interactions

Medicine interaction studies in healthy adult subjects have been conducted to investigate the effect of mesalazine, as in ZYLAMENE SR, on the pharmacokinetics and safety of three commonly used antibiotics. There were no clinically significant interactions of mesalazine with amoxicillin, metronidazole or sulfamethoxazole.

The following medicine interactions have been reported:

- Caution is recommended for the concomitant use of ZYLAMENE SR with known nephrotoxic medicines, including nonsteroidal anti-inflammatory drugs (NSAIDs) and azathioprine, as these may increase the risk of renal adverse reactions.
- Mesalazine inhibits thiopurine methyltransferase. In patients receiving azathioprine or 6-mercaptopurine and/or any other medicines known to cause myelotoxicity, caution is recommended for concurrent use of ZYLAMENE SR as this can increase the potential for blood dyscrasias, bone marrow failure and associated complications (see sections 4.4 and 4.8).
- Administration with coumarin-type anticoagulants, e.g. warfarin, could result in decreased anticoagulant activity. Prothrombin time should be closely monitored if this combination is essential.

ZYLAMENE SR is recommended to be administered without regard to food (see sections 4.2 and 5.2).

Interference with laboratory tests:

Use of ZYLAMENE SR may lead to falsely elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalazine's main metabolite, *N*-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Mesalazine as in ZYLAMENE SR is known to cross the placental barrier.

Congenital malformations and other adverse outcomes (including an event of hydrops fetalis and

fetal anaemia in one infant) were reported in infants born to mothers who were exposed to mesalazine during pregnancy.

Breastfeeding

Low concentrations of mesalazine and higher concentrations of its *N*-acetyl metabolites have been detected in human breast milk. Acute diarrhoea has been reported in breastfed infants of mothers exposed to mesalazine. ZYLAMENE SR is not recommended for mothers breastfeeding their infants.

Fertility

Data on mesalazine show no sustained effect on male fertility.

4.7 Effects on ability to drive and use machines

ZYLAMENE SR can cause side effects, such as dizziness and somnolence. Caution is advised before driving a vehicle or operating machinery, until the effects of ZYLAMENE SR are known.

4.8 Undesirable effects

The most frequent reported adverse drug reactions (ADRs) during acute treatment were colitis, abdominal pain, abnormal liver function test, diarrhoea, flatulence, nausea, headache, which were not dose related and occurred in less than 3 % of patients receiving mesalazine.

Adverse drug reactions (ADRs) associated with mesalazine		
System organ class	**Frequency**	**Adverse drug reaction**
Blood and lymphatic system disorders	*Less frequent:*	Thrombocytopenia, agranulocytosis
	Frequency unknown:	Aplastic anaemia, leukopenia, neutropenia, pancytopenia

Immune system disorders	*Frequent:*	Hypersensitivity
	Frequency unknown:	Anaphylactic reaction, adverse drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema
Nervous system disorders	*Frequent:*	Headache
	Less frequent:	Dizziness, somnolence, tremor
	Frequency unknown:	Increased intracranial pressure, neuropathy
Ear and labyrinth disorders	*Less frequent:*	Ear pain
Cardiac disorders	*Less frequent:*	Tachycardia
	Frequency unknown:	Myocarditis, pericarditis
Vascular disorders	*Less frequent:*	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	*Less frequent:*	Pharyngo-laryngeal pain
	Frequency unknown:	Hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis), bronchospasm
Gastrointestinal disorders	*Frequent:*	Abdominal distension, abdominal pain, colitis, diarrhoea, dyspepsia, vomiting, flatulence, nausea
	Less frequent:	Pancreatitis, rectal polyp
Hepatobiliary disorders	*Frequent:*	Abnormal liver function test
	Less frequent:	Increased alanine aminotransferase (ALT)
	Frequency unknown:	Hepatitis, hepatotoxicity, cholelithiasis

Skin and subcutaneous tissue disorders	*Less frequent:*	Acne, alopecia, urticaria, pruritus, rash, photosensitivity
	Frequency unknown:	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	*Frequent:*	Arthralgia, back pain
	Less frequent:	Myalgia
	Frequency unknown:	Systemic lupus erythematosus-like syndrome, lupus-like syndrome
Renal and urinary disorders	*Less frequent:*	Renal failure, nephrolithiasis
	Frequency unknown:	Interstitial nephritis, nephrotic syndrome
Reproductive system and breast disorders	*Frequency unknown:*	Oligospermia (reversible)
General disorders and administration site conditions	*Frequent:*	Asthenia, fatigue, face oedema, pyrexia

Description of selected adverse reactions

Increased intracranial pressure:

Cases of increased intracranial pressure with papilloedema (pseudotumor cerebri or benign intracranial hypertension) have been reported with the use of mesalazine. If undetected, this condition may result in restriction of the visual field and may progress to permanent loss of vision. ZYLAMENE SR should be discontinued if this syndrome occurs.

Photosensitivity:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ZYLAMENE SR is important. It allows continued monitoring of the benefit/risk balance of ZYLAMENE SR. 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

ZYLAMENE SR is an aminosalicylate, and signs of salicylate toxicity include tinnitus, vertigo, headache, confusion, drowsiness, pulmonary oedema, dehydration because of sweating, diarrhoea and vomiting, hypoglycaemia, hyperventilation, disruption of electrolyte balance and blood pH and hyperthermia.

Conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Hypoglycaemia, fluid and electrolyte imbalance should be corrected by the administration of appropriate therapy. Adequate renal function should be maintained.

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: A07E C02.

Mechanism of action

Mesalazine (5-aminosalicylic acid) is a salicylate that is used for its local effects in the treatment of inflammatory bowel disease.

The mechanism of action of mesalazine is not fully understood but appears to have a topical anti-inflammatory effect on the colonic epithelial cells. Mucosal production of arachidonic acid

metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Mesalazine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key pro-inflammatory cytokines. More recently, it has been proposed that impairment of PPAR-γ nuclear receptors (γ-form of peroxisome proliferator-activated receptors) may be implicated in ulcerative colitis. PPAR-γ receptor agonists have shown efficacy in ulcerative colitis and evidence has been accumulating that the mechanism of action of mesalazine may be mediated by PPAR-γ receptors.

Pharmacodynamic effects

The pharmacodynamic action of mesalazine occurs in the colonic/rectal mucosae local to the delivery of the medicine from ZYLAMENE SR into the lumen.

There is information suggesting that the severity of colonic inflammation in ulcerative colitis patients treated with mesalazine is inversely correlated with mucosal concentrations of mesalazine. However, plasma concentrations representing systemically absorbed mesalazine are not believed to contribute extensively to efficacy.

5.2 Pharmacokinetic properties

Absorption

Gamma-scintigraphy studies have shown that a single dose of mesalazine 1,2 g passed rapidly and intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labelled tracer in the colon, indicating that mesalazine had spread throughout this region of the gastrointestinal tract. Complete disintegration and release of mesalazine occurred after approximately 17,4 hours.

The total absorption of mesalazine 2,4 g or 4,8 g given once daily for 14 days to healthy volunteers

was found to be approximately 21 – 22 % of the administered dose.

In a single-dose study, mesalazine 1,2 g, 2,4 g and 4,8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalazine were detectable after 2 hours and reached a maximum by 9 – 12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects. Mesalazine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was dose proportional between 1,2 g and 4,8 g mesalazine. Maximum plasma concentrations (C_{max}) of mesalazine increased approximately dose proportionally between 1,2 g and 2,4 g and disproportionally between 2,4 g and 4,8 g mesalazine, with the dose-normalised value at 4,8 g representing, on average, 74 % of that at 2,4 g based on geometric means.
Administration of a single dose of mesalazine 4,8 g with a high-fat meal (SPD476-106) resulted in further delay in absorption, and plasma concentrations of mesalazine were detectable 4 hours following dosing. However, a high-fat meal increased systemic exposure of mesalazine (mean C_{max}: ↑ 91 %; mean AUC: ↑ 16 %) compared to results in the fasted state. The observed differences in mesalazine exposure due to concomitant food intake are not considered to be clinically relevant. Therefore, ZYLAMENE SR can be taken without regard to food.

In a single- and multiple-dose pharmacokinetic study of mesalazine, 2,4 g or 4,8 g was administered once daily with standard meals to 28 healthy volunteers per dose group. Plasma concentrations of mesalazine were detectable after 4 hours and were maximal by 8 hours after the single dose. Steady state was generally achieved by 2 days after dosing. Mean AUC at steady state was only modestly greater (1,1- to 1,4-fold) than predictable from single-dose pharmacokinetics.

In a single-dose pharmacokinetic study of mesalazine, 4,8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young [18 – 35 years], 28 elderly [65 – 75 years], 15

elderly [> 75 years]). Increased age resulted in increased systemic exposure (up to approximately 2-fold, based on AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) to mesalazine and its metabolite *N*-acetyl-5-aminosalicylic acid, but did not affect the percentage of mesalazine absorbed. Increased age resulted in a slower apparent elimination of mesalazine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Distribution

Following dosing of mesalazine, mesalazine has a small volume of distribution of approximately 18 L. Mesalazine is 43 % bound to plasma proteins when *in vitro* plasma concentrations were 2,5 µg/mL.

Metabolism

The metabolism of mesalazine takes place by acetylation. The only major metabolite of mesalazine (5-aminosalicylic acid) is *N*-acetyl-5-aminosalicylic acid, which is pharmacologically inactive. The metabolite formation occurs by *N*-acetyltransferase (NAT) activity in the liver and in the cytosol of intestinal mucosal cells, principally by NAT-1. Although this enzyme is known to be subject to genetic polymorphism, NAT-1 genotypes have been shown not to be predictive of mesalazine efficacy or toxicity.

Elimination

Elimination of mesalazine is mainly via the renal route following metabolism to *N*-acetyl-5-aminosalicylic acid (acetylation). Of the approximately 21 – 22 % of the dose absorbed, less than 8 % of the dose was excreted unchanged in the urine at steady state after 24 hours, compared with greater than 13 % for *N*-acetyl-5-aminosalicylic acid. The terminal half-lives for mesalazine and its major metabolite after administration of mesalazine 2,4 g and 4,8 g were, on average, 7 – 9 hours and 8 – 12 hours, respectively.

Paediatrics

No pharmacokinetic study was conducted in paediatric patients.

Elderly patients

Systemic exposure to mesalazine increased by up to 2-fold in elderly subjects (> 65 years) compared with younger adult subjects (18 – 35 years) after a 4,8 g single dose of mesalazine. Systemic exposures in individual subjects were inversely correlated to renal function as assessed by estimated creatinine clearance. The potential impact on the safe use of ZYLAMENE SR in the elderly population in clinical practice should be considered (see section 4.4).

Renal impairment

Systematic pharmacokinetic studies were not conducted in subjects with renal impairment.

Hepatic impairment

Systematic pharmacokinetic studies were not conducted in subjects with hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Magnesium stearate

Sodium carboxymethyl cellulose

Sodium starch glycolate

Hypromellose

Microcrystalline cellulose

Methacrylic acid copolymer

Triethyl citrate

Talc

Isopropyl alcohol

Opadry 03F565028 Brown (consisting of hypromellose, talc, macrogol, titanium dioxide [E171], iron oxide red [E172], iron oxide yellow [E172]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle well closed until required for use.

6.5 Nature and contents of container

225 mL white HDPE bottle with child resistant PP cap and activated carbon cannister.

Pack sizes: 60 or 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park, Building B, Ground Floor

22 Karee Street

Centurion

0157

8. REGISTRATION NUMBER

56/11.10/0649

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

06 February 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.