SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ASACOL ENEMA (2 g, rectal suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 50 ml enema: Mesalazine (5-aminosalicylic acid) 2 g

Antioxidant: Sodium metabisulphite 0,05 g

Preservative: Sodium benzoate 0,1 % m/v

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal suspension.

Brownish suspension with a characteristic odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ASACOL ENEMA is used for the treatment and maintenance of remission in ulcerative colitis.

4.2 Posology and method of administration

Posology

Adult dose: Two gram administered at night per rectum.

Method of administration

Rectal use.

Before using the enema: The bottle should be warmed to body temperature in a basin or bowl of warm water for about 10 minutes. The bottle should be shaken well immediately before inserting the enema.

Inserting the enema: The screw cap must be twisted off from the bottle and the applicator tip must be twisted on. The applicator tip can be lubricated with vaseline. For the enema administration the patient should lie on the left side

with the left leg extended and the right leg bent. After inserting the applicator tip into the rectum the liquid should be pressed out gently and slowly. The tip should be withdrawn with the container still compressed.

The patients should try to stay in the administration position for 5 to 10 minutes or until the urge to pass the enema has disappeared. The enema should be retained in the bowel if possible without evacuation of the bowels until the next morning.

4.3 Contraindications

Hypersensitivity to mesalazine or to any of the excipients (see section 6.1).

History of allergy to salicylates.

Severe liver impairment.

Severe renal impairment (GFR less than 30 ml per minute).

Safety in pregnancy and lactation has not been established.

Safety and efficacy have not been established in children.

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 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.

Renal impairment

Caution should be exercised in patients with impaired renal function raised serum creatinine or proteinuria. The possibility of mesalazine-induced nephrotoxicity, which may be reversible on withdrawal, should be suspected in patients developing renal failure during treatment. Treatment with ASACOL ENEMA should be stopped immediately if there is evidence of renal impairment and patients should seek immediate medical advice.

Serious skin side effects

Serious cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with ASACOL ENEMA treatment. ASACOL ENEMA must be

discontinued at the first appearance of symptoms of serious skin adverse reactions such as skin rash, mucosal lesions or any other sign of hypersensitivity.

Nephrolithiasis

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

Hepatic impairment

There have been reports of increased liver enzyme levels in patients taking preparations containing mesalazine. Caution is recommended if ASACOL ENEMA is administered to patients with liver impairment (see section 4.3).

Blood dyscrasia

Serious blood dyscrasia has been reported.

Patients should be monitored with care to avoid blood dyscrasia resulting from developing bone marrow depression. Haematological investigations including a complete blood count should be performed prior to initiation and whilst on therapy. Such tests are generally recommended within 14 days of initiation of therapy with 2 to 3 repeat tests each after another 4 weeks. If the results are normal, tests are recommended quarterly. In case additional signs of illness appear, further control tests are necessary. This procedure is to be followed, especially if a patient develops signs and symptoms suggestive of blood dyscrasia during treatment, such as unexplained bleeding, haematoma, purpura, anaemia, persistent fever or sore throat.

Treatment with ASACOL ENEMA should be stopped immediately if there is a suspicion or evidence of blood dyscrasia (signs of unexplained bleeding, bruising, purpura, anaemia, persistent or sore throat) and patients should seek immediate medical advice.

Lung function impairment

In case of lung function impairment, especially asthma, patients need to be monitored very closely.

Cardiac hypersensitivity reactions

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

Hypersensitivity to sulphasalazine

In patients with a history of hypersensitivity to sulphasalazine, therapy should be initiated only under close medical supervision. Treatment must be stopped immediately if acute symptoms of intolerance occur such as abdominal cramps, acute abdominal pain, fever, severe headache or rash.

Gastric and duodenal ulcers

In case of existing gastric or duodenal ulcers, treatment should begin with caution based on theoretical grounds.

Geriatric patients

Use in the elderly should be handled with caution and ASACOL ENEMA should only be prescribed to patients having a normal or non-severely impaired renal and hepatic function.

Co-administration of immunosuppressive medicines such as azathioprine or 6-MP can precipitate leucopoenia (see section 4.5).

Concurrent use of NSAIDs or azathioprine may increase the risk of renal reactions (see section 4.5).

Excipients

ASACOL ENEMA contains 100 mg of sodium benzoate per dose, equivalent to 100 mg/100 ml. Sodium benzoate may cause non-immunological immediate contact reactions by a possible cholinergic mechanism.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

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

ASACOL ENEMA can increase the myelosuppressive effects of azathioprine and 6-mercaptopurine or thioguanine. As a result, life-threatening infection can occur.

Patients should be closely observed for signs of infection and myelosuppression. Haematological parameters, especially the leucocyte, thrombocyte, and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy, see section 4.4. If white blood cells are stable after 1 month, testing every 4 weeks for the following 12 weeks followed by monitoring in 3 months intervals appears to be justified.

Concurrent use of nephrotoxic medicines, such as NSAIDs or azathioprine may increase the risk of renal adverse reactions (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Lactation

Low concentrations of mesalazine and its N-acetyl metabolite have been detected in human breast milk. Safety in lactation has not been established.

Fertility

No effects on fertility have been observed.

4.7 Effects on ability to drive and use machines

ASACOL ENEMA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

Organ specific allergic reactions affecting the heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue have been reported.

Treatment must be stopped immediately if acute symptoms of intolerance occur such as abdominal cramps, acute abdominal pain, fever, severe headache and rash.

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

Side effects are presented by system organ class according to the following frequencies: Very common: ≥ 10 % patients; common: ≥ 1 % and < 10 % patients; uncommon: ≥ 0,1 % and < 1 % patients; rare: ≥ 0,01 % and < 0,1 % patients.

The only common undesirable side effects were medicine ineffective (3,0 %) and flatulence (1,5 %).

b) Tabulated summary of adverse reactions

System Organ Class	**Rare ≥ 1/10 000 to < 1/1 000**	**Very rare < 1/10 000**	**Frequency not known**
Blood and lymphatic system disorders		altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia) and eosinophilia (as part of an allergic reaction)	
Immune system disorders		hypersensitivity reactions such as allergic exanthema, medicine fever, lupus erythematosus syndrome, pancolitis	Hypersensitivity reaction including anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Nervous system disorders	headache, dizziness	peripheral neuropathy	
Cardiac disorders	myocarditis, pericarditis		
Respiratory, thoracic and mediastinal disorders	interstitial pneumonia	allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis	pleurisy
Gastrointestinal disorders	abdominal pain, diarrhoea, flatulence, nausea, vomiting	acute pancreatitis	

Hepato-biliary disorders		changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic	
Skin and subcutaneous tissue disorders	photosensitivity*	alopecia	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders		myalgia, arthralgia	
Renal and urinary disorders	nephrotic syndrome, renal failure which may be reversible on withdrawal	impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	nephrolithiasis**
Reproductive system and breast disorders		oligospermia (reversible)	
General disorders and administration site conditions			intolerance to mesalazine with exacerbation of symptoms of underlying disease, local reaction

* see section c)

** see section 4.4 for further information

c) Description of selected adverse reactions

An unknown number of adverse reactions mentioned above is probably associated to the underlying IBD rather than ASACOL ENEMA. This holds true especially for gastrointestinal adverse reactions.

To avoid blood dyscrasia resulting from developing bone marrow depression patients should be monitored with care, see section 4.4.

Co-administration of ASACOL ENEMA with myelosuppressive medicines such as azathioprine, or 6-MP, or thioguanine, life-threatening infection can occur, see section 4.5.

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 the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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

In case of accidental oral ingestion symptoms of overdosage include that of salicylism, e.g. dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, mental confusion, hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis. Depression of the central nervous system may lead to coma, cardiovascular collapse and respiratory failure.

There is no specific treatment for overdosage of ASACOL ENEMA but early lavage is recommended, if accidentally taken by mouth.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 11.10 Medicines acting on gastro-intestinal tract, special combinations

ATC code: A07EC02

Mesalazine enema acts locally, probably involving the inhibition of prostaglandin and leukotriene synthesis.

5.2 Pharmacokinetic properties

Mesalazine is mostly excreted in the faeces either as 5-aminosalicylic acid (5-ASA) or N-acetyl-5-ASA. About 20 percent of the 5-ASA released in the colon is absorbed and rapidly acetylated to N-acetyl-5-ASA, which is excreted in the urine.

The acetylated metabolite (active ingredient) has a half-life of approximately ten hours and that of the parent compound approximately one hour.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate

Sodium metabisulfite

Purified water

Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

6.5 Nature and contents of container

50 ml single enema.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Road

Irene, Pretoria

0157

8. REGISTRATION NUMBER(S)

Z/11.10/205

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 27 June 1996

10. DATE OF REVISION OF THE TEXT

Date of Revision: 03 July 2023

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