Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

COLIZEM 1,2 g (Enteric Coated Prolonged –Release Tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COLIZEM 1,2 g

Each enteric coated prolonged–release tablet contains mesalazine 1, 2 g.

Sugar free

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Enteric Coated Prolonged –Release Tablet

COLIZEM 1,2g

Reddish brown, oval shaped film coated tablets printed with RG70 in black color on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

COLIZEM 1,2 g is indicated for the treatment and maintenance of remission in ulcerative colitis

4.2 Posology and method of administration

Adults, including the elderly (>65 years):

For induction of remission: 2,4 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 **COLIZEM**. 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 **COLIZEM** in patients with hepatic or renal impairment (see section 4.3)

Paediatric population

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

Specific studies have not been reported to investigate mesalazine in patients with hepatic or renal impairment (see **section 4.3** and **4.4**).

Method of administration

COLIZEM 1, 2 g is intended for once daily, oral administration. The tablets must not be crushed or chewed and should be taken with food.

4.3 Contraindications

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

4.4. Special warnings and precautions for use

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

Reports of renal impairment, including minimal change nephropathy, and acute/chronic interstitial nephritis and renal failure have been associated with mesalazine as in **COLIZEM**. **COLIZEM** 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, whilst on treatment.

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

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

Mesalazine as in **COLIZEM** has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence has not been reported, it has been reported to occur in patients in reported studies of mesalazine or sulphasalazine. 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 **COLIZEM** must not be reintroduced.

There have been reports of increased liver enzyme levels in patients taking preparations containing mesalazine such as **COLIZEM.** Caution is recommended if **COLIZEM** is administered to patients with hepatic impairment.

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

Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of **COLIZEM.**

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.

Porphyria

Safety has not been established.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per the maximum recommended dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Caution is recommended for the concomitant use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine as these may increase the risk of renal adverse reactions.

No clinically significant interactions of mesalazine with amoxicillin, metronidazole or sulfamethoxazole have been reported

Mesalazine inhibits thiopurine methyltransferase. In patients receiving azathioprine or 6-mercaptopurine and/or any other active substances known to cause myelotoxicity, caution is recommended for concurrent use of mesalazine as this can increase the potential for blood dyscrasias, bone marrow failure, and associated complications.

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.

Interference with laboratory tests

Use of mesalazine may lead to spuriously 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-acetylaminosalicylic 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.

There is limited reported experience with mesalazine in pregnancy. Mesalazine crosses the placental barrier, but provides foetal concentrations much lower than those reported with adult therapeutic use. The reported animal studies do not indicate harmful effects of mesalazine in pregnancy, embryonal/foetal development, parturition or postnatal development. Adverse outcomes (including disturbances in blood counts such a leukopenia, thrombocytopenia, and anaemia) were reported in infants born to mothers who were exposed to mesalazine during pregnancy. Mesalazine should be used during pregnancy only when the benefits outweigh the risks. Caution should be exercised when using high doses of mesalazine. Congenital malformations and other adverse outcomes (including one event of hydrops fetalis and foetal anaemia in one infant) were reported in infants born to mothers who were exposed to mesalamine during pregnancy.

Breastfeeding

Low concentrations of mesalazine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk.
Mesalazine is excreted in breast milk. Acute diarrhoea has been reported in breastfed infants. **COLIZEM** is not recommended for mothers breastfeeding their infants.

Acetylated form of mesalazine is excreted in breast milk at higher concentration. Caution should be exercised if using mesalazine while breast-feeding and only if the benefit outweighs the risks. Sporadically acute diarrhoea has been reported in breast fed infants.

Fertility

No sustained effect on male fertility has been reported with mesalazine.

4.7 Effects on ability to drive and use machines

No currently available reported data suggest that mesalazine affects the ability to drive or operate machinery.

COLIZEM may cause dizziness and somnolence which may affect the ability to drive or operate machinery.

4.8 Undesirable effects

The most frequently reported ADRs during acute treatment were flatulence, colitis, abdominal pain, abnormal liver function test, diarrhoea, nausea or headache, which were not dose related.

System Organ Class	**Frequent**	**Less Frequent**	**Frequency Unknown**
Blood and lymphatic system disorders		Thrombocytopenia	Agranulocytosis, Aplastic anaemia, Leukopenia, Neutropenia, Pancytopenia,
Immune system disorders	Hypersensitivity (including rash, pruritis, urticaria and facial oedema		Angioedema. Anaphylactic reaction, drug reaction with eosinophilia and systemic symptoms (DRESS)
Nervous system disorders	Headache	Dizziness, Somnolence, Tremor	Neuropathy Intracranial pressure increased,
Ear and labyrinth disorders		Ear pain	

Cardiac disorders		Tachycardia	Myocarditis, Pericarditis
Vascular disorders		Hypertension, Hypotension	
Respiratory, thoracic and mediastinal disorders		Pharyngolaryngeal pain	Hypersensitivity pneumonitis (including interstitial Pneumonitis, eosinophilic pneumonitis) Allergic alveolitis, Bronchospasm, Interstial lung disease
Gastrointestinal disorders	Flatulence, Nausea, Abdominal distension, Abdominal pain, Colitis, Diarrhoea, Dyspepsia, Vomiting	Pancreatitis, rectal polyp	
Hepatobiliary disorders	Abnormal liver function test (e.g., ALT; AST, Bilirubin)	Increased alanine aminotransferase	Hepatotoxicity, Cholelithiasis, hepatitis
Skin and subcutaneous tissue disorders		Acne, alopecia, prurigo, pruritus, rash, urticarial,	Stevens-Johnson syndrome, photosensitivity
Musculoskeletal, connective tissue and bone disorders	Arthralgia, back pain		Lupus-like syndrome, Systemic-lupus erythematosus-like syndrome Myalgia
Renal and urinary disorders		Renal failure, Nephrolithiasis	Interstitial nephritis, Nephrotic syndrome, Nephrogenic,

			diabetes insipidus
Reproductive system and breast disorders			Oligospermia (reversible)
General disorders and administrative site disorders	Asthenia, Face oedema, Fatigue, Pyrexia		

Reporting of suspected adverse reactions

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

4.9 Overdose

COLIZEM is an aminosalicylate, and signs of salicylate toxicity include tinnitus, vertigo, headache, confusion, drowsiness, pulmonary oedema, dehydration as a result of sweating, diarrhoea and vomiting, hypoglycaemia, hyperventilation, disruption of electrolyte balance and blood-pH and hyperthermia.

Conventional therapy for **COLIZEM** 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. Medicines acting on the Gastro-intestinal tract, other

Pharmacotherapeutic group: Aminosalicylic acid and similar agents

ATC code: A07E C02

Pharmacodynamic properties

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 pharmacodynamic action of mesalazine occurs in the colonic/rectal mucosae. There is reported information suggesting that the severity of colonic inflammation in ulcerative colitis patients treated with mesalazine is inversely correlated with mucosal concentrations of mesalazine.

5.2 Pharmacokinetic properties

Absorption

Gamma-scintigraphy studies have shown that a single dose of **COLIZEM**

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 of **COLIZEM** and complete release of mesalazine occurred after approximately 17,4 hours.

The total absorption of mesalazine from **COLIZEM** 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, **COLIZEM** 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 **COLIZEM**. Maximum plasma concentrations (Cmax) of mesalazine increased approximately dose proportionally between 1,2 g and 2,4 g and disproportionally between 2,4 g and 4,8 g **COLIZEM**, with the dose-normalized 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 **COLIZEM** 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 Cmax: ↑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, **COLIZEM** can be taken without regard to food.

In a single- and multiple-dose pharmacokinetic study of **COLIZEM**, 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 achieved generally 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 **COLIZEM**, 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 AUC0-t, AUC0-∞, and Cmax) 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 **COLIZEM**, 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 **COLIZEM** 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 paediatrics.

Elderly

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 **COLIZEM**.

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 **COLIZEM** in the elderly population in clinical practice should be considered (see section 4.4).

Renal Impairment

Systematic pharmacokinetic study was not conducted in subjects with renal impairment.

Hepatic Impairment

Systematic pharmacokinetic study was not conducted in subjects with hepatic impairment.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Carboxymethyl Cellulose Sodium(Blanose CMC 7MF PH), Carboxymethyl Cellulose Sodium(Blanose CMC 7HXF PH), Colloidal Silicon Dioxide NF, Hypromellose, Sodium Starch Glycollate, Magnesium Stearate, Microcrystalline Cellulose and Puried Water

Enteric Coating

Ferric Oxide NF (Red), Isopropyl Alcohol, Methacrylic Acid and Methyl Methacrylate Copolymer (1:1) NF (Type A) (EUDRAGIT L 100),

Methacrylic Acid and Methyl Methacrylate Copolymer (1:2) NF (Type B) (EUDRAGIT S 100),

Polyethylene Glycol 6000 NF (Finegrade, Clariant),

Purified Water , Talc, Titanium Dioxide, Triethyl Citrate NF

Tablet Printing Material

Isopropyl Alcohol, Opacode Black S-1-17823

Opacode Black S-1-17823

Ammonium Hydroxide 28% NF, Oxide Black NF, Isopropyl Alcohol, N-Butyl Alcohol NF, Propylene Glycol, Shellac Glaze~45% (20% esterified) in Ethanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from moisture.

Return all unused or expired medicines to your pharmacist for safe disposal.

Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

6.5 Nature and contents of container

HDPE Bottle Pack:

The product can be supplied in a pack size of 60's and 120's comprising of an HDPE bottle and a child resistant closure with an induction seal liner.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1

Roodepoort, 1724

South Africa

8 REGISTRATION NUMBER(S)

57/11/0064

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 December 2024

10 DATE OF REVISION OF THE TEXT

10 December 2024