PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr MEZERA®

Mesalazine*

Suppositories, 1 g / suppository, Rectal

Foam, 1 g / actuation (14 actuations per can), Rectal

Mfr. Std.

*(also known as 5-aminosalicylic acid, 5-ASA or mesalamine)

Lower Gastrointestinal Tract Anti-Inflammatory

ATC A07EC02

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Skin	12/2021
7 WARNINGS AND PRECAUTIONS, General	12/2023
7 WARNINGS AND PRECAUTIONS, Renal	12/2023
7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance	12/2023
7 WARNINGS AND PRECAUTIONS, Skin	12/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Suppositories

MEZERA (mesalazine) suppositories are indicated for the treatment of:

- Acute mild to moderate ulcerative proctitis.

Foam

MEZERA (mesalazine) foam enema is indicated for the treatment of:

- Mildly active ulcerative colitis of the sigmoid colon and rectum.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

MEZERA is contraindicated in:

- patients with severe renal impairment (GFR<30mL/min/1.73m^2) (see 7 WARNINGS AND PRECAUTIONS, Renal).
- patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic).
- patients who are hypersensitive to this drug, to salicylates or their derivatives, including acetylsalicylic acid (e.g. Aspirin®), or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- patients with existing gastric or duodenal ulcer.
- patients with urinary tract obstructions.
- infants under 2 years of age.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- *Hepatic Impairment*: MEZERA is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate liver function impairment, caution should be exercised and MEZERA should be used only if the expected benefit clearly outweighs the risks to the patient. Appropriate assessments and monitoring of liver function should be performed prior to and during treatment, at the discretion of the treating physician (see 2 CONTRAINDICATIONS, and 7 WARNINGS AND PRECAUTIONS, Hepatic).
- *Renal Impairment*: MEZERA is contraindicated in patients with severe renal impairment. In patients with mild to moderate renal function impairment, caution should be exercised and MEZERA should be used only if the benefits outweigh the risks. Appropriate assessments of renal function should be done prior to initiation of therapy and periodically while on treatment especially during the initial phase of treatment (see 2 CONTRAINDICATIONS, and 7 WARNINGS AND PRECAUTIONS, Renal).
- *Hematologic*: Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician, given the risk of serious blood dyscrasias when MEZERA is used alone or concomitantly with 6-mercaptopurine or azathioprine. MEZERA should be used only if the benefits clearly outweigh the risks in patients with underlying bleeding or clotting disorders (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

4.2 Recommended Dose and Dosage Adjustment

- Daily dosing is continued until a significant response is achieved or the patient achieves remission. Treatment should be continued for at least 6 weeks, to reach endoscopic and/or histological remission.
- Health Canada has not authorized an indication for pediatric use.

Suppositories

The usual dose of MEZERA suppositories is one suppository containing 1 g of mesalazine, self-administered once daily at bedtime. The suppository should be retained for 1 to 3 hours or longer to achieve the maximum benefit. While the effect of the suppositories may be seen within 3 to 21 days, the usual course of therapy would be from 3 to 6 weeks depending on symptoms and sigmoidoscopic findings.

Foam

The usual dose for MEZERA foam enema is two actuations (each containing 1 g mesalazine for a total daily dose of 2 g mesalazine) to be administered once daily at bedtime.

If the patient has difficulty in holding the amount of foam released with two actuations, the foam can also be administered in two divided doses: one at bedtime and the other during the night (after evacuation of the first single dose) or in the early morning.

4.4 Administration

- The best results are achieved if the bowels are evacuated prior to insertion of MEZERA suppository and administration of MEZERA foam enema.
- MEZERA foam enema should be used at room temperature (between 15 and not more than 30°C). The canister is first fitted with an applicator and then shaken for about 20 seconds before the applicator is inserted into the rectum as far as comfortable for the patient. To administer a dose, the pump dome is fully pushed down and released. Note that the spray will only work properly when held with the pump dome pointing down. Following the first or second activation depending upon the need of the individual patient (see below) the applicator should be held in position for 10-15 seconds before being withdrawn from the rectum.

4.5 Missed Dose

If a dose of MEZERA foam enema or suppository is missed, it should be administered as soon as possible, unless it is almost time for the next dose, in which case, the patient should skip the missed dose and continue as per the regular dosing schedule. A patient should not use two MEZERA doses at the same time to make up for a missed dose.

5 OVERDOSAGE

There is no experience with MEZERA overdosage. However, because mesalazine is an aminosalicylate, the symptoms of overdose may mimic the symptoms of salicylate overdose including confusion, diarrhea, drowsiness, headache, hyperventilation, sweating, tinnitus, vertigo, and vomiting. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration; therefore, measures used to treat salicylate overdose may be applied to mesalazine overdose. Under ordinary circumstances, local mesalazine absorption from the colon is limited.

There is no specific antidote and symptomatic treatment at hospital is required. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Close monitoring of renal function is required in order to maintain adequate renal function.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Rectal	Suppository, 1 g / suppository	Hard fat (Witepsol H-12)
	Foam Enema, 1 g / actuation	Cetostearyl alcohol, disodium edetate, polysorbate 60, propylene glycol, sodium metabisulfite, with a propellant mixture of propane, n butane and isobutane.

MEZERA (mesalamine) products are gluten-free and phthalate-free.

Suppositories

Each smooth light beige, torpedo-shaped MEZERA suppository contains 1 g mesalazine. Each box contains 6 strips of 5 suppositories for a total of 30 suppositories.

Foam

MEZERA foam enema 1 g/actuation is a white-greyish to slightly reddish-violet, creamy firm foam, packaged in an aluminum pressurized container with metering valve containing 80 g of suspension (14 actuations each resulting in release of 1 g mesalazine). Each canister contains foam for 7 days of treatment. The foam canister is packaged together with 14 single-use PVC applicators coated with white soft paraffin and liquid paraffin for administration of the foam. Each actuation of 17.5 – 30 mL delivers 1 g mesalazine.

7 WARNINGS AND PRECAUTIONS

General

Caution should be exercised when treating patients allergic to sulfasalazine due to the potential risk of cross sensitivity reactions between sulfasalazine and mesalazine (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

MEZERA has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

MEZERA foam enema contains 3.44 g propylene glycol in each actuation of MEZERA foam enema. Propylene glycol may cause lactic acidosis, hyperosmolality, hemolysis and CNS depression. Slight to mild skin irritation due to propylene glycol may occur. This medicine contains sodium metabisulphite and cetostearyl alcohol. Sodium metabisulphite may rarely cause severe hypersensitivity reactions and bronchospasm. Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Carcinogenesis and Mutagenesis

Carcinogenicity studies in animals and mutagenicity tests were negative (see 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

Cardiac side effects, including pericarditis and myocarditis have been rarely reported with the use of MEZERA.

Cases of pericarditis have also been reported as manifestation of inflammatory bowel disease. Discontinuation of MEZERA may be warranted in some cases, but rechallenge with MEZERA can be performed under careful clinical observation should the continued therapeutic need for MEZERA be present.

Driving and Operating Machinery

There are no data available on the effects of MEZERA on the ability to drive and use machines.

Gastrointestinal

Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or sulfasalazine (SAS) therapy, should be investigated in order to exclude pericarditis and pancreatitis either as adverse drug reactions to MEZERA or secondary manifestations of inflammatory bowel disease. Acute intolerance syndrome may also cause abdominal pain (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

Hematologic

Following treatment with MEZERA, serious blood dyscrasias (including myelosuppression) have been reported very rarely. The risk is further increased when MEZERA products are used concomitantly with 6 mercaptopurine or azathioprine (see 9.4 Drug-Drug Interactions). Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician. If the patient develops unexplained bleeding, bruising, purpura, anemia, fever or sore throat, hematological investigations should be performed. If there is suspicion of blood dyscrasia, treatment with MEZERA should be discontinued.

MEZERA should be used only if the benefits clearly outweigh the risks in patients with underlying bleeding or clotting disorders.

Hepatic/Biliary/Pancreatic

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with 5-ASA/mesalazine products. Therefore, MEZERA is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised and MEZERA should be used only if the expected benefit clearly outweighs the risks to the patient. Appropriate assessment and monitoring of liver function (e.g. like ALT or AST) should be performed prior to and during treatment, at the discretion of the treating physician.

Renal

Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with MEZERA products and pro-drugs of mesalazine.

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.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g., in toilets cleaned with sodium hypochlorite contained in certain bleaches).

MEZERA is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction, caution should be exercised and MEZERA should be used only if the benefits outweigh the risks.

It is recommended that all patients have an evaluation of renal function (e.g. serum creatinine) prior to initiation of therapy and periodically while on treatment especially during the initial phase of treatment. MEZERA induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. The concurrent use of other known nephrotoxic agents may increase the risk of renal reactions, thus requiring increased monitoring frequency of renal function.

Respiratory

Patients with chronic lung function impairment, especially asthma, are at risk of hypersensitivity reactions with MEZERA products and should be closely monitored. Patients with asthma should be treated with care with MEZERA foam enema since sulfite contained in the foam may cause hypersensitivity reactions. In isolated cases, such hypersensitivity reactions may be experienced also by non-asthmatics.

Sensitivity/Resistance

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to MEZERA or other compounds that contain or are converted to mesalazine. Therefore, caution should be exercised when treating patients allergic to sulfasalazine due to the potential risk of cross sensitivity reactions between sulfasalazine and mesalazine. These patients should be instructed to discontinue therapy if signs of rash or pyrexia become apparent.

Acute Intolerance Syndrome

MEZERA 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 determined, it has occurred in 3% of patients in controlled clinical trials of mesalazine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt treatment discontinuation is required.

Skin

Serious Skin Reaction

Use of mesalazine has been associated with the following serious and life-threatening skin reactions:

- Drug reaction with eosinophilia and systemic symptoms (DRESS),
- Severe cutaneous adverse reactions (SCARs),
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

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.

Photosensitivity

Patients treated with mesalazine or sulfasalazine who have pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Patients should be advised to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate well controlled studies of MEZERA in pregnant women. Mesalazine is known to cross the placental barrier, and no clinical studies have been performed in pregnant women. Premature labor, congenital malformations, and other adverse pregnancy outcomes (including serious events such as ectrodactyly, oligohydramnios, congenital nephrotic syndrome, and fetal tachycardia) were reported in infants born to mothers who were exposed to mesalazine during pregnancy. One case each of fetal anemia and hydrops fetalis were also reported in one infant.

MEZERA should be used during pregnancy only if the benefits clearly outweigh the risks to the foetus.

7.1.2 Breast-feeding

No controlled studies with MEZERA during breast-feeding have been carried out. In nursing mothers, mesalazine and its inactive main metabolite, N-acetyl-5-ASA, are excreted in breast milk. The concentration of mesalazine is much lower than in maternal blood, but the metabolite N- acetyl-5-ASA appears in similar concentrations. Caution should be exercised, and MEZERA should be used in nursing mothers only if the benefits outweigh the risks.

When MEZERA is used in nursing women, infants should be monitored for changes in stool consistency. If the infant develops diarrhea, breast-feeding should be discontinued. Cases of diarrhea in breastfed infants exposed to mesalazine have been reported.

The propylene glycol component of MEZERA rectal foam is susceptible to reach the foetus and found in breast milk. Caution should be exercised and MEZERA rectal foam should be used in nursing mothers only if the benefits outweigh the risks.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Specific clinical studies of MEZERA in geriatric population have not been conducted. Some clinical studies of MEZERA included insufficient numbers of subject's ≥ 65 years of age. However, the results from these studies cannot be used to determine whether they respond differently from younger subjects. Other reported clinical experience with mesalazine has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function or concomitant disease or other drug therapy.

MEZERA is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, closer monitoring renal function may be needed (see 2 CONTRAINDICATIONS, and 7 WARNINGS AND PRECAUTIONS, Renal).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse drug reactions were in the gastrointestinal system.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Suppositories

In a 6-week, single-blind, randomized, multi-centre clinical study (SAS-6/UCA) to compare the efficacy and safety of MEZERA 1 g suppositories (1 g mesalazine/day) vs. mesalazine 500 mg suppositories (500 mg TID) in patients with acute ulcerative proctitis, 200 patients received MEZERA 1 g suppositories, and 203 patients received mesalazine 500 mg suppositories. The rate of patients reporting at least 1 adverse event was 19.0% and 21.2% in the 1 g and 500 mg suppository groups respectively. Most adverse reactions were mild or moderate in severity. The following treatment-emergent adverse reactions, without regards to causality, were reported in the study (Table 2):

Table 2 – Treatment-Emergent Adverse Reactions Reported by at Least 1% of Patients Treated with MEZERA Suppositories 1g – Study SAS-6

	Treatment Group	
Treatment-Emergent Adverse Reactions	**MEZERA Suppository 1 g Daily n = 200 (%)**	**Mesalazine Suppository 500 mg TID n = 203 (%)**
Blood and lymphatic system disorders		
Leukopenia	1.0	0.5
Gastrointestinal disorders		
Colitis ulcerative	1.5	2.5
Constipation	1.5	0.5
Infections and infestations		
Nasopharyngitis	2.5	3.0
Investigations		
Lipase increased	2.0	1.5
Musculoskeletal and connective tissue disorders		
Arthralgia	1.0	0
Nervous system disorders		
Headache	2.5	5.4

Foam

In a double-blind, randomized, placebo-controlled clinical study (SAF-4/UCA) involving 111 patients, the rate of patients reporting at least 1 adverse event was 29.6% and 42.1% in the MEZERA foam enema (2 g mesalazine/day) and placebo foam enema groups respectively. Most adverse reactions were mild or moderate in severity. The following treatment-emergent adverse reactions, without regard to causality, were reported in the study (Table 3):

Table 3 – Treatment-Emergent Adverse Reactions Reported by at Least 1% of Patients Treated with MEZERA Foam Enema– Study SAF-4

	Treatment Group	
Treatment-Emergent Adverse Reactions	**MEZERA Foam Enema 2 g Daily n = 54 (%)**	**Placebo N = 57 (%)**
Blood and lymphatic system disorders		
Anemia hypochromic	3.7	5.3
ESR increased	1.9	0
Gastrointestinal disorders		
Abdominal Pain	3.7	10.5
Diarrhea	3.7	7.0
Flatulence	1.9	1.8
Hemorrhoid	1.9	0
General disorders and administration site conditions		
Condition aggravated*	1.9	5.3
Fever	1.9	3.5
Hepatobiliary disorders		
SGOT increased	1.9	1.8
Nervous system disorders		
Dysesthesia	3.7	3.5
Headache	3.7	3.5
Psychiatric disorders		
Hallucination	1.9	0
Reproductive system and breast disorders		
Vaginitis	1.9	0
Respiratory, thoracic and mediastinal disorders		
Pharyngitis	5.6	5.3
Coughing	1.9	0
Laryngitis	1.9	0

*worsening of ulcerative colitis
ESR: erythrocyte sedimentation rate, SGOT: serum glutamic-oxaloacetic transaminase

8.3 Less Common Clinical Trial Adverse Reactions

Other less common (<1%) drug-related adverse events reported with MEZERA rectal formulations in the pivotal clinical studies for suppository or foam enema included the following:

Eye disorders: Visual disturbance.

Gastrointestinal disorders: Anal/perianal burning/discomfort, abdominal distension, colic, meteorism.

General disorders and administration site conditions: Application site irritation, application site pain, malaise.

Nervous system disorders: Dizziness.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

This information is not available for MEZERA.

8.5 Post-Market Adverse Reactions

The following adverse drug reactions have been identified during the post-approval use of MEZERA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)

Cardiac disorders: Myocarditis (rare [<1/1,000]), pericarditis (rare)

Gastrointestinal disorders: Acute pancreatitis

Hepatobiliary disorders: Changes in liver function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis

Immune system disorders: Hypersensitivity reactions such as allergic exanthema, pyrexia, lupus erythematosus syndrome, pancolitis

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia

Nervous system disorders: Peripheral neuropathy

Pregnancy and Fetal Outcomes: Premature labor, ectrodactyly, fetal anemia, hydrops fetalis, oligohydramnios, congenital nephrotic syndrome and fetal tachycardia were reported with mesalazine treatment.

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)

Respiratory, thoracic and mediastinal disorders: Allergic and fibrotic lung reactions (including dyspnea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)

Skin and subcutaneous tissue disorders: Rash and pruritus (common), alopecia, photosensitivity (rare)*, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN)†

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

†Drug reactions with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN): Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interaction between azathioprine, 6-mercaptopurine and aminosalicylates (including mesalazine) can increase the risk of leukopenia. Other potential interactions with a number of drugs could occur (see 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Interactions in terms of individual behavioural risks have not been established.

9.4 Drug-Drug Interactions

No investigations of interaction between MEZERA and other drugs have been performed. However, there have been reports of interactions between products containing mesalazine and other drugs.

Interaction between azathioprine, 6-mercaptopurine and aminosalicylates including mesalazine, has been reported with oral mesalazine. Concomitant treatment with mesalazine can increase the risk of myelosuppression in patients receiving azathioprine, 6-mercaptopurine or thioguanine. An increase in whole blood 6-thioguanine nucleotide (6 TGN) concentrations has been reported although the mechanism of this interaction remains unclear.

Mesalazine could also increase renal and hematologic toxicity of methotrexate by additive effect and diminished absorption of folic acid.

Caution should be exercised when mesalazine and sulfonylureas are prescribed concomitantly as the hypoglycemic effect of sulfonylureas may be enhanced. Interactions with warfarin, methotrexate, probenecid, sulfinpyrazone, spironolactone, furosemide and rifampicin cannot be excluded. Potentiation of undesirable glucocorticoid effects on the stomach is possible.

The concurrent use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine may increase the risk of renal reactions.

A theoretical interaction of salicylates with Varicella Virus Vaccine (chicken pox vaccine) might increase the risk of Reye's syndrome; as a result, the use of salicylates (including mesalazine) is discouraged for six weeks following Varicella vaccination.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalazine/mesalamine.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Mesalazine (5-ASA) is the active moiety of the prodrug sulfasalazine which acts to suppress inflammatory bowel disease. The mechanism of action of mesalazine (5-aminosalicylic acid or 5-ASA) is not fully understood, but appears to be topical rather than systemic. Inflammatory intestinal disease is often accompanied by diffuse tissue reactions including ulceration and cellular infiltration of lymphocytes, plasma cells, eosinophils, polymorphonuclear cells and activated phagocytic cells.

The interference of mesalazine with either leukotriene or prostaglandin metabolism may play a major role in suppressing the inflammatory response mechanism. Mesalazine prevents accumulation of thromboxane B2 and 6-keto-prostaglandin F_1. Both mesalazine and sulfasalazine (SAS) reverse H2O, and Cl-secretion and increase Na+ secretion in experimentally-induced colitis in guinea pigs. Sulfasalazine (SAS) and mesalazine are known to inhibit polymorphonuclear cell migration possibly via lipoxygenase inhibition at concentrations lower than those required to inhibit prostaglandin synthesis. It is thus possible that both SAS and mesalazine are capable of inhibiting both pathways via lipoxygenase inhibition.

Intestinal secretion is stimulated not only by prostaglandins but also by the metabolites of arachidonic acid generated via the lipoxygenase pathway. Upon phagocytic activation and arachidonic acid metabolism activation, reactive oxygen metabolites are generated. Mesalazine acts as a dose-dependent antioxidant which scavenges oxygen derived free radicals produced by activated phagocytes. In addition, mesalazine associates with the membrane surface, allowing chain breaking antioxidant activity when peroxidation is initiated within the membrane. Mesalazine is able to block initiation of oxidation from solution as well as propagation within the membrane. Mesalazine also inhibits the formation of both eicosanoids and cytokines.

10.2 Pharmacodynamics

Although the mesalazine mode of action is not clear, it appears to be multi-factorial. Mesalazine is thought to affect the inflammatory process through its ability to inhibit prostaglandin synthesis, interfere with leukotriene synthesis and consequent leukocyte migration as well as act as a potent scavenger of free radicals. Regardless of the mode of action, mesalazine appears to be active mainly topically rather than systemically.

Rectal administration of mesalazine allows for direct targeting of free mesalazine to the sites of inflammation along the mucosal lumen of the rectum, sigmoid and distal large bowel.

10.3 Pharmacokinetics

Mesalazine is considered to act locally from the lumen of the gastrointestinal tract. Therefore, plasma concentrations of 5-ASA and its main metabolite N-acetyl-5-ASA are thought not to be relevant for the efficacy. There is no evidence for a quantitative correlation of safety issues to plasma concentrations of 5-ASA or its metabolite.

Absorption

In healthy subjects mean peak plasma concentrations of mesalazine after a single rectal dose of 1g mesalazine (MEZERA suppository) were 192 ± 125 ng/mL (range 19 – 557 ng/mL), those of the main metabolite N-acetyl-5-ASA were 402 ± 211 ng/mL (range 57 – 1070 ng/mL). Time to reach the peak plasma concentration of mesalazine was 7.1 ± 4.9 h (range 0.3 – 24 h). A summary of the pharmacokinetic data is presented in Table 4.

Table 4 - Plasma Levels Following Rectal Administration of Mesalazine Suppositories (1 g)

Pharmacokinetic Parameters	MEZERA 1 g Suppositories	
	Mesalazine Mean# [SD]	N-Acetyl-5-ASA Mean# [SD]
C_{max} [ng/mL]	192.36 [125.33]	401.58 [210.81]
t_{max} [hr]	7.06 [4.86]	8.81 [5.64]
$t_{1/2}$ [hr]	8.27 [9.86]	10.80 [13.19]
$AUC_{(0-24)}$ [hr*ng/mL]	1933.71 [1765.42]	4893.33 [3767.03]
Ae_{0-24h} [mg]	1.20 [1.07]	94.00 [69.21]
Ae_{0-48h} [mg]	1.43 [1.27]	[83.82]

Arithmetic means

In an open, randomised, cross-over study, healthy volunteers were given 7 doses of MEZERA foam enema each dose consisting of 2 applicatorfuls equivalent to 2 g mesalazine per day. The C_{max} values after the first and last dose (steady state, 7 doses) are 985.1 ng/mL at t_{max} of 2.3 h and 774.9 ng/mL at t_{max} of 2.4 h, respectively. A summary of the pharmacokinetic data is presented in Table 5.

Table 5 - Plasma Levels Following Rectal Administration of Mesalazine Foam Enema (2 g)

Pharmacokinetic Parameters in Healthy Subjects	MEZERA Foam Enema (Single Dose of 2 Applicatorfuls per Day)	
	Mesalazine Mean [SD]	N-Acetyl-5-ASA Mean [SD]
After Dose 1		
C_{max} [ng/mL]	985.1 [682.4]	1216.1 [649.1]
t_{max} [hr]	2.3 [1.3]	2.9 [1.0]
$t_{1/2}$ [hr]	2.4 [2.0]	4.3 [3.2]
$AUC_{(0-\infty)}$ [hr*ng/mL]	3794.3 [2568.2]	8462.1 [6025.8]
Ae_{0-48h} [mg]	2.1 [1.8]	136.7 [121.0]
After Dose 7 (Steady State)		
C_{max} [ng/mL]	774.9 [434.5]	955.0 [365.4]

Pharmacokinetic Parameters in Healthy Subjects	MEZERA Foam Enema (Single Dose of 2 Applicatorfuls per Day)	
	Mesalazine Mean [SD]	N-Acetyl-5-ASA Mean [SD]
t_{max} [hr]	2.4 [1.1]	3.1 [1.7]
$t_{1/2}$ [hr]	5.5 [4.8]	3.6 [1.9]
$AUC_{(0-\infty)}$ [hr*ng/mL]	3541.0 [2730.4]	6738.3 [3938.0]
Ae_{0-48h} [mg]	4.7 [6.5]	138.8 [111.2]

Arithmetic means

In an open, non-randomised, single dose study, patients with active ulcerative proctitis or proctosigmoiditis were administered a single dose of MEZERA foam enema consisting of 2 applicatorfuls, equivalent to 2 g mesalazine. Results showed a C_{max} value of 1661.3 ng/mL for 5-ASA at t_{max} of 1.3 hour, and for N-acetyl-5-ASA a median Cmax of 1579.3 ng/mL at a t_{max} of 2.4 hours. The urinary recovery of 5-ASA + N-acetyl-5-ASA within 48 hours after single dose application of 2 g mesalazine was 5.5%. Pharmacokinetic data for MEZERA foam enema in patients with active ulcerative proctitis or proctosigmoiditis are summarised in Table 6.

Table 6 - Plasma Levels Following Rectal Administration of Mesalazine Foam Enema (2 g) in patients with Active Ulcerative Proctitis or Proctosigmoiditis

Pharmacokinetic Parameters in Patients	MEZERA Foam Enema (Single Dose of 2 Applicatorfuls)	
	Mesalazine Mean [SD]	N-Acetyl-5-ASA Mean [SD]
C_{max} [ng/mL]	1661.3 [1238.4]	1579.3 [948.3]
t_{max} [hr]	1.3 [1.0]	2.4 [0.9]
$t_{1/2}$ [hr]	1.6 [1.1]	2.6 [1.6]
$AUC_{(0-\infty)}$ [hr*ng/mL]	5285.1 [3325.9]	7967.0 [4412.4]
Ae_{0-48h} [µMol]	[105.2]	812.3 [465.6]

Arithmetic means

Distribution:

Mesalazine administered as suppositories distribute in rectal tissue to some extent. In patients with ulcerative proctitis treated with mesalazine 1 g suppositories, rectal tissue concentrations for mesalazine and N-acetyl-5-ASA have not been rigorously quantified.

A combined pharmacoscintigraphic/pharmacokinetic study showed that spreading of MEZERA foam enema is homogeneous and fast, and is almost complete within 1 hour. It reaches the gut regions rectum, sigmoid colon, and left-sided colon depending on the extent of inflammation.

Table 7 shows the rectal and colonic distribution of MEZERA foam enema in healthy subjects. Table 8 shows the rectal and colonic distribution of MEZERA foam enema in patients with left-sided ulcerative colitis.

Table 7 - Rectal and Colonic Distribution of MEZERA Foam Enema in Healthy Subjects

Distribution Region	MEZERA Foam Enema 2 g Dose	
	5 min [% of Total Dose]	12 hours [% of Total Dose]
Ascending colon	0	0
Transverse colon	0	0
Descending colon	0	7.00
Sigmoid	28.50	28.50
Rectum	46.25	39.50

Table 8 - Rectal and Colonic Distribution of MEZERA Foam Enema in Patients with Left-Sided Ulcerative Colitis

Distribution Region	MEZERA Foam Enema 2 g Dose	
	5 min [% of Total Dose]	12 hours [% of Total Dose]
Ascending colon	0	0
Transverse colon	0	0
Descending colon	0	5.00
Sigmoid	33.60	22.20
Rectum	66.40	52.80

Metabolism:

Metabolism of mesalazine occurs mainly in the intestinal mucosa and, to a lesser extent, in the liver. The main metabolite is N-acetyl-5-aminosalicylic acid, which is –like 5-ASA – predominantly eliminated by the renal and fecal routes. It appears to have no therapeutic activity or specific toxic effects. The acetylation step appears irreversible. As metabolism occurs mainly in the intestinal mucosa, it has not been possible to differentiate between a rapid and slow acetylation form as in the case of sulfasalazine/sulfapyridine. The plasma protein binding of mesalazine and acetylated mesalazine is 43% and 78%, respectively.

The influence of renal and hepatic impairment on pharmacokinetics of mesalazine has not been evaluated.

Elimination

Mesalazine and its metabolite N-Ac-5-ASA are eliminated via the feces (major part), renally (varies between 20 and 50%, dependant 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.

In healthy subjects, after a single rectal dose of 1 g mesalazine (MEZERA 1g Suppository) approx. 14 % of the administered 5-ASA dose were recovered in the urine during 48 hours.

Based on urinary excretion data, only about 8% of the mesalazine in the rectal foam enema is absorbed to the systemic compartment.

Special Populations and Conditions

This information is not available for this drug product.

11 STORAGE, STABILITY AND DISPOSAL

Suppositories

MEZERA suppositories must be stored between 15 and 30°C. Keep away from direct heat, light and humidity.

Foam

MEZERA foam enema should be stored between 15 to 30°C. Contents under pressure. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 50°C. Discard 12 weeks after first use. Do not refrigerate or freeze.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

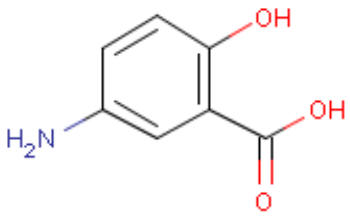
Drug Substance

Proper name: Mesalazine (INN, Ph. Eur., BP)
Mesalamine (USAN)
[also known as 5-aminosalicylic acid (5-ASA)]

Chemical name: 5-amino-2-hydroxybenzoic acid

Molecular formula and molecular mass: $C_7H_7NO_3$ 153.14

Structural formula:



Physicochemical properties:

Description: 5-aminosalicylic acid is an almost white or light grey or light tan to pink powder or crystals.

Solubility: Very slightly soluble in water, practically insoluble in ethanol (96%). Dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

Melting Range: 272°-280°C

14 CLINICAL TRIALS

Two pivotal clinical studies were performed for MEZERA (mesalazine): one pivotal study for MEZERA suppositories 1 g; and one pivotal study for MEZERA foam enema 1 g/actuation.

14.1 Clinical Trials by Indication

Table 9 - Summary of patient demographics for clinical trials in ulcerative colitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (ITT/PP) (n)	Mean age (Range) [a]	Sex Ethnicity [a]
Suppository 1 g (Patients With Mildly to Moderately Active Ulcerative Proctitis)					
SAS-6	Active-control, single-blind, multicentre, randomised, parallel-group comparative	Investigational drug: MEZERA suppository 1 g - OD x 6 weeks Daily dose: 1 g Reference Drug: Mesalazine suppository 500 mg – TID x 6 weeks Daily dose: 1.5 g *Per rectum*	200/182 203/172	42 years (18-74 years)	Male: 44% Female:56 % Caucasian: 100%
Foam Enema 1 g/Actuation (Patients With Mildly to Moderately Active Distal Ulcerative Colitis)					
SAF-4	Placebo-control, double-blind, multicentre, randomized, parallel-group	MEZERA foam enema 1 g - 2 actuations daily x 6 weeks Placebo – 2 actuations daily x 6 weeks *Per rectum*	54/42 57/38	45 years (19-69 years)	Male: 44% Female:56 % Caucasian: 100%

OD = Once daily; TID = 3 times daily; PP = Per Protocol (population for efficacy analysis); ITT = Intent-to-treat
[a] ITT analysis

For both studies, treatment was self-administered by the patient.

Suppositories

The clinical efficacy and safety of MEZERA 1 g suppositories were demonstrated in Study SAS-6, a 6-week, multicentre, randomized, parallel group therapeutic equivalence trial, involving 403 patients with active, mild to moderate ulcerative proctitis.

Subjects were randomized to receive MEZERA 1 g suppositories OD or 0.5 g mesalazine suppositories TID for 6 weeks. The primary efficacy endpoint was the clinical remission defined as Disease Activity Index (DAI) < 4 at the final visit week 6 or at withdrawal. DAI was defined as the sum of the scores of four parameters: weekly stool frequency, weekly rectal bleeding, mucosal appearance and physician's rating of disease activity.

The two treatment groups showed no relevant differences with regard to demographic characteristics at baseline. The majority of patients (75.2%) had recurrent disease at baseline. The median duration of the last remission phase was 6 months. Only a small proportion (4.5%) had had previous bowel operations. The mean number of stools per week was 22.9 (SD 14.6), and the mean number of bloody stools per week was 15.4 (SD 13.2). Median duration of ulcerative proctitis was 2.2 years in the MEZERA 1 g daily group, and 3.8 years in the mesalazine 500 mg TID group. The two treatment groups showed no relevant differences with regard to disease characteristics at baseline.

Foam

The clinical efficacy and safety of MEZERA foam enema was demonstrated in a double-blind, randomized, placebo-controlled multicenter study with 2 parallel groups (SAF-4). The objective was to assess the efficacy of MEZERA 2 g foam enema compared to placebo foam enema administered rectally once daily. 111 patients were randomized, 54 for MEZERA and 57 for placebo treatment.

Primary evaluation of efficacy was assessment of clinical remission at the end of the study as defined by a score of ≤ 4 of the Clinical Activity Index (CAI), associated with an at least 2-point decrease. Secondary efficacy endpoints evaluated Endoscopic Index and Histological Index, global assessments by the patient and the investigator.

Demographic characteristics were similar between groups. The proportion of patients with proctitis was lower in the MEZERA foam enema group compared to the placebo group (24.1% vs. 35.1%); the disease duration was longer in the MEZERA foam enema group (median 33.2 months vs. 15.4 months). However, the time since the current episode (1.8 months) and measures of disease severity were similar between the groups.

Study Results

Suppositories

Table 10 - Clinical Remission (DAI < 4) at End of Study - Study SAS-6

	Number (%) of Patients With Clinical Remission at the Final/Withdrawal Examination		Difference Between Proportions[a] [95% CI]	p-value[b]
	MEZERA 1 g OD	Mesalazine 500 mg TID		
Per Protocol	160 (87.9%)	156 (90.7%)	–2.8% [–9.2%, 3.6%]	0.00027
Intent-to-treat	168 (84.0%)	172 (84.7%)	–0.7% [–7.8%, 6.4%]	0.00008

[a] Difference between proportions [MEZERA 1 g OD – mesalazine 0.5 g TID]; asymptotic confidence interval (CI).
[b] Observed p-value (one sided).
CI = confidence interval; DAI = Disease activity index; OD = once daily; TID = three times daily

The majority of patients in both groups reached clinical remission at study end (Table 10).

Table 11 - Secondary Endpoints (DAI, CAI, HI and EI) at End of Study (Per-Protocol) – Study SAS-6

Change	Disease Activity Index[a]		Clinical Activity Index[b]		Histological Index		Endoscopy Index[b]	
	MEZERA 1 g OD n = 182	Mesalazine 500 mg TID n = 172	MEZERA 1 g OD n = 182	Mesalazine 500 mg TID n = 172	MEZERA 1 g OD n = 182	Mesalazine 500 mg TID n = 172	MEZERA 1 g OD n = 176	Mesalazine 500 mg TID n = 164
Remission	87.9%	90.7%	87.9%	92.4%	2.2%[c]	2.9%[c]	84.7%	89.6%
Improvement[e]	9.3%	7.0%	94.5%	93.6%	62.6%	60.5%	10.8%	6.1%
No change	1.6%	1.2%	n.a.	n.a.	31.3%	33.7%	4.5%	4.3%
Deterioration	1.1%	1.2%	n.a.	n.a.	3.8%	2.9%	---	---

[a] Remission: DAI < 4 at LOCF; Improvement/Deterioration: decrease/increase by ≥ 1 point from baseline to LOCF and > 3 at LOCF
[b] Remission: CAI ≤ 4 at LOCF; Improvement: decrease in CAI by ≥ 1 point from baseline to LOCF.
[c] Patients with HI = 0 at baseline and at final examination (this variable does not have a remission category.)
[d] Remission: EI < 4 at final examination; Improvement/Deterioration: decrease/increase by ≥ 1 point from baseline to final examination and EI ≥ 4
[e] Patients with remission were not included in the number of patients with improvement.
DAI = Disease Activity Index; CAI = Clinical Activity Index; HI = Histological Index; EI = Endoscopy Index;
LOCF = Last observation carried forward; OD = Once daily; TID = Three times daily

Secondary endpoints of endoscopic and histological improvement rates showed remission/normalization or improvement in the majority of patients (Table 11).

Both MEZERA 1 g OD and mesalazine 500 mg TID were efficacious in patients with active ulcerative proctitis. MEZERA 1 g once daily suppositories proved to be therapeutically equivalent to three times daily 500 mg mesalazine suppositories. Both treatments were very well accepted, but patients preferred to take suppositories once daily.

Foam

Table 12 - MEZERA Foam Enema - Efficacy Results Active Distal Ulcerative Colitis (ITT analysis) – Study SAF-4 (LOCF)

Endpoint	MEZERA Foam Enema 2 g Daily	Placebo	p-value
Patients in Clinical Remission (CAI ≤4, and ΔCAI ≥2 at study end) [n (%)]	35/54 (64.8%)	23/57 (40.4%)	0.0082
ΔCAI at study end [mean (SD)]	-2.5 (3.0)	-1.0 (2.9)	n.s.
Decrease in Number of Stools/week [mean (SD)]	-9.2 (16.9)	-6.6 (19.6)	n.s.
Patients in Endoscopic remission (EI < 4) at study end [n (%)]	26/46 (56.5%)	17/46 (37.0%)	0.047

Endpoint	MEZERA Foam Enema 2 g Daily	Placebo	p-value
Patients with Histological Improvement (ΔHI ≥ 1) at study end [n (%)]	26/44 (59.1%)	18/44 (40.9%)	n.s.

bid = twice daily; CAI = Clinical Activity Index (0-29); EI = Endoscopic index (0-12); HI = Histological Index (1-5); n.s. = not significant; SD = Standard deviation

The response rate (primary efficacy parameter) was significantly higher in the MEZERA group (64.7%) compared to the placebo group (40.4%). The frequency of patients with an endoscopic remission was significantly higher in the MEZERA group (56.5%) compared to placebo group (37.0%). Histological index demonstrated a trend to more improvement in the MEZERA group (Table 12).

The relative frequencies of patients who experienced a treatment failure was generally low in both treatment groups. Because of the small numbers of treatment failures in both groups, the lower rate of treatment failure in the MEZERA group (9/54, 16.7%) did not reach significance vs that in the placebo group (12/57, 21.1%).

This study demonstrated that administration of MEZERA foam enema at a dose of 2 g mesalazine, given once daily for 6 weeks, is an effective and well tolerated treatment of mild to moderate proctitis, proctosigmoiditis or left-sided ulcerative colitis with statistically significant superiority over placebo.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Animal studies to date show the kidney to be the only significant target organ for mesalazine toxicity in rats and dogs. At high doses (640 mg/kg/day), the lesions produced consisted of papillary necrosis and multifocal proximal tubular injury. In rats, the no-effect levels were 160 mg/kg/day for females and 40 mg/kg/day for males (minimal and reversible tubular lesions seen) after 13 weeks of oral administration. In dogs, the no-effect level in both males and females was 40 mg/kg/day after 6 months of oral administration. In this six-month oral toxicity study in dogs, doses of 80 mg/kg/day (about 1.4 times the recommended human intra-rectal dose, based on body surface area) and higher, caused renal pathology similar to that described for the rat. Aside from gastric lesions, heart lesions and bone marrow depression seen in some of the rats at the 640 mg/kg level and considered secondary effects of kidney damage, no other signs of systemic toxicity were noted at daily doses up to 160 mg/kg in rats and 120 mg/kg in dogs for 13 weeks and six months, respectively.

In the 12-month oral toxicity study in dogs, keratoconjunctivitis sicca (KCS), a lesion relatively common lesion in dogs, occurred at oral doses of 40 mg/kg/day and above.

Carcinogenicity

Administration of doses of 0, 50, 100 and 320 mg/kg/day for 127 weeks in rats did not result in significant differences in unscheduled deaths, clinical signs, nodules or masses, between groups. Ophthalmoscopic investigations revealed no treatment-related changes. Treatment with mesalazine was not associated with oncogenic changes or an increased tumor risk. The assessment of hematology, clinical biochemistry and urinalysis indicated no changes of toxicological significance at 13, 26 and 52 weeks of treatment.

After 127 weeks, analysis of the lesions indicated slight substance-related and dose-dependent toxic changes as degenerative kidney damage and hyalinization of tubular basement membrane and Bowman's capsule in the 100 mg and 320 mg/kg/day groups. Ulceration of the gastric mucosa and atrophy of the seminal vesicles were also more frequent in the 320 mg/kg/day group.

Genotoxicity

Mesalazine was not mutagenic in the Ames test, *E. coli* reverse mutation assay, mouse micronucleus test, sister chromatid exchange assay, or in a chromosomal aberrations assay.

Reproductive and Developmental Toxicology

Teratology studies with mesalazine have been performed in rats at oral doses up to 320 mg/kg/day and in rabbits at oral doses up to 495 mg/kg/day (about 1.7 and 5.4 times the recommended human intra-rectal dose, respectively). The battery of tests completed to date has shown that mesalazine is devoid of embryotoxicity and teratogenicity in rats and rabbits; that it does not affect male rat fertility after five weeks of oral administration at 296 mg/kg/day; and that it lacks the potential to affect late pregnancy, delivery, lactation or pup development in rats.

Special Toxicology (Other studies)

Nephrotoxic potential of 5-aminosalicylic acid

Owing to its structural relationship to phenacetin, the aminophenols and salicylates, mesalazine was included in a series of compounds studied following identification of antipyretic-analgesic nephropathy in humans. Mesalazine also produced papillary necrosis, following single intravenous doses ranging from 150 mg/kg to 872 mg/kg in rats in addition to the proximal tubule necrosis seen with acetylsalicylic acid (e.g. Aspirin®) and phenacetin derivatives. These findings are consistent with the renal changes observed in the toxicity studies with mesalazine (see above).

It has been shown that oral doses of mesalazine of 30 mg/kg and 200 mg/kg daily for four weeks failed to produce any adverse effects on kidney function or histology in rat.

Mesalazine suppository irritation study

The local tolerance of mesalazine 1 g suppositories was tested over 28 days in dogs with a rectal administration 100 mg/kg b.w./day (approximately 7-fold above the recommended human daily rectal dose). At this dose, neither local nor systemic intolerance reactions were observed.

Mesalazine foam local irritation study in dogs

The local tolerance of mesalazine foam was tested over 14 days in dogs receiving a daily rectal dose of 4 g of foam, corresponding to 880 mg/animal/day mesalazine (approximately 3-fold above the recommended human daily rectal dose). Macroscopic and histopathological examinations of the rectum and colon revealed no changes considered to be related to treatment with MEZERA foam enema.

Animal pharmacology studies

Animal pharmacology tests were conducted on mesalazine using the oral route of administration for most tests, at a dose of 500 mg/kg in order to simulate practice-relevant conditions. In the paw-edema test with carrageen injection, 200 mg/kg *per os* proved ineffective, but 500 mg/kg mesalazine *per os* exhibited mild antiphlogistic action.

In the animal renal function tests (natriuresis and diuresis), no biologically relevant effects of 200 mg/kg *per os* were demonstrated. After 600 mg/kg, marked functional changes were observed: increases in total urinary output, natriuresis and proteinuria. The urinary sediment contained an increased number of erythrocytes and epithelial cells. Both potassium elimination and specify weight were reduced. It can be concluded from these experiments that even high doses of mesalazine have no effect on vital parameters. Disturbances in renal function are to be expected only at dosages equivalent to a single dose at least 8 to 10 times the daily dose in man.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr MEZERA ®

Mesalazine Suppositories, Mfr. Std.

Read this carefully before you start taking **MEZERA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MEZERA**.

What is MEZERA used for?

- Treatment of active mild to moderate ulcerative proctitis. Ulcerative proctitis is a condition where your rectum becomes inflamed and develops sores or ulcers.

How does MEZERA work?

MEZERA is believed to work by interfering with certain chemicals in your body that cause inflammation (e.g., prostaglandins). This will helps reduce the inflammation (swelling and pain) in the rectum and lower part of the large bowel.

What are the ingredients in MEZERA?

Medicinal ingredient: Mesalazine, also known as 5-aminosalicylic acid, 5-ASA or mesalamine.

Non-medicinal ingredient: Hard fat (Witepsol H-12). MEZERA products are gluten-free and phthalate-free.

MEZERA comes in the following dosage forms:

Suppositories of 1 g

Do not use MEZERA if you:

- have severe kidney disease.
- have severe liver disease.
- have ulcers of the stomach or small intestine.
- have a blockage along the urinary tract.
- are allergic to this drug or to any ingredient of MEZERA. See “What are the ingredients in MEZERA?”, above.
- are allergic to salicylates such as Aspirin®.
- are under 2 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MEZERA. Talk about any health conditions or problems you may have, including if you:

- have any kidney or liver problems.
- have lung or breathing problems such as asthma.
- have had previous inflammation of the heart. Talk to your doctor if you suspect that you are experiencing problems with your heart. See "Serious side effects and what to do about them" table, below.
- have a history of allergy to sulfasalazine.
- have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after using mesalazine.

Other warnings you should know about:

Urine discoloration: You may notice red-brown urine discoloration after using toilets treated with bleach products. This is because of a chemical reaction between mesalazine and bleach and is harmless.

Monitoring and Testing: During treatment your doctor may want to keep you under close medical supervision and you may need to have regular blood and urine tests.

Kidney Stones: Kidney stones may develop with use of mesalazine. Symptoms may include blood in urine, urinating more often and pain in your back, side, belly or groin. Be sure to drink enough liquids while you are taking MEZERA. Talk to your doctor about how much water or other liquids you should be drinking.

Serious Skin Reactions: Serious skin reactions including drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis have been reported in association with mesalazine treatment. Stop using mesalazine and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in "Serious side effects and what to do about them" table.

Pregnancy and Breastfeeding: If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your doctor.

- Avoid becoming pregnant while you are taking MEZERA. It may harm your unborn baby.
- Tell your doctor right away if you become pregnant or think you are pregnant during treatment with MEZERA.
- Taking MEZERA during pregnancy have been reported to cause
    - Early labor
    - Birth defects in babies. The baby may develop kidney and heart issues.
- MEZERA is passed into human breastmilk. Talk to your doctor about how to feed your baby.
- If you breastfeed your baby while taking MEZERA, your baby could develop / start to have diarrhea. <u>It is important to monitor your baby's stool and contact your doctor right away if they have diarrhea.</u> Your doctor may advise you to stop breastfeeding your baby.

Sun Sensitivity: If you have conditions such as atopic dermatitis or eczema, you may be more sensitive to the sun while taking MEZERA. Your doctor may tell you to avoid sun exposure, wear protective clothing, or use a sunscreen while outdoors.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MEZERA:

- Medicine used to prevent organ transplant rejection called azathioprine
- Medicines used to treat cancer such as 6-mercaptopurine, thioguanine and methotrexate
- Medicine used to treat ulcerative colitis such as aminosalicylates (including MEZERA)
- Medicine used to treat blood clots called warfarin
- Medicines used to treat gout such as probenecid and sulfinpyrazone
- Medicines used to treat high blood pressure such as spironolactone and furosemide
- Medicine used to treat bacterial infections called rifampicin
- Medicine used to treat inflammation called corticosteroids, for example prednisone
- Vaccine against chickenpox (varicella vaccine)

The use of mesalazine with drugs known to affect the kidney may increase the risk of kidney reactions. These drugs include some anti-inflammatory drugs (NSAIDs) and azathioprine.

How to take MEZERA:

Treatment is usually continued for at least 6 weeks.

Not to be taken by mouth.

If possible, go to the toilet and empty your bowels before.

1. Detach one suppository from the strip.
2. Remove the plastic wrapper.
3. Do not handle the suppository too much as it melts at body heat.
4. Insert gently and fully into the rectum, pointed end first.
5. May be easier to insert with a small amount of lube gel on the tip.

Usual dose:

You should use MEZERA suppositories regularly and consistently to achieve the desired effect.

1 suppository (1 g) is inserted into the rectum, once daily at bedtime. For maximum benefit, try to keep the suppository in the rectum for at least one to three hours.

Overdose:

If you think you, or a person you are caring for, have taken too much MEZERA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of MEZERA, use it as soon as possible, unless it is almost time for the next dose. Do not use two doses of MEZERA at the same time to make up for a missed dose.

What are possible side effects from using MEZERA?

These are not all the possible side effects you may have when taking MEZERA. If you experience any side effects not listed here, tell your healthcare professional.

The most commonly reported side effects are: abdominal pain, an abnormal sense of touch, diarrhoea,

constipation, or flatulence (gas).

Other side effects reported with MEZERA include: disturbed vision, burning, pain or discomfort around the anus, bloating, dizziness, headache, hair loss, muscle or joint pain, lowered sperm count (reversible when MEZERA is discontinued), numbness in hands and feet, decreased platelet count in the blood, allergic and fibrotic lung reactions (including difficulty breathing, cough, bronchospasm (lung contraction), alveolitis (alveoli inflammation), pulmonary eosinophilia (lung inflammation from an increase of a type of white blood cells, eosinophils), lung infiltration, pneumonitis (lung inflammation)) and increased sensitivity of your skin to sun and ultraviolet light (photosensitivity).

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Skin Reactions: rash, itching		✓	
UNCOMMON			
Kidney stones (hard little pebbles that form in your kidneys): blood in urine, urinating more often and pain in your back, side, belly or groin.		✓	
RARE			
Myocarditis/ Pericarditis (inflammation of the heart muscle and lining around the heart): abnormal heartbeat, chest pain that may resemble a heart attack, fatigue, fever and other signs of infection including headache, muscle aches, sore throat, diarrhea, or rashes, joint pain or swelling, leg swelling, shortness of breath.		✓	
VERY RARE		✓	
Acute Intolerance Syndrome: cramping, acute stomach pain, blood and excessive stools (diarrhea), fever, headache and rash. These symptoms could be a sign of a serious condition which occurs rarely but means your treatment would have to be stopped immediately.		✓	
Pancreatitis (inflamed or swollen pancreas): abdominal pain and feeling sick.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Serious skin reactions including drug reactions with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, widespread rash, fever and enlarged nodes. These serious skin rashes can be preceded by fever and flu-like symptoms.			✓
Blood problems: unexplained bruising, unusual bleeding (for example, nose bleeds), anemia (feeling weak), fever, sore throat.		✓	
Kidney problems (such as inflammation and scarring of the kidney or kidney failure): blood in the urine, fever, increased or decreased urine output, mental status changes (drowsiness, confusion, coma), nausea, vomiting, rash, swelling of the body, weight gain (from retaining fluid).		✓	
Hepatitis including liver failure (inflammation of the liver): jaundice (yellowing of the skin and eyes) and flu-like symptoms.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

MEZERA suppositories must be stored between 15 and 30°C. Keep away from direct heat, light and humidity.

If you want more information about MEZERA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.avirpharma.com), or by calling 1-888-430-0436.

This leaflet was prepared by:

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr MEZERA ®

Mesalazine Foam Enema, Mfr. Std.

Read this carefully before you start taking **MEZERA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MEZERA**.

What is MEZERA used for?

- Treatment of mildly active ulcerative colitis. Ulcerative colitis is a condition where your colon (bowel) and rectum become inflamed and develop sores or ulcers.

How does MEZERA work?

MEZERA is believed to work by interfering with certain chemicals in your body that cause inflammation (e.g., prostaglandins). This will helps reduce the inflammation (swelling and pain) in the rectum and lower part of the large bowel.

What are the ingredients in MEZERA?

Medicinal ingredient: Mesalazine, also known as 5-aminosalicylic acid, 5-ASA or mesalamine.

Non-medicinal ingredients: cetostearyl alcohol, disodium edetate, polysorbate 60, propylene glycol, sodium metabisulfite, with a propellant mixture of propane, n-butane, and isobutane. MEZERA products are gluten-free and phthalate-free.

MEZERA comes in the following dosage forms:

Foam enema of 1 g / actuation

Do not use MEZERA if you:

- have severe kidney disease.
- have severe liver disease.
- have ulcers of the stomach or small intestine.
- have a blockage along the urinary tract.
- are allergic to this drug or to any ingredient of MEZERA. See “What are the ingredients in MEZERA?”, above.
- are allergic to salicylates such as Aspirin®.
- are under 2 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MEZERA. Talk about any health conditions or problems you may have, including if you:

- have any kidney or liver problems.
- have lung or breathing problems such as asthma.

- have had previous inflammation of the heart. Talk to your doctor if you suspect that you are experiencing problems with your heart. See “Serious side effects and what to do about them” table, below.
- have a history of allergy to sulfasalazine.
- have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after using mesalazine.

Other warnings you should know about:

MEZERA foam enema contains propylene glycol, sodium metabisulphite and cetostearyl alcohol, which may cause:

- A buildup of acidity in the blood (Lactic acidosis), with symptoms of muscle aches, rapid breathing, nausea and stomach pain.
- Blood sugar issues (hyperosmolality) with symptoms of excessive thirst, dry mouth, increased urination, fever, drowsiness, confusion and hallucinations.
- Blood issues (hemolysis) with symptoms of pale skin, fatigue, weakness, fever, signs of confusion, dizziness, or light-headedness.
- Central Nervous System (CNS) depression, with symptoms of decrease heartrate, decreased rate of breathing and loss of consciousness.
- Severe hypersensitivity reactions.
- Bronchospasm.
- Skin reactions.

Stop taking MEZERA and talk to your doctor if you experience any of these issues during your treatment.

Urine discoloration: You may notice red-brown urine discoloration after using toilets treated with bleach products. This is because of a chemical reaction between mesalazine and bleach and is harmless.

Monitoring and Testing: During treatment your doctor may want to keep you under close medical supervision and you may need to have regular blood and urine tests.

Kidney Stones: Kidney stones may develop with use of mesalazine. Symptoms may include blood in urine, urinating more often and pain in your back, side, belly or groin. Be sure to drink enough liquids while you are taking MEZERA. Talk to your doctor about how much water or other liquids you should be drinking.

Serious Skin Reactions: Serious skin reactions including drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis have been reported in association with mesalazine treatment. Stop using mesalazine and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in “Serious side effects and what to do about them” table.

Pregnancy and Breastfeeding: If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your doctor.

- Avoid becoming pregnant while you are taking MEZERA. It may harm your unborn baby.
- Tell your doctor right away if you become pregnant or think you are pregnant during treatment with MEZERA.

- Taking MEZERA during pregnancy have been reported to cause
    - Early labor
    - Birth defects in babies. The baby may develop kidney and heart issues.
- MEZERA is passed into human breastmilk. Talk to your doctor about how to feed your baby.
- If you breastfeed your baby while taking MEZERA, your baby could develop / start to have diarrhea. It is important to monitor your baby's stool and contact your doctor right away if they have diarrhea. Your doctor may advise you to stop breastfeeding your baby.

Sun Sensitivity: If you have conditions such as atopic dermatitis or eczema, you may be more sensitive to the sun while taking MEZERA. Your doctor may tell you to avoid sun exposure, wear protective clothing, or use a sunscreen while outdoors.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MEZERA:

- Medicine used to prevent organ transplant rejection called azathioprine
- Medicines used to treat cancer such as 6-mercaptopurine, thioguanine and methotrexate
- Medicine used to treat ulcerative colitis such as aminosalicylates (including MEZERA)
- Medicine used to treat blood clots called warfarin
- Medicines used to treat gout such as probenecid and sulfinpyrazone
- Medicines used to treat high blood pressure such as spironolactone and furosemide
- Medicine used to treat bacterial infections called rifampicin
- Medicine used to treat inflammation called corticosteroids, for example prednisone
- Vaccine against chickenpox (varicella vaccine)

The use of mesalazine with drugs known to affect the kidney may increase the risk of kidney reactions. These drugs include some anti-inflammatory drugs (NSAIDs) and azathioprine.

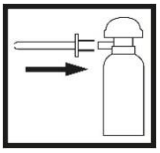
How to take MEZERA:

Treatment is usually continued for at least 6 weeks.

If possible, go to the toilet and empty your bowels before.

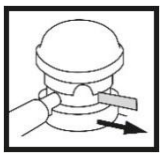
Prepare to use the foam:

Figure 1



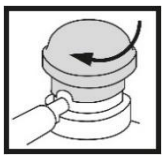
1. Store and use MEZERA foam enema at room temperature (15 - 30°C).
2. Push the applicator firmly onto the spout of the spray can (Figure 1).
3. Shake the spray can for 20 seconds.

Figure 2



4. Remove the safety tab from under the pump dome (Figure 2).

Figure 3



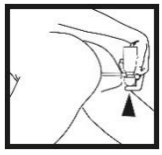
5. Twist the dome on the top of the spray can until the semi-circular gap is in line with the nozzle (Figure 3). The spray can is now ready for use.

Use the foam:

Figure 4

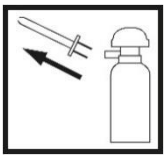
6. Place your index finger on the top of pump dome. Turn the can upside down (Figure 4). The spray can will only work when held with the pump dome pointing down.

Figure 5



7. Insert the applicator into your rectum as far as possible (Figure 5). The best way to do this is to place one foot on a chair or stool.
8. Push down the pump dome fully once. Slowly release it.
9. Wait 10-15 seconds for the foam to be delivered. For the second spray, push the dome again and release slowly. Wait a further 10-15 seconds.

Figure 6



10. Remove the applicator and dispose of it in the plastic bag provided (Figure 6). Take a new one for each use.
11. Wash your hands and try not to empty your bowels until the next morning.

Usual dose:

You should use MEZERA foam enema regularly and consistently to achieve the desired effect.

2 spray actuations (1 g/spray) once daily at bedtime. If you have difficulty retaining this amount of foam, it may also be used in two separate doses: one at bedtime and the other during the night or early in the morning (after excreting the first dose). The foam is provided with 14 single-use applicators. Each canister contains enough foam for 14 spray actuations, which corresponds to 7 days of treatment. The applicators can be used to track your treatment (number of dose used/remaining).

Overdose:

If you think you, or a person you are caring for, have taken too much MEZERA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of MEZERA, use it as soon as possible, unless it is almost time for the next dose. Do not use two doses of MEZERA at the same time to make up for a missed dose.

What are possible side effects from using MEZERA?

These are not all the possible side effects you may have when taking MEZERA. If you experience any side effects not listed here, tell your healthcare professional.

The most commonly reported side effects are: abdominal pain, an abnormal sense of touch, diarrhoea, constipation, or flatulence (gas).

Other side effects reported with MEZERA include: disturbed vision, burning, pain or discomfort around the anus, bloating, dizziness, headache, hair loss, muscle or joint pain, lowered sperm count (reversible when MEZERA is discontinued), numbness in hands and feet, decreased platelet count in the blood, allergic and fibrotic lung reactions (including difficulty breathing, cough, bronchospasm (lung contraction), alveolitis (alveoli inflammation), pulmonary eosinophilia (lung inflammation from an increase of a type of white blood cells, eosinophils), lung infiltration, pneumonitis (lung inflammation)) and increased sensitivity of your skin to sun and ultraviolet light (photosensitivity).

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Skin reactions: rash, itching		✓	
UNCOMMON			
Kidney stones (hard little pebbles that form in your kidneys): blood in urine, urinating more often and pain in your back, side, belly or groin.		✓	
RARE			
Myocarditis/ Pericarditis (inflammation of the heart muscle and lining around the heart): abnormal heartbeat, chest pain that may resemble a heart attack, fatigue, fever and other signs of infection including headache, muscle aches, sore throat, diarrhea, or rashes, joint pain or swelling, leg swelling, shortness of breath.		✓	
VERY RARE			
Acute Intolerance Syndrome: cramping, acute stomach pain, blood and excessive stools (diarrhea), fever, headache and rash. These symptoms could be a sign of a serious condition which occurs rarely but means your		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
treatment would have to be stopped immediately.			
Pancreatitis (inflamed or swollen pancreas): abdominal pain and feeling sick.		✓	
Serious skin reactions including drug reactions with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis: reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, widespread rash, fever and enlarged nodes. These serious skin rashes can be preceded by fever and flu-like symptoms.			✓
Blood problems: unexplained bruising, unusual bleeding (for example, nose bleeds), anemia (feeling weak), fever, sore throat.		✓	
Kidney problems (such as inflammation and scarring of the kidney or kidney failure): blood in the urine, fever, increased or decreased urine output, mental status changes (drowsiness, confusion, coma), nausea, vomiting, rash, swelling of the body, weight gain (from retaining fluid).		✓	
Hepatitis including liver failure (inflammation of the liver): jaundice (yellowing of the skin and eyes) and flu-like symptoms.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

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- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

MEZERA foam enema should be stored between 15 to 30°C. Contents under pressure. Do not place in hot water or near radiators, stoves or other sources of heat. Do not puncture or incinerate container or store at temperatures over 50°C. Do not refrigerate or freeze. Discard 12 weeks after first use.

If you want more information about MEZERA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.avirpharma.com), or by calling 1-888-430-0436.

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