PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr MEZERA®

Mesalazine*

Mesalazine Suppositories, 1 g / suppository, Mfr. Std.
Mesalazine Foam Enema, 1 g / actuation (14 actuations per can), Mfr Std.

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

LOWER GASTROINTESTINAL TRACT ANTI-INFLAMMATORY

A07EC02

AVIR Pharma Inc.
660 Boul. Industriel
Blainville, QC
Canada, J7C 3V4
www.avirpharma.com

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients	
Rectal	Suppository, 1 g / suppository	None	*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*
	Foam Enema, 1 g / actuation	Sodium metabisulfite	

INDICATIONS AND CLINICAL USE

Suppositories

MEZERA (mesalazine) suppositories are indicated for the treatment of acute mild to moderate ulcerative proctitis.

Foam

MEZERA foam enema is indicated for the treatment of mildly active ulcerative colitis of the sigmoid colon and rectum.

Geriatrics (≥ 65 years of age): The safety and efficacy of MEZERA have not been established in geriatric patients.

Pediatrics (< 18 years of age): Clinical studies with MEZERA have not been performed in the pediatric population.

CONTRAINDICATIONS

MEZERA (mesalazine) is contraindicated in:

- patients with severe renal impairment (GFR<30mL/min/1.73m^2) (see WARNINGS AND PRECAUTIONS).
- patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS).

- 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 or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.
- cases of existing gastric or duodenal ulcer.
- patients with urinary tract obstructions.
- infants under 2 years of age.

WARNINGS AND PRECAUTIONS

General

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.

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 withdrawal is required.

MEZERA foam enema contains propylene glycol that may cause lactic acidosis, hyperosmolality, hemolysis and CNS depression. Slight to mild skin irritation due to propylene glycol may occur. This medicine contains cetostearyl alcohol that may cause local skin reactions (e.g. contact dermatitis).

Effects on Ability to Drive and Use Machinery

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

Carcinogenesis and Mutagenesis

Carcinogenicity studies in animals and mutagenicity tests were negative (see TOXICOLOGY).

Cardiovascular

Cardiac side effects, including pericarditis and myocarditis have been rarely reported with the use of MEZERA[1].

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[2,3].

Gastrointestinal

Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or sulfasalazine (SAS) therapy (18%)[4], should be investigated in order to exclude pericarditis and pancreatitis either as adverse drug reactions to MEZERA or secondary manifestations of inflammatory bowel disease.

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 DRUG INTERACTIONS - Drug-Drug Interactions)[5-6]. 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 (mesalazine) 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 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. parameters 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.

MEZERA is contraindicated in patients with severe renal impairment (see 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 (mesalazine) 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.

Special Populations

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[4,7].

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

Animal studies did not show evidence of impaired fertility or harm to the foetus due to mesalazine (see TOXICOLOGY). However, because animal reproduction studies are not always predictive of human response, MEZERA should be used during pregnancy only if clearly needed.

Nursing Women

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[8-11]. 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 as hypersensitivity reactions manifested as diarrhea in the infants have been reported[4,11-13]. If the infant develops diarrhea, breast-feeding should be discontinued.

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.

Pediatrics (<18 years of age)

The safety and efficacy of MEZERA has not been established in children.

Geriatrics (≥65 years of age)

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 (mesalazine) 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, it may be useful to monitor renal function.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In randomized controlled or open studies, the overall adverse reaction profile was similar with MEZERA (mesalazine) suppositories and foam enema in patients with mild to moderate active ulcerative colitis. MEZERA suppositories were evaluated in 200 patients with ulcerative proctitis. MEZERA foam enema was evaluated in 332 patients with ulcerative colitis. Among these patients who participated in the safety and efficacy studies, the majority of subjects did not experience drug-related adverse events associated with MEZERA rectal formulations. The majority of reported events were mild or moderate in severity. The most common adverse drug reactions were in the gastrointestinal system.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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. The following adverse events, without regards to causality, were reported in the study (Table 1):

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

Treatment-Emergent Adverse Events	Treatment Group	
	MEZERA Suppository 1 g Daily (N = 200)	Mesalazine Suppository 500 mg TID (N = 203)
	%	%
Headache	2.5	5.4
Nasopharyngitis	2.5	3.0
Lipase increased	2.0	1.5
Colitis ulcerative	1.5	2.5
Constipation	1.5	0.5
Arthralgia	1.0	0
Leukopenia	1.0	0.5

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. The following adverse events, without regard to causality, were reported in the study (Table 2):

Table 2 Adverse Events Reported by at Least 1% of Patients Treated with MEZERA Foam Enema– Study SAF-4

Treatment-Emergent Adverse Events	Treatment Group	
	MEZERA Foam Enema 2 g Daily (N = 54)	Placebo (N = 57)
	%	%
Pharyngitis	5.6	5.3
Abdominal Pain	3.7	10.5
Anemia hypochromic	3.7	5.3
Diarrhea	3.7	7.0
Dysesthesia	3.7	3.5
Headache	3.7	3.5
Condition aggravated*	1.9	5.3
Coughing	1.9	0
ESR increased	1.9	0
Fever	1.9	3.5
Flatulence	1.9	1.8
Hallucination	1.9	0
Hemorrhoid	1.9	0
Laryngitis	1.9	0
SGOT increased	1.9	1.8
Vaginitis	1.9	0

* worsening of ulcerative colitis

ESR: erythrocyte sedimentation rate, SGOT: serum glutamic-oxaloacetic transaminase

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

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been identified during the post-approval use of MEZERA (mesalazine). 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. Except where indicated, frequency is very rare (< 1/10,000):

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

Nervous system disorders: Peripheral neuropathy

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

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

Gastrointestinal disorders: Acute pancreatitis

Renal and urinary disorders: Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency, nephrolithiasis

Skin and subcutaneous tissue disorders: Alopecia, photosensitivity (rare)*

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia

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

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

Reproductive system disorders: Oligospermia (reversible)

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

DRUG INTERACTIONS

Interaction between azathioprine, 6-mercaptopurine and aminosalicylates (including mesalazine) can increase the risk of leukopenia[1-6]. Other potential interactions with a number of drugs could occur (see Drug-Drug Interactions).

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[1-6].
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.

Drug-food, drug-herb, or drug-laboratory interactions have not been studied.

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[14-16].

DOSAGE AND ADMINISTRATION

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.

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. The best results are achieved if the bowels are evacuated prior to insertion of MEZERA suppository.

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.

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.

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.

The best results are achieved if the bowels are evacuated prior to administration of MEZERA foam enema.

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. A patient should not use two MEZERA doses at the same time to make up for a missed dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

There is no experience with adverse drug reactions as a result of MEZERA (mesalazine) 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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[17].

The interference of mesalazine with either leukotriene or prostaglandin metabolism may play a major role in suppressing the inflammatory response mechanism[17-23]. Mesalazine prevents accumulation of thromboxane B2 and 6-keto-prostaglandin F_1[18]. Both mesalazine and sulfasalazine (SAS) reverse H_2O, and Cl-secretion and increase Na+ secretion in experimentally-induced colitis in guinea pigs[24]. SAS and mesalazine are known to inhibit polymorphonuclear cell migration possibly via lipoxygenase inhibition[23] 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[17].

Intestinal secretion is stimulated not only by prostaglandins but also by the metabolites of arachidonic acid generated via the lipoxygenase pathway[17,23,25]. Upon phagocytic activation and arachidonic acid metabolism activation, reactive oxygen metabolites are generated[25]. Mesalazine acts as a dose-dependent[26] antioxidant which scavenges oxygen derived free radicals produced by activated phagocytes [17,27]. 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[28]. Mesalazine also inhibits the formation of both eicosanoids and cytokines[20,27].

Pharmacodynamics

MEZERA (mesalazine) contains mesalazine (a 5-aminosalicylic acid or 5-ASA), the active principle of the prodrug sulfasalazine[29-31]. 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[18,23], interfere with leukotriene synthesis and consequent leukocyte migration[18,19] as well as act as a potent scavenger of free radicals[17]. Regardless of the mode of action, mesalazine appears to be active mainly topically rather than systemically[32].

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.

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 3.

Table 3 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 4.

Table 4 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]
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]

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 Cmax value of 1661.3 ng/mL for 5-ASA at tmax of 1.3 hour, and for N-acetyl-5-ASA a median Cmax of 1579.3 ng/mL at a tmax 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 5.

Table 5 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]

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

Table 6 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 7 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[7,29], 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.

Excretion:

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.

STORAGE AND STABILITY

Suppositories

MEZERA (mesalazine) 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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. Non-medicinal ingredients: Hard fat (Witepsol H-12).

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). Non-medicinal ingredients are cetostearyl alcohol, disodium edetate, polysorbate 60, propylene glycol, sodium metabisulfite, with a propellant mixture of propane, n-butane, and isobutane. 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

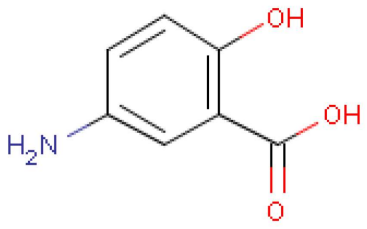
Drug Substance

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

CLINICAL TRIALS

Study Demographics and Trial Design

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.

Table 8 summarizes the study demographics and trial design. For both studies, treatment was self-administered by the patient.

Table 8 Summary of Patient Demographics and Trial Design for Pivotal Clinical Trials in Ulcerative Colitis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (ITT/PP)	Mean Age (Range)[a]	Gender Ethnicity[a]
Suppository 1 g (Patients With Mildly to Moderately Active Ulcerative Proctitis)					
SAS-6[33]	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[34]	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

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 (Sutherland et al. 1987)[35].

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.

Results

Suppositories

The majority of patients in both groups reached clinical remission at study end (Table 9).

Table 9 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

Secondary endpoints of endoscopic and histological improvement rates showed remission/normalization or improvement in the majority of patients (Table 10).

Table 10 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

Both MEZERA 1 g OD and mesalazine 500 mg TID were highly 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

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 11).

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%).

Table 11 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
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

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.

DETAILED PHARMACOLOGY

Animal Studies

Mesalazine (5-ASA) is the active moiety of the prodrug sulfasalazine which acts to suppress inflammatory bowel disease. 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. No adverse effect of mesalazine on the following parameters or in the following animal pharmacology tests could be established: tremorine antagonism, hexobarbital sleep time, motor activity, anticonvulsant action (metrazol and electric shock), blood pressure, heart rate, respiratory rate (up to 10 mg/kg, i.v.), tocolysis (antispasmodic assay), local anaesthesia, antihyperthermal and antipyretic effects. 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.

Human Studies

See ACTION AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

Long-term Toxicity

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[36,37].

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.

Mutagenicity

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.

Reproduction Studies

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.

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. Calder *et al.* has reported in rats that in addition to the proximal tubule necrosis seen with acetylsalicylic acid (e.g. Aspirin®) and phenacetin derivatives, mesalazine also produced papillary necrosis, following single intravenous doses ranging from 150 mg/kg to 872 mg/kg[38-40]. These findings are consistent with the renal changes observed in the toxicity studies with mesalazine (see above).

Diener *et al.*[41] have 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.

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