P R O D U C T M O N O G R A P H

Pr PENTASA®

Mesalazine*

Extended-release tablets 500 mg and 1 g
Rectal suspension, 1 g and 4 g/100 mL (enema)
Suppository 1 g

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

Lower Gastrointestinal anti-inflammatory

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	500 mg and 1g	None*
Rectal	1 g and 4 g Enema	None*
Rectal	1 g Suppository	None*

*For a complete listing see Dosage Forms, Composition and Packaging section of the Product Monograph

INDICATIONS AND CLINICAL USE

PENTASA (mesalazine) extended-release tablets are indicated for:

- Treatment of mild to moderate active ulcerative colitis and for long-term maintenance therapy in order to maintain remission and prevent relapse of active disease.
- Management of mild to moderate Crohn's Disease and maintenance of Crohn's Disease in remission induced by surgery or medication

PENTASA rectal suspension is indicated for the treatment of acute distal ulcerative colitis extending to the splenic flexure and for long-term maintenance therapy in order to maintain remission and prevent relapse of active disease. Clinical experience has shown that topical PENTASA (i.e. enemas/suppositories) is superior to oral PENTASA (i.e. tablets) with regard to therapeutic efficacy in distal ulcerative colitis (see Table 2 - Clinical experience from pivotal trials).

PENTASA suppositories are indicated for the treatment of acute ulcerative proctitis and for long-term maintenance therapy in order to maintain remission and prevent relapse of active disease.

Pediatrics (< 18 years of age):

The safety and effectiveness of mesalazine have not been established in children.

Geriatrics (≥65 years of age):

The safety and efficacy of PENTASA have not been established in geriatrics patients.

CONTRAINDICATIONS

PENTASA is contraindicated in:

1. Patients with existing gastric or duodenal ulcer;

2. Patients with urinary tract obstruction, renal parenchymal disease or severe renal impairment. Very rarely, mesalazine may induce nephrotoxicity which would be additive in these patients. Renal function should be determined prior to beginning therapy (e.g. serum creatinine), and the benefits of therapy versus the increased risk of nephrotoxicity carefully assessed. See WARNINGS AND PRECAUTIONS.

3. Patients who are hypersensitive to any salicylates (including mesalamine/mesalazine) or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

4. Patients with severe hepatic impairment See WARNINGS AND PRECAUTIONS.

5. 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 PENTASA 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.

Mesalazine 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.

In patients with mild to moderate renal impairment, mesalazine products should be used only if the benefits outweigh the risks. Therefore, caution should be exercised, and it is recommended that all patients have an evaluation of renal function prior to initiation of therapy, and periodically while on treatment (see Renal).

In patients with mild to moderate impaired liver function, mesalazine products should be used only if the expected benefits outweigh the risks to the patient. Caution should be exercised (see Hepatic/Biliary/Pancreatic).

PENTASA extended-release tablets should not be chewed, broken or crushed but should be swallowed whole.

Gastrointestinal
Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of the product. Acute intolerance syndrome: See WARNINGS AND PRECAUTIONS - General.

Cardiovascular
Mesalazine induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported rarely with mesalazine and other mesalazine -containing preparations. Caution should be taken in prescribing this medication to patients with conditions predisposing to the development of myocarditis or pericarditis.

Hematologic
Following mesalazine treatment, serious blood dyscrasias (including myelosuppression) have been reported rarely. The risk is further increased when mesalazine products are used concomitantly with 6-mercaptopurine or azathioprine (see **Drug Interactions – 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, anaemia, fever or sore throat, haematological investigations should be performed. If there is suspicion of blood dyscrasia, mesalazine treatment should be discontinued.

Hepatic/Biliary
There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with mesalazine products. Therefore, mesalazine is contraindicated in patients with severe hepatic impairment (see **Contraindications**). In patients with mild to moderate liver function impairment, caution should be exercised and mesalazine products should only be used if the expected benefit clearly outweighs the risks to the patients. Appropriate assessment and monitoring of liver function 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 mesalazine products and pro-drugs of mesalazine. Mesalazine is contraindicated in patients with severe renal impairment (see **Contraindications**). In patients with mild to moderate renal dysfunction, caution should be exercised and mesalazine products 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, 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 mesalazine products and should be closely monitored.

Special Populations

Pregnant Women
There are no adequate and well controlled studies of mesalazine in pregnant women. Mesalazine is known to cross the placental barrier.

PENTASA should be used during pregnancy only if benefits outweigh the risks. The underlying condition itself (Inflammatory bowel disease/IBD) may increase risks for the pregnancy outcome.

Limited published human data on mesalazine show no increase in the overall rate of congenital malformations. Limited published data on the class of mesalamine products show an increased rate of preterm birth, stillbirth, and low birth weight. These adverse pregnancy outcomes are also associated with active inflammatory bowel disease

Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anemia) have been reported in new-borns of mothers being treated with PENTASA.

Nursing Women
In nursing mothers, mesalazine is excreted in breast milk at concentration much lower than in maternal blood, but the metabolite N-acetyl-5-ASA appears in similar concentrations. Caution should be exercised, and PENTASA should be used in nursing mothers only if the benefits outweigh the risks. Hypersensitivity reactions like diarrhea in the infants cannot be excluded. No controlled studies with PENTASA during breast feeding have been carried out. If the infant develops diarrhoea, breast-feeding should be discontinued**.**

Fertility
Semen abnormalities and infertility in men, which are associated with sulfasalazine, have not been reported with PENTASA during controlled clinical trials. Semen quality significantly may improve when patients are transferred from sulfasalazine to PENTASA.

Decreased sperm count and impaired sperm motility have been only rarely reported with mesalazine. This effect may be reversible when treatment is discontinued.

Pediatric Use (<18 years of age)
The safety and efficacy of PENTASA have not been established in children. The potential benefits of therapy should be weighed against the possible risks.

Geriatrics (≥ 65 years of age)
There are no clinical efficacy studies of mesalazine in geriatrics patients.

Results of a single-dose pharmacokinetic study indicate that following the administration of a mesalamine-containing product, the systemic exposure to mesalamine may be increased by up 2-fold in elderly subjects (> 65 year), as compared with younger adult subjects (18-35 years). Systemic exposures were inversely correlated with renal function. Therefore, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy.

ADVERSE REACTIONS

The following adverse events (AEs) were reported in the CAMMP clinical study (Table-1) using the PENTASA extended release tablets in adult patients with mild to moderate ulcerative colitis. A total of 143 patients received PENTASA Extended-release tablets of which 93 patients received PENTASA 4g /day for 8-week (induction phase) and 70 went on to a 24 week maintenance phase at 2 g/day.

Table-1 Adverse events, occurring in ≥ 2% of patients treated with Pentasa Extended-release tablets formulation (CAMMP Study 2011)

	PENTASA® Extended-release tablets **N=143**
Patients with any adverse event	**52.4%**
Nasopharyngitis	8.4%
Headache	7.7%
Nausea	4.2%
Influenza	3.5%
Gastroenteritis	3.5%
Colitis ulcerative	2.8%
Abdominal pain	2.8%
Fatigue	2.8%
Cough	2.8%
Pyrexia	2.1%
Flatulence	2.1%
Back pain	2.1%
Dizziness	2.1%
Pharyngolaryngeal pain	2.1%

In this clinical trial, other AEs occurring in less than 2% of patients included rash & pruritus, dyspepsia, vomiting, diarrhoea, haemorrhoids, rectal haemorrhage, hepatic enzyme increased, myalgia/arthralgia, pain in extremity, otitis media, and pneumonia.

Other clinical studies and post marketing data

Table 2 - Frequency of adverse effects, based on other clinical trials reports with other Pentasa formulations, and from post-marketing surveillance data with all Pentasa formulations

Frequency of adverse effect	Organ system affected	Symptom
Common (≥ 1% and < 10%)	General disorders and administration site conditions	**Only with rectal formulations:** Anal discomfort Irritation at the application site Pruritus (anal) Tenesmus (rectal)
	Nervous system disorders	Headache Idiopathic intracranial hypertension Anxiety Hypoesthesia
	Cardiovascular System	Hypertension
	Gastro-intestinal disorders	Diarrhea Abdominal pain Nausea Vomiting Gastroenteritis viral Flatulence
	Skin and subcutaneous tissue disorders/infections	Rash including urticaria, erythematous rash Exanthema Varicella
	Renal	Urinary Tract Infection
Rare (≥ 0.01% and < 0.1%)	Nervous system disorders	Dizziness
	Cardiac disorders	Myocarditis* Pericarditis*
	Gastro-intestinal disorders	Increased amylase Acute pancreatitis*
	Skin and subcutaneous tissue disorders/infections	Photosensitivity**
Very rare (< 0.01%)	General disorders and administration site conditions	Drug fever
	Skin and subcutaneous tissue	Reversible alopecia Dermatitis allergic Erythema multiforme, and Stevens-Johnson Syndrome (SJS)
	Hepato-biliary disorders	Increase in transaminases Cholestasis parameters (e.g. alkaline phosphatase, gamma-glutamyltransferase and bilirubin)

Frequency of adverse effect	Organ system affected	Symptom
		Hepatotoxicity (including hepatitis, cholestatic hepatitis*, cirrhosis, hepatic failure)
	Renal and urinary disorders	Nephropathy (renal function impairment, including interstitial nephritis*) Nephrotic syndrome Renal insufficiency Urine discoloration
	Reproductive system disorders	Oligospermia reversible
	Respiratory, thoracic and mediastinal disorders	Allergic and fibrotic lung reactions (including dyspnoea, coughing, bronchospasm, allergic alveolitis) [Pulmonary eosinophilia Interstitial lung disease Pulmonary infiltration Pneumonitis /Bronchitis Pleurisy
	Musculo-skeletal, connective tissue and bone disorders	Myalgia Arthralgia Isolated reports of lupus-erythematosus-like syndrome (systemic lupus erythematosus)
	Blood and lymphatic system disorders	Altered blood counts (anaemia, aplastic anaemia, agranulocytosis, neutropenia, leukopenia, including granulocytopenia, pancytopenia, thrombocytopenia and eosinophilia as part of an allergic reaction).
	Nervous system disorders	Peripheral neuropathy
	Immune system disorders	Hypersensitivity reaction including anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
	Gastro-intestinal disorders	Pancolitis

* The mechanism of 5-ASA-induced myocarditis and pericarditis, pancreatitis, nephritis and hepatitis is unknown, but may be of allergic origin. It is important to note that several of these disorders may also be attributable to the underlying inflammatory bowel disease itself.
** More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Gastrointestinal:
Abdominal distension, anorexia, duodenal ulcer, eructation, esophageal ulcer, fecal incontinence, bloody stools or diarrhea, intestinal obstruction, melena, dysphagia, mouth ulcer, oral moniliasis, pancreatitis, rectal bleeding, rectal urgency, thirst.

Diarrhea is a commonly reported adverse event (about 3% frequency in clinical trials; somewhat less from spontaneous post-market surveillance reports), which is not dose-related. Diarrhea is also a symptom of the underlying disease, and may indeed be indicative of inadequate dosage with PENTASA in some patients. Rarely mesalazine may exacerbate the inflammatory bowel disease itself.

It may be noted that melena has been reported as an adverse event rarely during mesalazine therapy, but it has not been definitely linked to treatment. Gastrointestinal bleeding has been assumed from observations of bloody diarrhea or stools. Again, blood in fecal matter may be a symptom of the underlying disease and has not been definitely linked to treatment.

Dermatological:
Acne, alopecia, dry skin, eczema, erythema nodosum, erythematous rash, hirsutism, nail disorder, photosensitivity, pruritus, skin discoloration, sweating, Stevens-Johnson Syndrome (SJS).

Reversible alopecia has been reported in mesalazine -treated patients, as well as in placebo-treated patients, indicating that hair loss could be part of the underlying disease. Two cases of alopecia in patients on treatment with mesalazine at a dose of 4 g/day were confirmed by positive rechallenge. In one of the cases, the hair loss improved after dosage reduction to 2 g/day. However, the available data are insufficient to establish a dose relationship with mesalazine treatment generally.

Three cases of erythema nodosum have been reported in connection with PENTASA therapy. The causality was assessed as probable (1 case), possible (1 case) and not related (1 case) due to negative dechallenge. Erythema nodosum is a well-known extra-intestinal manifestation of inflammatory bowel disease.

Nervous System:
Anxiety, abnormal dreams, dizziness, insomnia, somnolence, paraesthesia.

Cardiovascular:
Postural hypotension, tachycardia.

Respiratory:
Dyspnea, increased coughing, pharyngitis.

Metabolic:
Alkaline phosphatase increase, amylase increase, C reactive protein increase, creatinine increase, GGTP increase, LDH increase, proteinuria, SGOT increase, SGPT increase, weight decrease, weight increase.

Rise in liver enzymes by 3 to 5 times the normal range may be expected in a small percentage of patients treated with PENTASA. This variable and transient occurrence is difficult to relate definitely to drug treatment due to the concomitant drug therapy usual with patients, and due to enzyme fluctuations caused by the disease itself. In many cases, the enzyme increases resolve without drug discontinuation or reduction. In most cases, enzyme

abnormalities are reversed on discontinuation of therapy. Rarely, increase in liver enzymes is indicative of developing hepatitis.

Similarly, increases in serum amylase and lipase levels by 3 to 5 times the normal range may occur, and are usually reversible upon dosage reduction or discontinuation. Very rarely, patients develop pancreatitis.

Weight loss is an expected consequence of inflammatory bowel disease. Weight gain is usually indicative of a positive clinical response to PENTASA therapy.

Renal/genitourinary:
Albuminuria**,** urinary frequency, urinary infection, urination disorder, vaginitis, isolated cases of nephrotic syndrome and interstitial nephritis.

Hematologic:
Agranulocytosis.

Immunological:
Anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Other:
Anemia, appetite decrease, arthralgia, breast pain, chest pain/pressure, chills, conjunctivitis, dry eyes, eye pain, ecchymosis, edema, eosinophilia, ESR increase, fatigue, fever, flu syndrome, leg cramps, malaise, menorrhagia, myalgia, scotoma, sore throat.

DRUG INTERACTIONS

Overview
There is a potential risk of myelosuppression, particularly leucopenia when aminosalicylates are co-administered with azathioprine or 6-mercaptopurine. Regular monitoring of white blood cells is recommended and dosage regime of thiopurines should be adjusted accordingly.

There is a potential risk of renal failure when aminosalicylates are co-administered with other nephrotoxic agents such as NSAIDs and azathioprine.

Drug-Drug Interactions
No investigations of interaction between PENTASA and other drugs have been performed. However, there have been reports of interactions between products containing mesalazine and other drugs. 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. In patients receiving azathioprine or 6-mercaptopurine, concurrent use of mesalazine can increase the potential for blood disorders, especially leucopenia.

Caution should be exercised when mesalazine and sulfonyl ureas are prescribed concomitantly since the blood-sugar reducing effect of sulfonyl ureas may be enhanced. Interactions with coumarin, probenecid, sulfinpyrazone, spironolactone, furosemide and rifampicin cannot be excluded. Mesalazine may delay the excretion of methotrexate.

Drug-Food Interactions
The effect of food on the new formulation of PENTASA 500 mg extended release tablets has not been established. The new formulation was only administered under fed conditions (after a high fat meal) in a comparative bioavailability study comparing the new and former PENTASA extended release tablet formulations for safety purposes [for results see CLINICAL TRIALS, ORAL DOSAGE FORMS, Comparative Bioavailability Data]. In addition, PENTASA 500 mg extended release tablets were administered mainly with food, as part of an unrestricted diet in the pivotal phase 3 trial that was submitted for approval of the new PENTASA 500 mg extended release tablet formulation.

For this reason, PENTASA 500 mg extended release tablets should be taken with food. See DOSAGE AND ADMINISTRATION, Extended-release tablets 500 mg.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Several reports of possible interference with measurement, 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/5-ASA.

DOSAGE AND ADMINISTRATION

Extended-release tablets 500 mg and 1g:
Management of mild to moderate active ulcerative colitis and maintenance therapy: Therapy should be initiated at 0.5 g four times daily (2 g daily dose). The dose may be increased to 1 g four times daily (4 g daily dose) if additional therapeutic benefit is needed.

Management of mild to moderate Crohn's disease: The optimal dose is 1 g four times daily (4 g daily dose). For patients with Crohn's Disease in remission, a dose of 3 g daily in divided doses is recommended.

PENTASA extended-release tablets should not be chewed, broken or crushed but should be swallowed whole.

PENTASA extended-release tablets should be taken with meals.

Rectal suspension: The recommended dose ranges from 1 g to 4 g of mesalazine, depending on disease activity. PENTASA may be self-administered once daily at bedtime. Dosage may be adjusted according to the individual patient's needs consistent with therapeutic goals. Prolonged retention is expected to achieve the best therapeutic response.

Suppositories: The usual dose of PENTASA suppositories is one suppository containing 1 g of mesalazine, self-administered once daily at bedtime. Prolonged retention is expected to achieve the best therapeutic response. The frequency of dosage may be adjusted according to the individual patient's needs consistent with therapeutic goals.

OVERDOSAGE

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

Symptoms of Overdosage:
There is no clinical experience with PENTASA overdosage. Single oral doses of mesalazine up to 5 g/kg in pigs and a single intravenous dose of mesalazine at 920 mg/kg in rats were not lethal.

Since PENTASA is an amino salicylate, symptoms of salicylate toxicity such as acid-base balance disorder, hyperventilation, pulmonary edema, vomiting, dehydration and hypoglycaemia may occur.

There is no specific antidote and the management of overdose is supportive and symptomatic. In cases of suspected overdose, symptomatic treatment at hospital is required. Fluid and electrolyte, as well as acid/base imbalances, should be corrected by the administration of appropriate intravenous therapy. Close monitoring of renal function is required in order to maintain adequate renal function. No cases of overdose have been reported.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mesalazine is an aminosalicylate, gastrointestinal anti-inflammatory agent. Aminosalicylates are considered to be one of the first line therapy(s) for inflammatory bowel diseases.

Mesalazine is the active component of sulfasalazine, which has been used for a long time in the treatment of ulcerative colitis and Crohn's disease.

The therapeutic value of mesalazine appears to be due to local effect on the inflamed intestinal tissue, rather than to systemic effect.

Increased leukocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B4, and increased free radical

formation in the inflamed intestinal tissue are all present in patients with inflammatory bowel disease. Mesalazine has in-vitro and in-vivo pharmacological effects that inhibit leukocyte chemotaxis, decrease cytokine and leukotriene production and scavenge for free radicals. The mechanism of action of mesalazine is, however, still not understood.

Pharmacodynamics

Regardless of its mode of action, mesalazine appears to exert its therapeutic effect by topical action on the affected areas of inflammation.

PENTASA tablets are composed of mesalazine extended-release granules that allows for a predictable, uniform, and continuous release of drug throughout the small (duodenum, jejunum and ileum) and large bowel (colon), at all enteral pH conditions. The release is not significantly compromised by diarrhea or increased bowel acidity, conditions which accompany active inflammatory bowel disease.

The PENTASA dosage forms designed for rectal administration, enemas and suppositories, are well suited to deliver the active ingredient, mesalazine, directly to affected areas along the mucosal lumen of the rectum, sigmoid and distal large bowel.

Pharmacokinetics: Oral Dosage Forms

Absorption:
Based on urinary excretion data, 20% to 30% of the mesalazine in PENTASA is absorbed. In contrast, when mesalazine is administered orally as an unformulated 1 g aqueous suspension, mesalazine is approximately 80% absorbed. Plasma mesalazine concentration peaked at approximately 1 μg/mL three hours after a 1 g dose of PENTASA, and declined in a biphasic manner.

N-acetyl-5-ASA, the major metabolite of 5-ASA, peaked at approximately 3 hours at 1.8 μg/mL and its concentration followed a biphasic decline. Pharmacological activities of N-acetyl-5-ASA are unknown and other metabolites have not been identified.

Oral mesalazine pharmacokinetics were non-linear when PENTASA capsules were dosed from 250 mg to 1 g four times daily, with steady-state mesalazine plasma concentrations increasing about nine times, from 0.14 μg/mL to 1.21 μg/mL, suggesting saturable first-pass metabolism. N-acetyl-5-ASA pharmacokinetics was linear.

Co-administration of mesalazine tablets and a high fat meal was found to inhibit mesalazine and N-acetyl-5-ASA systemic absorption. Bioavailability of mesalazine decreased by about 70% and peak concentration decreased by about 60% as compared to the fasting state. N-acetyl-5-ASA pharmacokinetics was affected to a lesser extent, i.e., a 24% decrease in bioavailability and peak concentration. When food was present, less free mesalazine was eliminated in the feces (33%), although 15.2% more salicylates were eliminated in the feces than under fasting conditions. The same effect was observed after administration of mesalazine in a suspension, indicating that the interaction involves mesalazine, not the PENTASA delivery system.

The effect of food on the new formulation of PENTASA 500 mg extended release tablets has not been established.

Distribution:
Scintigraphic studies have shown that in the stomach, PENTASA extended release tablets disintegrate immediately into discrete extended release microgranules which are spread throughout the entire gastro-intestinal tract. The microgranules are emptied from the stomach within 17 $\pm$ 5 minutes under fasted conditions and within about 30 minutes when a breakfast meal is served 5 minutes post-dose. Therefore the residence time in the stomach is not affected by post-dose food intake. The transit time through the small intestine has been shown to be 213 $\pm$ 45 minutes after which the microgranules arrive in the caecum. The small intestinal transit is not affected by post-dose food intake since no statistically significant difference could be detected between conditions in which subjects were fasted and those in which a meal was administered 5 minutes post-dose. The small intestinal transit time was 3.7 hours in fasted subjects and 3.1 hours in a fasted subject that had a breakfast meal 5 minutes post-dose. The microgranules reside in the colon for about 8 hours. The independence of food intake and intestinal transit has also been shown in another study, where the gastric emptying and small intestinal transit mesalazine microgranules occurred within the digestive period and synchronous with the meal.

Metabolism:
Mesalazine is rapidly acetylated to N-acetyl-5-ASA. Pharmacological activities of N-acetyl-5-ASA are unknown and other metabolites have not been identified.

Excretion:
In published single dose studies of PENTASA tablets, Rasmussen (1982) and Rijk (1988), both reported total combined fecal and urinary excretion to be 77% of total dose. Total fecal recovery varied slightly between reports. About 130 mg of free mesalazine was recovered in the feces following a single 1 g PENTASA dose. Forty-six percent of the dose was eliminated in the feces as mesalazine and N-acetyl-5-ASA. Elimination of free meslazine and salicylates in feces increased proportionately with the dose of PENTASA. N-acetyl-5-ASA was the primary compound excreted in the urine (19% - 30%) following PENTASA dosing.

The literature describes a mean terminal half-life of 42 minutes for mesalazine following intravenous administration. Because of the continuous release and absorption of mesalazine from PENTASA throughout the gastrointestinal tract, the true elimination half-life cannot be determined after oral administration.

Pharmacokinetics: Rectal Dosage Forms

Absorption:
The local and systemic bioavailability of PENTASA enema and PENTASA suppositories were assessed in 12 healthy volunteers under steady-state conditions. Systemic absorption of mesalazine was low. 15% of the 2 g daily dose was recovered in the urine (mostly as the acetylated metabolite) after administration of the enema, with 10% urinary recovery observed

after administration of the suppositories. This compares to 20% to 30% of the mesalazine dose being absorbed systemically following oral administration.

Maximum plasma concentrations of mesalazine and of N-acetyl-5-ASA (approximately 0.7 μg/mL and 1.2 μg/mL respectively for the enema; 0.3 μg/mL and 0.8 μg/mL respectively for the suppositories) were reached 2 hours following administration of the enema and 5 to 6 hours following administration of the suppositories.

Local availability, as shown by recovery of free mesalazine in the feces, was higher for both the enema (mean 30%) and the suppositories (mean 45%) than for the oral dosage forms of mesalazine.

Bondesen et al demonstrated that systemic absorption from mesalazine enemas was pH dependent, showing a significantly greater absorption at pH 7.4 (mean C_{max} in plasma 1.18 μg/mL for mesalazine, 0.55 μg/mL for N-acetyl-5-ASA) than at pH 4.8 (C_{max} 0.35 μg/mL for mesalazine, 0.55 μg/mL for N-acetyl-5-ASA). In another study, Bondesen et al demonstrated that systemic absorption of 5-ASA occurred to a similar degree in the right and the left parts of the colon, both being significantly lower than the absorption from the small intestine.

Systemic absorption of mesalazine was shown to be dose and volume dependent. Using a concentration of 4 g of mesalazine in 100 mL enema, Campieri et al observed mean plasma levels of approximately 4 μg/mL for total (free and acetylated) mesalazine, which was approximately double of the level observed with 2 g of mesalazine enema. Systemic absorption was also increased when the volume of the enema was doubled, as shown by significant increase in urinary recovery. These same authors also showed that systemic absorption of mesalazine was significantly decreased in patients with active disease as compared to those in remission. They found no evidence of accumulation of total mesalazine in plasma after repeated daily administration of 2 g or 4 g enemas for 15 days to patients with active disease. This was also confirmed by Almer and collaborators with patients in remission, given 4 g enemas once a day for 7 days. Low systemic absorption of mesalazine from the suppository dosage form was also confirmed by Norlander et al who found mean peak plasma levels of 0.2 μg/mL for mesalazine, 0.6 μg/mL for N-acetyl-5-ASA and urinary excretion of 10.8% (almost all as N-acetyl-5-ASA) following a single 500 mg dose of mesalazine given as a suppository to 12 healthy, fasting volunteers.

Distribution:
The extent of colonic distribution of mesalazine was studied in patients with active left-sided ulcerative colitis, using scintigraphic imaging of ^{99m}Tc-labelled enemas and suppositories. These studies showed that the retrograde spread of mesalazine from 100 mL enemas, containing either 1 g or 4 g of the active compound, usually extended beyond the rectosigmoid, reliably reaching the areas of inflammation up to and including the splenic flexure. With the suppositories, the spread of ^{99m}Tc-labelled mesalazine was confined to the rectum and adjacent sigmoid colon, thereby acting on the inflamed mucosa in patients whose disease was localized in those areas.

Excretion:
With regard to the clinically important local availability of free mesalazine, the values, measured in terms of fecal excretion, ranged from 26% (48-hour recovery) to 29.4% (24-hour recovery) and 30% (48-hour recovery), following administration of the enema and from 45% (48-hour recovery) to a high of 64.8% (72-hour recovery) following administration of suppositories. This compares to approximately 13% of the orally administrated dose of mesalazine being excreted in the feces as free mesalazine.

STORAGE AND STABILITY

Storage and Stability Information

PENTASA extended-release tablets (500 mg and 1 g) should be stored between 15°C and 30°C. Protect from light.

PENTASA rectal suspension (enema) and PENTASA suppositories should be stored at controlled room temperature, preferably below 25°C. They should be dispensed in their respective containers.

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NOTE: ALL PENTASA PRODUCTS ARE PHTHALATE FREE

Extended-release Tablets: contains either 500 mg or 1 g of mesalazine with the following non-medicinal ingredients: Microcrystalline cellulose, ethylcellulose, magnesium stearate, povidone, talc.

Pentasa tablets do not contain gluten, phthalates, or lactose.

PENTASA 500 mg Extended Release Tablets are round, white-grey to pale brown speckled tablets with a scoreline on one side and embossed "500 mg" on one side and "PENTASA" on the other. They are available in HDPE bottles containing 240 tablets, 500 tablets and 40 tablet samples and in unit dose blister strips of 10 tablets, in packages of 10 strips.

PENTASA 1g Extended Release Tablets are oblong, white-grey to pale brown speckled tablets embossed PENTASA on both sides. They are available in HDPE bottles containing 120 tablets, 20 tablet samples and in unit dose blister strips of 10 tablets, in packages of 6 strips.

Rectal Suspension: is available in strengths of 1 g or 4 g per 100 mL with the following non-medicinal ingredients: sodium acetate, disodium edetate, sodium metabisulfite, purified water, with hydrochloric acid to adjust the pH to 4.8. Each unit dose of rectal suspension

enema contains mesalazine in concentrations of either: 1 g/100mL or 4 g/100 mL. Each carton contains 7 enemas together with 7 hygienic bags.

PENTASA rectal suspension is supplied in a low density polyethylene (LDPE) bottle.

Suppositories: contain 1 g of mesalazine with the following non-medicinal ingredients: polyethylene glycol, povidone, talc, magnesium stearate. Each suppository contains 1 g of mesalazine. Suppositories are packaged in blister cards of 5 suppositories per card. Each carton contains 6 cards of 5 suppositories for a total of 30 suppositories and finger protectors.

PENTASA suppositories are sealed in aluminium blisters made of double aluminium push through foils.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: 5-aminosalicylic acid (5-ASA)

mesalazine (INN)

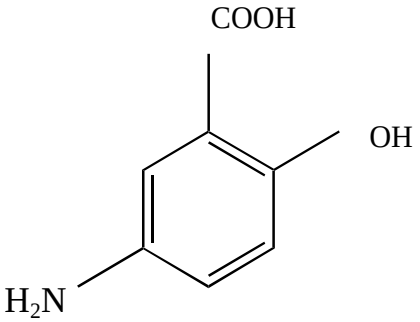
mesalamine (USAN

Chemical name: 2-hydroxy-5-aminobenzoic acid

Molecular formula: $C_7H_7O_3N$

Molecular weight: 153.14

Structural formula:



Description:
Chemically, the medicinal ingredient of PENTASA (mesalazine) is 2-hydroxy-5-aminobenzoic acid. It is a white to tan coloured powder with a melting range of 283ºC – 287ºC. It is slightly soluble in cold water and alcohol, more soluble in hot water and soluble in hydrochloric acid. A saturated aqueous solution has a pH of 3.0 - 4.5 and a pKa of 2.74.

CLINICAL TRIALS

Clinical Experience

The clinical experience from pivotal trials is summarized in Table 3.

Table 3 - Clinical experience from pivotal trials

Preparation/reference	Condition	Dose	Duration of treatment	% Clinical response			% Reported Adverse Events sorted by GI (gastro-intestinal) events and non-GI events
				Total clinical efficacy	Sigmoid /endo-scopy	Remission rate	
ACTIVE ULCERATIVE COLITIS AND ULCERATIVE COLITIS IN REMISSION							
Oral-Tablets CAMMP Study 2011 N= 156	Active mild to moderate ulcerative colitis	4 g/day	8 weeks	Overall Improvement: 63.6% (all subjects) 59.3% (left sided disease) 73.9% (Extensive disease)		48.1%	AEs at 2%, but < 5% included abdominal pain 2.1%, dyspepsia, 0.7%, fatigue 2.1%, pyrexia 2.1%, gastroenteritis, 3.5%. influenza 2.8%, back pain 2.1%, dizziness 2.1%, cough 2.8%, pharyngolaryngeal pain 2.1%
Oral-Tablets CAMMP Study 2011 N= 129	mild to moderate ulcerative colitis in remission	2 g/day	24 weeks	Relapse Rate: 20.4% (all subjects) 16.7% (left sided) 30.8% (extensive disease)		Week 8: 85.7% Week 16: 77.6%	
Oral - capsules Hanauer et al, 1993 N= 374	Active mild to moderate ulcerative colitis	1 g/day 2 g/day 4 g/day	8 weeks	21% 29% 29%	40% 44% 48%		**16**% **total adverse events** GI events: diarrhea 4.6%; nausea 4.6%; bloody stools 1.4% abdominal pain 1.4%; anorexia 1.8%; rectal urgency 0.4%; vomiting 1.8% Non GI events: headache 2.5%; rash

Preparation/reference	Condition	Dose	Duration of treatment	% Clinical response			% Reported Adverse Events sorted by GI (gastro-intestinal) events and non-GI events
				Total clinical efficacy	Sigmoid /endo-scopy	Remission rate	
							1.8%; fever 1.4%
ACTIVE CROHN'S DISEASE							
Oral - capsules Singleton et al, 1993 N= 310	Active Crohn's Disease	1 g/day 2 g/day 4 g/day	16 weeks	36% 39% 64%		23% 23% 11%	**18.3**% **total adverse events** GI events: nausea with vomiting 7.4%; nausea 6.1%;abdominal pain 4.3%; diarrhea 3.9% Non GI events: headache 5.2%; rash 3.5%
CROHN'S DISEASE IN REMISSION							
Oral - delayed release tablets Gendre et al, 1993 N= 161	Crohn's Disease in remission	2 g/day	24 months			45%	**11.3**% **total adverse events** GI events: diarrhea 5.0%; nausea 3.8%; vomiting 1.3%; Non GI events: dizziness 1.3%
ACTIVE PROCTITIS AND DISTAL ULCERATIVE COLITIS*							
Rectal - enema Data on file at Ferring Pharmaceuticals	Active mild to moderate ulcerative proctosigmoiditis	1 g 2 g 4 g nightly	8 weeks	66% 69% 74%			**8.7**% **total adverse events** GI events: abdominal pain 3.2%; diarrhea 2.3%; nausea 1.8% Non GI events: headache 1.4%
Rectal - suppository Data on file at Ferring Pharmaceuticals	Active mild-moderate ulcerative proctitis	1 g nightly	2 weeks	65%	69%		**1 case of diarrhea (3.8%)**

* Topical PENTASA (i.e. enemas/suppositories) is superior to oral PENTASA (i.e tablets) with regard to therapeutic efficacy in distal ulcerative colitis

ORAL DOSAGE FORMS

Ulcerative Colitis: induction and maintenance of remission

In an active-controlled, double-blind, non-inferiority, randomized trial (CAMMP study) patients with active mild to moderate ulcerative colitis were treated with PENTASA tablets 4 g/day for 8 weeks (active phase) and 2 g/ day for 24 weeks (maintenance phase). The results are presented in Table 4 below.

Table 4 Summary of primary efficacy results

Phase & endpoints	PENTASA tablets 500 mg
Active Phase	
Overall improvement at week 8: n/N (%)	50/78 (64.1%)
Maintenance Phase	
Relapse before week 24: n/N (%)	15/61 (24.6%)

Overall improvement is a complete remission or a clinical response to therapy as measured by the UCDAI. A relapse of UC is defined as a UCDAI score of ≥ 3 and an endoscopy score of ≥ 1. The control arm using a former tablet formulation is not shown here. In the same CAMMP trial, at the end of the active phase (week 8), mucosal healing (endoscopic score =0) was observed in 47% of patients. However, this was one of many secondary endpoints, therefore, the interpretation of the results should be cautious.

In a placebo-controlled, double-blind, randomized trial of 374 patients with active mild to moderate ulcerative colitis, PENTASA when given alone at total daily doses of 2 g to 4 g, improved the macroscopic appearance of the colonic mucosa and improved the physician's overall clinical assessment of disease activity. The 4 g dose significantly improved the appearance of the colonic mucosa as assessed by histologic scoring. In addition, doses of 2 g or more relieved the predominant clinical symptoms that accompanied the active phase of ulcerative colitis by reducing the number of trips to the toilet, improving stool consistency, decreasing rectal bleeding, lessening rectal urgency, and reducing abdominal/rectal pain.

In a pivotal study of the PENTASA extended-release 5-ASA formulation compared to sulfasalazine therapy in patients with an established diagnosis of ulcerative colitis, but who had been in remission for between 1 month and 5 years, extended-release 5-ASA was demonstrated to be a safe and effective drug and equivalent to sulfasalazine in the maintenance of remission states. The ongoing remission rates after 6 and 12 months of treatment were 63% and 54% for the extended-release 5-ASA formulation, and 72% and 46% for sulfasalazine, respectively.

Comparative Bioavailability Data
One single-dose, randomized, double-blinded, two-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy male and female volunteers. The rate and extent of absorption of 5-acetylsalicylic acid was measured and compared following a single oral dose (1 x 500 mg) of PENTASA 500 mg extended-release tablets (New formulation) and PENTASA 500 mg extended-release tablets (Former formulation). The results from a total of sixty-three (63) volunteers are summarized in the following table.

Summary Table of the Comparative Bioavailability Data

5-aminosalicylic acid (1 x 500 mg extended-release tablet) From measured data Least Squares Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Least Squares Mean**	**90% Confidence Interval**
AUC_T (ng h/mL)	**858.97 1166.17 (97.33)**	**798.10 973.32 (60.91)**	**107.6**	**90.9 – 127.4**
AUC_∞[¥] (ng h/mL)	**923.99 1260.17 (95.99)**	**853.39 1049.42 (55.83)**	**108.3**	**87.4 – 134.2**
C_{max} (ng/mL)	**348.19 535.33 (107.58)**	**305.24 421.29 (81.94)**	**114.1**	**92.3 – 141.1**
T_{max}[§] (h)	**4.50 (2.00 – 12.00)**	**4.50 (2.50 – 13.00)**		
$T_{½}$[€¥] (h)	**1.28 (59.78)**	**1.81 (109.15)**		

***Pentasa (5-ASA) 500 mg extended release tablets (New formulation)**
† Pentasa (5-ASA) 500 mg extended release tablets (Old formulation)
[¥] Calculated for 48/63 subjects (Test) and 47/63 subjects (Reference) only
[§] Expressed as the median (range) only
[€] Expressed as the arithmetic mean (CV%) only

Crohn's Disease:
Results from two randomized, double-blind, placebo-controlled clinical trials involving 542 patients with Crohn's Disease, indicated that a daily dose of 4 g significantly reduced Crohn's Disease Activity Index (CDAI) compared to placebo. The mean (S.E.M.) decrease in CDAI from pre-treatment to study end was 53 (9) for the 4 g group compared to 22 (9) for the placebo group, a difference that was highly significant (p=0.0114).

In a randomized, double-blind, placebo-controlled trial conducted in 293 patients with Crohn's Disease in remission, a daily 3 g dose of PENTASA administered for a period of up to 48 weeks reduced the relapse rate (21% versus 41%; p=0.018) and increased the median time to relapse when compared with placebo.

Results from a meta-analysis (Messori et al, 1994) of nine randomized clinical trials (3 with the PENTASA formulation) also indicated that 5-ASA significantly reduced the frequency of relapse in patients with Crohn's Disease in remission. Pooled relapse-free rates in the treatment group were 84% and 72% at 1 and 2 years respectively; corresponding rates in the control group were 60% and 52%.

RECTAL DOSAGE FORMS

The efficacy and safety of PENTASA enema were assessed in two multicentre, double-blind, randomized, controlled trials.

One of these trials compared the efficacy and safety of 1 g, 2 g and 4 g 5-ASA enemas against placebo during an 8-week period in patients with acute exacerbation of ulcerative proctosigmoiditis. This US study involved 287 randomized patients (70-73 per group). Efficacy was assessed in terms of clinical symptoms (including stool frequency, consistency, urgency, rectal bleeding and rectal/abdominal pain), macroscopic appearance of the affected mucosa (determined by sigmoidoscopy, scored from 0 to 15 according to vascular pattern, friability, presence of erythema, mucus/pus, granularity/ulcerations) and microscopic grading (0 for normal mucosa, 3 for high-grade, active, ulcerative inflammatory bowel disease) of the rectal biopsy specimens.

PENTASA enema was shown to be significantly ($p<0.01$) superior to placebo in all efficacy parameters for each of the three doses. No dose-response relationship was demonstrated across the three PENTASA enema doses. All three doses were effective in inducing remission by at least one of the three remission parameters (physician's global assessment, sigmoidoscopic index, biopsy score): thus, 66% of the patients in the 1 g PENTASA enema group, 69% in the 2 g PENTASA enemas group and 74% in the 4 g PENTASA enema group achieved remission on this basis.

Safety in this multicentre trial was assessed by documenting all adverse events during treatment and from the results of laboratory tests. The type and frequency of adverse events reported for placebo and the three PENTASA enema doses were comparable (See ADVERSE REACTIONS).

PENTASA was discontinued in 4.6% of patients due to treatment-related adverse events, as compared to 5.7% of patients discontinued for the same reason in the placebo group. In addition, no significant changes in laboratory parameters were observed and there was no apparent cross-sensitivity in patients with known allergy to sulfasalazine.

In another multicentre, double-blind trial, conducted in Europe and involving 123 randomized patients with active mild to moderate proctosigmoiditis, PENTASA enema (1 g 5-ASA/100 mL) was tested against prednisolone enema (25 mg/100 mL) as active control for up to four-weeks duration of treatment. The criteria for evaluation of efficacy included grading of clinical symptoms (i.e. number of daily bowel movements, blood in stool, pus in stool, abdominal pain) and sigmoidoscopic scores. Remission was defined in terms of physician's assessments of clinical and sigmoidoscopic disease activities. Safety was assessed by documentation of adverse events and by the results of laboratory tests. At the end of the 28-day treatment period, overall favourable outcome, in terms of remission or

improvement, was achieved by 77% of patients in the PENTASA group and by 72% of patients in the prednisolone group, the difference not being statistically significant. These results include 53% and 43% of patients in the PENTASA and prednisolone groups respectively, who showed both clinical and sigmoidoscopic remission. The adverse events observed were all mild and reversible and there was no statistically significant difference in their frequency between the two groups. No significant changes or abnormalities were observed in the following laboratory values: hemoglobin, reticulocytes, neutrophils, platelets, erythrocyte sedimentation rate, plasma orosomucoid, serum creatinine, urinary sediment and protein.

The clinical efficacy and safety of PENTASA 1 g suppositories were demonstrated in a multicentre, double-blind, randomized, placebo-controlled trial, involving 50 patients with active, mild to moderate ulcerative proctitis, for a two-week duration of treatment. Efficacy was assessed in terms of clinical symptoms (including daily stool frequency, presence of blood, discharge of mucus, rectal/abdominal pain) and proctoscopic scores. Clinical remission (defined as <4 stool frequency, absence of blood, mucus, rectal/abdominal pain) was achieved by 65.4% of patients in the PENTASA suppositories group vs. 25% in the placebo group ($p=0.005$). Proctoscopic remission, defined as absence of ulcerations or of bleeding either spontaneously or on contact, was reached by 69.2% of patients on PENTASA suppositories vs. 33.4% of patients on placebo ($p=0.05$). In this study, one patient in the PENTASA group experienced diarrhea on the first day of treatment only, whereas one patient in the placebo group experienced an increased frequency of bowel movements necessitating discontinuation of treatment.

The usefulness of PENTASA enema and suppositories for maintenance treatment and for preventing relapse of patients in remission from ulcerative colitis was also demonstrated by several investigators.

In one long-term study of up to 15 months duration, patients in remission received a 4 g PENTASA enema every other day, at bedtime. The dose could be tapered (i.e. the dosing frequency reduced) with the approval of both investigators and patient. On this regimen, 12 of 15 patients (80.0%), who were treated for 12 months, were maintained in remission.

In another, randomized, double-blind, placebo-controlled study, nine of twelve (75.0%) patients randomized to receive 1 g mesalazine enema/day remained in remission for one year. The difference between relapse rate on 1 g 5-ASA enema (25.0%) versus placebo (84.6%) was significant ($p<0.005$).

In their study, Guarino and collaborators examined the role of 4 g mesalazine enema in the long-term management of patients with previously refractory distal ulcerative colitis. Of 20 such patients treated with nightly mesalazine enemas, 16 improved symptomatically, with 15 achieving clinical remission and 14 achieving sigmoidoscopic remission within 3 to 5 weeks. These authors showed, by following up patients for up to 16 months, that, once remission is achieved, patients can be well managed with continued use of 4 g mesalazine enemas at less-than-nightly intervals and prompt reinstitution of nightly enemas in case of disease flare-ups.

Using 1 g mesalazine suppositories in a once-a-day regimen, Campieri and co-workers succeeded in maintaining 10 of 19 patients (53%) in remission from distal ulcerative colitis for 6 months.

DETAILED PHARMACOLOGY

TOXICOLOGY

The kidney appears to be the major target organ for mesalazine toxicity in animal studies. No significant toxicities associated with the gastrointestinal tract, liver, or hematopoietic system in animals have been observed.

Acute toxicity studies

In the acute toxicity study in pigs, using single oral doses of up to 5 g/kg body weight, no deaths were observed. Single intravenous doses of 920 mg/kg in rats were not fatal.

Multidose toxicity studies

In 13-week oral studies, no toxic effects were seen at 2400 mg/kg/day in the mouse and 480 mg/kg/day in the rat. Renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, and renal tubular necrosis, were observed in mice at 4000 mg/kg/day and rats at 2770 mg/kg/day. Minimal degrees of papillary necrosis and tubular degeneration were found in male rats at 1150 mg/kg/day. Chronic (1-year) administration to rats at doses greater than or equal to 1200 mg/kg/day resulted in papillary necrosis and interstitial nephritis; 800 mg/kg/day was a "no observable effect" dose.

A 13-week study in monkeys demonstrated renal toxicity at doses of 500 mg/kg/day. Renal lesions included interstitial fibrosis and corticomedullary edema without evidence of active nephritis. Monkeys treated with doses of 125 and 250 mg/kg/day experienced no adverse renal effects. A 1-year chronic study in monkeys produced nephrosis with doses of 250 mg/kg/day and 500 mg/kg/day.

Carcinogenicity, mutagenicity, and reproduction studies

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of Salmonella typhimurium with and without metabolic activation. A micronucleus test in mice also indicated that PENTASA was not mutagenic.

No effects on fertility or reproductive performance were observed in male or female rats at doses up to 400 mg/kg/day (seven times the maximum human dose). Reproduction studies have been performed in rats and rabbits at doses up to seventeen times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to mesalazine.

Preclinical toxicology studies used unformulated mesalazine, which, when administered orally, has a greater systemic absorption than formulated PENTASA. The therapeutic dose of mesalazine in humans is approximately 30 mg/kg/day to 60 mg/kg/day.

REFERENCES

1. Almer S, Norlander B, Strom M, et al. Steady-state pharmacokinetics of a new 4-gram 5-aminosalicylic acid retention enema in patients with ulcerative colitis in remission. Scand. J. Gastroenterol. 1991; 26: 327-335.
2. Arment, M.E. and Vargas, J.H. Medical therapy for ulcerative colitis in childhood. Seminars in Ped. Surg. 1994; 3(1): 28 - 32.
3. Azad Khan A.K, Piris J, Truelove S.C. An experiment to determine the active therapeutic moiety of sulphasalzine. Lancet. 1977:892-895.
4. Barber G.B, Lee D.E, Antonioli D.A, et al. Refractory distal ulcerative colitis responsive to 5-aminosalicylate enemas. Am. J. Gastroenterol. 1985; 80: 612-4.
5. Biddle W.L, Greenberger N.J, Swan J.T, et al. 5-aminosalicylic acid enemas: effective agent in maintaining remission in left-sided ulcerative colitis. Gastroenterology. 1988; 94: 1075-9.
6. Biddle W.L, Miner P.B. Long-term use of mesalamine enemas to induce remission in ulcerative colitis. Gastroenterology. 1990; 99: 113-118.
7. Bondesen S, Bronnum Schou J, Pedersen V, et al. Absorption of 5-aminosalicylic acid from colon and rectum - short report. Br. J. Clin. Pharmacology. 1988; 25: 269-272.
8. Bondesen S, Haagen Nielsen O, Jacobsen O, et al. 5-Aminosalicylic acid enemas in patients with active ulcerative colitis. Scand. J. Gastroenterol. 1984; 19: 677-682.
9. Bondesen S, Rasmussen S.N, Rask-Madsen J, et al. 5-aminosalicylic acid in the treatment of inflammatory bowel disease. Acta Med Scand. 1987; 221: 227-242.
10. Bondesen, S. Mesalamine (Pentasa7) as prophylaxis in Crohn's Disease: a multi-center, controlled trial. Scand. J. Gastroenterol., 1991; 26 (F44): 68.
11. Bouhanick B., Fauvel J., Pont F. Biochemical misdiagnosis of pheochromocytoma in patients treated with sulfasalazine. JAMA (2010) 304: 1898-1901.
12. Campieri M, DeFranchis R, Bianchi Porro G, et al. Mesalazine (5-aminosalicylic acid) suppositories in the treatment of ulcerative proctitis or distal proctosigmoiditis. Scand. J. Gastroenterol. 1990; 25: 663-668.
13. Campieri M, Gionchetti P, Belluzzi A, et al. Optimum dosage of 5-aminosalicylic acid as rectal enemas in patients with active ulcerative colitis. Gut. 1991; 32: 929-931.
14. Campieri M, Gionchetti P, Belluzzi A, et al. 5-Aminosalicylic acid suppositories in the management of ulcerative colitis. Dis. Colon Rectum. 1989; 32: 398-399.
15. Campieri M, Gionchetti P, Belluzzi A, et al. Sucralfate, 5-aminosalicylic acid and placebo enemas in the treatment of distal ulcerative colitis. Eur. J. Gastroent. Hepatol. 1991; 3: 41-44.
16. Campieri M, Lanfranchi G.A, Bazzocchi G, et al. Treatment of ulcerative colitis with high-dose 5-aminosalicylic acid enemas. Lancet. 1981:270-271.
17. Campieri M, Lanfranchi G.A, Boschi S, et al. Topical administration of 5-aminosalicylic acid enemas in patients with ulcerative colitis. Studies on rectal absorption and excretion. Gut. 1985; 26: 400-405.
18. Campieri M, Lanfranchi G.A, Brignola C, et al. Retrograde spread of 5-aminosalicylic acid enema in patients with active ulcerative colitis. Dis. Colon Rectum. 1986; 29: 108-110.

19. Christensen, L.A., Fallingborg, J., Jacobsen, B. et al. Bioavailability of 5-aminosalicylic acid from slow release 5-aminosalicylic acid drug and sulfasalazine in normal children. Digestive Dis. Sci. 1993; 38: 1831 - 1836.
20. Christensen LA, Rasmussen SN, Hansen SH, et al. Salazosulfapyridine and metabolites in fetal and maternal body fluids with special reference to 5-aminosalicylic acid. Acta Obstet Gynecol Scand 1987; 66: 433-5.
21. Cuffari, C., Hunt, S., Bayliss, T.M. Utilization of Erythrocyte Metabolite Levels to Optimize Azathioprone Therapy in patients with Inflammatory Bowel Disease; GUT 2001; 48: 642-6.
22. Danish 5-ASA group. Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis - a randomized, double-blind multicenter trial. Dig. Dis. Sci. 1987; 32: 598-602.
23. De Boer NKH, Wong DR, Jharap B, et al. Dose-dependent influence of 5-aminosalicylates on thiopurine metabolism. Am J Gastroenterol 2007; 102: 2747-53.
24. Dew M.J, Cardwell M, Kidwai N.S, et al. 5-aminosalicylic acid in serum and urine after administration by enema to patients with colitis. J. Pharm. Pharmacol. 1983; 35: 323-374.
25. Dewit, O., Vanheuverzwyn, R., Desager, J-P., and Horsmans, Y. Interaction between Azathioprine and Aminosalicylates: An in vivo Study in Patients with Crohn's disease. Ailment. Pharm. Ther. 2002; 16: 79-85
26. Fallingborg, J., Christensen, L.A., Ingeman-Nielsen, M. et al. Measurement of gastrointestinal pH and regional transit times in normal children. J. Ped. Gastroenterol. Nut. 1990; 2: 211 - 214.
27. Friedman F.S, Richter J.M, Kirkham S.E, et al. 5-aminosalicylic acid enemas in refractory distal ulcerative colitis: a randomized, controlled trial. Am. J. Gastroenterol. 1986;86:412-8.
28. Gendre, J-P., Mary, J-Y., Florent, C. et al. Oral mesalamine (Pentasa7) as maintenance treatment in Crohn's Disease: a multicenter placebo-controlled study. Gastroenterology, 1990; 104: 435 - 439.
29. Griffiths, A., Koletzko, S., Sylvester, F. et al. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's Disease. J. Ped. Gastroenterol. Nutr. 1993; 17:186 - 192.
30. Guarino J, Chatzinoff M, Berk T, et al. 5-aminosalicyclic acid enemas in refractory distal ulcerative colitis: long term results. Am. J. Gastroenterol. 1987; 82: 732-737.
31. Hanauer S.B, Stathopoulos G. Risk-benefit assessment of drugs used in the treatment of inflammatory bowel disease. Drug Safety. 1991;6:192-219.
32. Hanauer, S.B., Krawitt, E.L., Robinson, M. et al. Long term management of Crohn's disease with mesalamine capsules (Pentasa7). Am. J. Gastroent., 1993;88(9): 1343 - 1351.
33. Hanauer, S.B., Schwartz, J., Robinson, M. et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Am. J. Gastroent., 1993; 88: 1188 - 1197.

34. Hardy, J.G., Harvey, W.J., Sparrow, R.A., et al. Localization of drug release sites from an oral sustained-release formulation of 5-ASA (Pentasa7) in the gastrointestinal tract using gamma scintigraphy. J. Clin. Pharmacol. 1993; 33: 712 - 718.
35. Hendy P, Chadwick G, Hart A. IBD: reproductive health, pregnancy and lactation. Frontline Gastroenterol 2015; 6: 38-43
36. Ho, G., Lees, C., Satsangi, J. Pharmacogenetics in Inflammatory Bowel Disease; Inflammatory Bowel Disease; Vol. 10, No. 2, March 2004: 148-158.
37. Ito T., Imai T., Kikumori T., Shibata A., Horiba T., Kobayashi H., Sawaki M., Watanabe R., Nakao A., Kiuchi T. Adrenal incidentaloma: review of 197 patients and report of a drug-related false-positive urinary normetanephrine result. Surg. Today (2006) 36: 961-965.
38. Jacobsen B.A, Abildgaard K, Rasmussen H.H, et al. Availability of mesalazine (5-aminosalicylic acid) from enemas and suppositories during steady-state conditions. Scand. J. Gastroenterol. 1991;26:374-378.
39. Layer, P.H., Goebell, H., Keller, J. et al. Delivery and fate of oral mesalamine microgranules within the human small intestine. Gastroenterology 1995; 108: 1427 - 1433.
40. Lowry, P.W., Franklin, C.L., Weaver, A.L., Gennett, Pike M., Mays, D.C., Tremaine, W.J., Lipsky, J.J., and Sandborn, W.J. *Measurement of Thiopurine Methyltransferase Activity and Azathioprine Metabolites in Patients with Inflammatory Bowel Disease*. GUT, 2001; 49: 665-670.
41. Lowry, P.W., Franklin, C.L., Weaver, A.L., Szumlanski, C.L., Mays, D.C., Loftus, E.V., Tremaine, W.J., Lipsky, J.J., Weinshilboum, R.M. and Sandbourn, W.J. Leucopenia Resulting from a Drug Interaction between Azathioprine or 6-mercapopurine and mesalamine, Sulphasalzine, or Balsalazide. GUT, 2001; 49: 656-664.
42. Marteau P, Tennenbaum R, Elefant E, et al. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. Aliment Pharmacol Ther 1998; 12: 1101-8.
43. Messori A., Brignola C, Trallori, G. et al. Effectiveness of 5-Aminosalicyclic acid for maintaining remission in patients with Crohn's disease: a meta-analysis. Am. J. Gastroenterol. 1994;89(5): 692-698.
44. Meyers F.A, Vitti R, Knight L, et al. Colonic distribution of 5-asa enemas in patients with ulcerative colitis. Gastroenterology. 1988; 94: A302.
45. Miner P.B Jr, Biddle R.N. Maintaining remission in distal ulcerative colitis and ulcerative proctitis. Can. J. Gastroenteral. 1990;4(7):476-480.
46. Miner, P., Schwartz, J., Aora, S. et al. Maintenance of remission in ulcerative colitis (UC) patients with controlled-release mesalamine capsules (Pentasa7). Gastroenterology, 1992;102: A666.
47. Norgard B, Fonager K, Pedersen L, et al. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: A Danish cohort study. Gut 2003; 52: 243-7.
48. Present, D.H. Interaction of 6-Mercaptopurine and Azathioprine with 5-Aminosalicyclic Acid Agents. Gastroenterology, 2000; 119 (1): 276.
49. Rasmussen, S.N., Binder, V., Maier, K. et al. Treatment of Crohn's Disease with Peroral 5-aminosalicyclic acid. Gastroenterology. 1983; 85: 1350-1353.

50. Rasmussen, S.N., Bondesen, E.F., Hvidberg, S. et al. 5-Aminosalicyclic acid in a slow release preparation: bioavailability, plasma level, and excretion in humans. Gastroenterology, 1982;83: 1062 - 1070.
51. Rasmussen, S.N., Lauritsen, K., Tage-Jensen, U. et al. 5-aminosalicylic acid in the treatment of Crohn's Disease: a 16-week double-blind, placebo-controlled, multicentre study with Pentasa7. Scand. J. Gastroenterol., 1987;22: 877 - 883.
52. Rijk, M.C.M., Van Schaik, A., and Van Tongeren, J.H.M. Disposition of 5-aminosalicylic acid by 5-aminosalicylic acid delivering compounds. Scand. J. Gastroenterol., 1988; 23: 107- 112.
53. Robinson M.G, Decktor D.L. Efficacy of 5-aminosalicylic acid enemas in the treatment of distal ulcerative colitis. Can. J. Gastroenterol. 1990;4(7):468-471.
54. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: A meta-analysis. Reprod Toxicol 2008; 25: 271-5.
55. Saverymuttu, S.H., Gupta, S., Keshavarzian, A. et al. Effect of a slow-release 5-aminosalicyclic acid preparation on disease activity in Crohn's Disease. Digestion, 1986; 33: 89 - 91.
56. Scagnelli, G.P, Barreiro, M.A. and Bank, L. Treatment of inflammatory bowel disease (IBD) with oral 5-amino salicylic acid (5-ASA) (Pentasa) in the pediatric age group. Gastroenterol. 1991; 100: A248.
57. Schwab, M., Herrlinger, K., Schaeffer, E., Stange, E.F. Treatment of Chronic Inflammatory Bowel Disease with Azathioprine, 6-Mercaptopurine and 6-Thioguanine. Clinical Pharmacology Aspects; Deutsche Med. Wochenschr; 126, No. 8, 378-84, 2003.
58. Singleton, J.W., Hanauer, S.B., Gitnick, G.L. et al. Mesalamine capsules for the treatment of active Crohn's Disease: result of a 16 week trial. Gastroenterology, 1993; 104: 1293 - 1301.
59. Sutherland L.R, Martin F, Greer S, et al. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis. Gastroenterology. 1987; 92: 1894-1898.
60. Thomson A.B.R. Review article: new developments in the use of 5-aminosalicylic acid in patients with inflammatory bowel disease. Aliment. Pharm. Ther. 1991;5:449-470.
61. Tiel-van Buul M.M.C, Mulder J.J, van Royen A, et al. Retrograde spread of Mesalazine (5-aminosalicylic acid) - containing enema in patients with ulcerative colitis. Clin. Pharmacokinet. 1991; 20: 247-251.
62. Tolia, V., Massoud, N., and Klotz, U. Oral 5-aminosalicylic acid in children with colonic chronic inflammatory bowel disease: clinical and pharmacokinetic experience. J. Ped. Gastroenterol. Nutr. 1989; 8(3): 333 - 338.
63. Walsh N. Sulfasalazine induced falsely positive urinary catecholamines. Rheumatology News 5[8], 11. 2006.
64. Williams C.N, Haber G, Aquino J.A, et al. Double-blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using 99m Tc-labeled 5-ASA suppositories. Dig. Dis. Sci. 1987; 32: 71S-75S.

65. Williams C.N. Efficacy and tolerance of 5-aminosalicylic acid suppositories in the treatment of ulcerative proctitis: A review of two double-blind, placebo controlled trials. Can. J. Gastroenterol. 1990:4(7):472-475.
66. Willoughby C.P, Piris J, Truelove S.C, et al. The effect of topical N-acetyl-5-aminosalicyclic acid in ulcerative colitis. Scand. Journ. Gastro. 1980;15:715-719.
67. Rijk MC, van Hogezand RA, van SA, van Tongeren JH. Disposition of 5-aminosalicylic acid from 5-aminosalicylic acid-delivering drugs during accelerated intestinal transit in healthy volunteers. Scand J Gastroenterol 1989 Dec;24(10):1179-85.

PART III: CONSUMER INFORMATION (TABLETS)

PrPENTASA®
Mesalazine extended release tablets
500 mg and 1g

This leaflet is part III of a three-part "Product Monograph" published when PENTASA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PENTASA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PENTASA tablets contain extended release granules of mesalazine (also known as 5-aminosalicylic acid, 5-ASA, or mesalamine), which is an anti-inflammatory drug for the treatment of and/or to help maintain remission and prevention of relapse in patients with Ulcerative Colitis or Crohn's Disease.

Ulcerative Colitis is a disease of the large bowel (colon) and back passage (rectum), where the lining of the gut becomes red and swollen (inflamed) resulting in symptoms of frequent and bloody stools together with stomach cramps.

Crohn's disease is a form of inflammatory bowel disease (IBD). It usually affects the intestines, but may occur anywhere from the mouth to the end of the rectum (anus).

What it does:
It is believed that PENTASA blocks the production and action of certain substances (cyclo-oxygenase, prostaglandins and others) involved in producing inflammation. PENTASA passes throughout the colon and rectum to treat this inflammation and reduces symptoms, such as bloody stools and diarrhea.

When it should not be used:
- If you are allergic to this drug or its ingredients or parts of the container (see What the nonmedicinal ingredients are)
- If you are allergic to a family of drugs known as salicylates (which includes acetylsalicylic acid (i.e. Aspirin†)
- If you have severe liver problems
- If you have severe kidney problems
- If you have a stomach or intestinal ulcer
- If you have a urinary tract obstruction
- If the patient is an infant under 2 years of age

What the medicinal ingredient is:
Mesalazine (also known as mesalamine, 5-ASA or 5-aminosalicylic acid).

What the important nonmedicinal ingredients are:
Microcrystalline cellulose, ethylcellulose, magnesium stearate, povidone and talc.

PENTASA tablets do not contain gluten, lactose or phthalates.

What dosage forms it comes in:
PENTASA 500 mg Extended Release Tablets are round, white-grey to pale brown speckled tablets embossed "500 mg" with a scoreline on one side and embossed PENTASA on the other.

PENTASA 1g Extended Release Tablets are oblong, white-grey to pale brown speckled tablets embossed PENTASA on both sides.

WARNINGS AND PRECAUTIONS

BEFORE you use PENTASA, talk to your doctor or pharmacist if:
- You have pyloric stenosis (a narrowing of the outlet from the stomach that causes contents of the stomach to remain there for a longer period of time)
- You have any kidney or liver problems
- You have digestive (peptic) ulcers
- You have had previously inflammation of the heart (which may be the result of an infection of the heart)
- You have chronic lung problems (e.g. asthma, bronchitis etc.)
- You think you might be pregnant or are breast-feeding, since mesalazine crosses the placenta in pregnancy and is excreted in breast milk in small quantities. You should ask your doctor for advice about taking PENTASA in these circumstances.
- You have had previous allergy (hypersensitivity reaction) to sulfasalazine (an ingredient in other medicines used to treat ulcerative colitis)
- You have had any allergies to this drug or its ingredients or parts of the container

INTERACTIONS WITH THIS MEDICATION

The simultaneous use of mesalazine with drugs known to affect the kidney, including some anti-inflammatory drugs (NSAIDS) and azathioprine, may increase the risk of renal (kidney) reactions.

In patients receiving azathioprine or 6-mercaptopurine, simultaneous use of mesalazine can increase the possibility of having abnormal blood cells.

Tell your doctor if you are taking anticoagulants (e.g. coumarin), probenecid, sulfinpyrazone, spironolactone, furosemide, rifampicin and methotrexate.

PROPER USE OF THIS MEDICATION

Always take PENTASA as directed by your doctor. Management of mild to moderate active ulcerative colitis and maintenance therapy in adults: 0.5 g four times daily (2 g daily dose). In some cases, your doctor may increase the dose up to 1 g four times daily (4 g daily dose) if required.

Management of mild to moderate Crohn's disease in adults: 1 g four times daily (4 g daily dose). For patients with Crohn's Disease in remission, the usual dose is 3 g daily in divided doses.

PENTASA extended-release tablets should not be chewed, broken or crushed but should be swallowed whole with plenty of water.

PENTASA extended-release tablets should be taken with meals.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take your tablets, then take them as usual the next day. Do not take a double dose to make up for a forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, PENTASA can cause side effects, although not everybody gets them. The most common side effects are abdominal pain, vomiting, rash, fatigue, fever, back pain, dizziness, headache, itching skin (pruritis), diarrhea and feeling sick (nausea).

Other less common side effects (seen in less than 1 in 100 patients) are dizziness, feeling sleepy or tired, trembling or shaking, ear or throat pain, inflammation of some areas of the heart (myocarditis and pericarditis) which can cause shortness of breath and chest pain or palpitations (rapid or irregular heartbeats), changes in blood pressure, painful or bloated stomach, hair loss, indigestion, acne, rash, joint aches or pains, back pain, weakness, increased sensitivity of your skin to sun and ultraviolet light (photosensitivity), swollen face, reduced kidney function, decrease in bile flow, an inflamed pancreas or colon (associated with pain in upper abdomen and back and feeling sick). Rarely, decreased sperm count and motility which may be reversible when treatment is stopped.

The following side effects are associated with other medicines containing mesalazine. These are: low blood cell counts; neuropathy (abnormal or damaged nerves giving a sensation of numbness and tingling), inflammation of the heart and lining around the heart; inflammation of the lung, difficulty in breathing; gall stones, hepatitis (inflammation of the liver giving rise to flu-like symptoms and jaundice), allergic swelling of tongue, lips and around eyes, skin redness, muscular pain, kidney problems (such as inflammation and scarring of the kidney).

If any of the side effects become serious or persist, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	**Blood problems** and symptoms such as unexplained bruising, unusual bleeding (for example, nose bleeds), anemia (feeling weak), fever, sore throat **Pancreatitis** (inflamed or swollen pancreas) and symptoms such as abdominal pain and feeling sick.		√	
	Acute Intolerance Syndrome – symptoms include 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.			√
	Allergic reaction – symptoms include swelling of the mouth, throat, difficulty in breathing and rash. **Hepatitis** including liver failure (inflammation of the liver) – symptoms include jaundice (yellowing of the skin and eyes) and flu-like symptoms.		√	

This is not a complete list of side effects. For any unexpected effects while taking PENTASA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C to 30°C). Protect from light.

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be provided by contacting the sponsor, Ferring Inc. at: 1-866-384-1314.

This leaflet was prepared by Ferring Inc.

FERRING
PHARMACEUTICALS

Last revised: May 2, 2018

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PART III: CONSUMER INFORMATION (ENEMA)

PrPENTASA®
Mesalazine rectal suspension
1 g/100 mL and 4 g/100mL (Enema)

This leaflet is part III of a three-part "Product Monograph" published when PENTASA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PENTASA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed PENTASA mesalazine (also known as 5-aminosalicylic acid, 5-ASA or mesalamine) enemas for treatment of acute distal Ulcerative Colitis extending to the splenic flexure and for long- term maintenance therapy in order to maintain remission and prevent relapse of active disease. Ulcerative Colitis occurs in the large bowel. Distal Ulcerative Colitis occurs in the last part of the bowel, from the rectum up to the splenic flexure shown by the light shaded area.

Currently there is no cure for Ulcerative Colitis, but medical therapy can bring the bleeding, diarrhea, and/ or cramping under control. Medications such as PENTASA are used to calm the inflamed tissue. To do this, the medication must cover the diseased area. Best results are obtained when the entire enema contents are used, so that complete coverage of the grey shaded area can occur.

What it does:
It is believed that PENTASA blocks the production and action of certain substances (cyclo-oxygenase, prostaglandins and others) involved in producing inflammation. PENTASA acts throughout the colon and rectum to treat this inflammation and reduces symptoms, such as bloody stools and diarrhea.

When it should not be used:
- If you are allergic to this drug or its ingredients or parts of the container (see What the nonmedicinal ingredients are)
- If you are allergic to a family of drugs known as salicylates (which includes acetylsalicylic acid (i.e. Aspirin†)
- If you have severe liver problems
- If you have severe kidney problems
- If you have a stomach or intestinal ulcer
- If you have a urinary tract obstruction
- If the patient is an infant under 2 years of age

What the medicinal ingredient is:
Mesalazine (also known as mesalamine, 5-ASA or 5-aminosalicylic acid)

What the important nonmedicinal ingredients are:
sodium acetate, sodium edetate, sodium metabisulfite, purified water, with hydrochloric acid to adjust the pH to 4.8.

PENTASA is phthalate free.

What dosage forms it comes in:
Enema: 1g per 100 mL and 4g per 100 mL

WARNINGS AND PRECAUTIONS

BEFORE you use PENTASA, talk to your doctor or pharmacist if:
- You have pyloric stenosis (a narrowing of the outlet from the stomach that causes contents of the stomach to remain there for a longer period of time)
- You have any kidney or liver problems
- You have digestive (peptic) ulcers.
- You have had previously inflammation of the heart (which may be the result of an infection of the heart)
- You have chronic lung problems (e.g. asthma, bronchitis)
- You think you might be pregnant or are breast-feeding, since mesalazine crosses the placenta in pregnancy and is excreted in breast milk in small quantities. You should ask your doctor for advice about taking PENTASA in these circumstances.
- You have had previous allergy (hypersensitivity reaction) to sulfasalazine (an ingredient in other medicines used to treat ulcerative colitis)
- You have had any allergies to this drug or its ingredients or components of the container

INTERACTIONS WITH THIS MEDICATION

The simultaneous use of mesalazine with drugs known to affect the kidney, including some anti-inflammatory drugs and azathioprine may increase the risk of renal reactions.

In patients receiving azathioprine or 6-mercaptopurine, simultaneous use of mesalazine can increase the possibility of having abnormal blood components.

Tell your doctor if you are taking anticoagulants (e.g. coumarin), probenecid, sulfinpyrazone, spironolactone, furosemide, rifampicin and methotrexate.

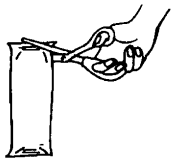
PROPER USE OF THIS MEDICATION

Directions for Adult Use

BEST RESULTS ARE ACHIEVED IF THE BOWEL IS EMPTIED IMMEDIATELY BEFORE THE ENEMA IS GIVEN. ONE ENEMA SHOULD BE USED AT BEDTIME FOR A PERIOD DIRECTED BY YOUR DOCTOR. RETAIN THE ENEMA OVERNIGHT FOR BEST RESULTS.

1. Removing the bottle

Remove the bottle from the protective foil pouch by using scissors as shown below. Be careful not to puncture the bottle inside.

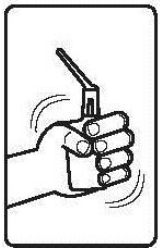


The enema should be used immediately after opening of the bag.

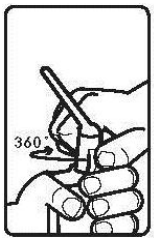
Preparing the medication for use

a. Begin by holding the bottle for a few minutes. Doing this raises the temperature of the medication closer to your body temperature reducing the temperature shock you might experience and making it easier to retain the enema.

b. Shake the bottle well until the medicine is evenly distributed in the liquid.



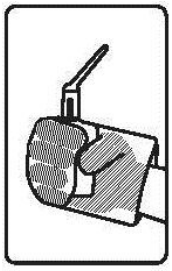
c. To break the seal, twist the nozzle clockwise one full turn (the nozzle should then be in the same direction as before turning).



d. Lubricate top part of rectal applicator including the tip with petroleum jelly (or other lubricant).

e. For sanitary and disposal purposes, a plastic bag is provided. Insert your hand into the bag and grasp the enema bottle.

f. Hold the container as shown in the picture.

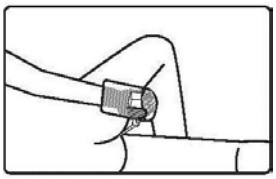


2. Administrating the enema

a. To administer the lubricated enema, lie on your left side with the left leg straight and the right leg bent forward for balance. This is called the ***administration position***.

3. Administration position

a. Carefully insert the applicator tip into the rectum. Maintain sufficient steady hand pressure while dispersing the bottle content. The bottle content should be applied within max. 30-40 seconds.

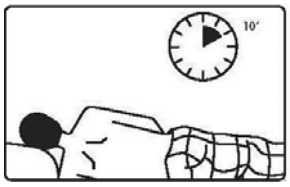


4. Disposal of the enema bottle

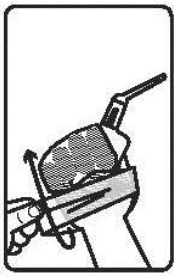
a. Once the bottle is empty, withdraw the tip with the bottle still compressed.

b. Pull up the plastic bag to encase the empty enema bottle.

c. The enema should be retained in the bowel. Remain relaxed in the *administration position* for 5-10 minutes or until the urge to pass the enema has disappeared. Try to retain the enema overnight.



d. Discard the empty bagged enema bottle and wash your hands.



If you have any questions do not hesitate to discuss them with your doctor or pharmacist.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your dose before bedtime, take the medication as soon as you remember IF you will be able to retain the enema. If this is not possible administer the next bedtime dose, the next evening.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, PENTASA can cause side effects, although not everybody gets them. The most common side effects are anal discomfort, irritation at the application site, tenesmus (feeling the urge to have a bowel movement), excessive gas, abdominal pain, vomiting, rash, fatigue, fever, back pain, dizziness, headache, itching skin (pruritis), diarrhea and feeling sick (nausea).

Other less common side effects (seen in less than 1 in 100 patients) are dizziness, feeling sleepy or tired, trembling or shaking, ear or throat pain, inflammation of some areas of the heart (myocarditis and pericarditis) which can cause shortness of breath and chest pain or palpitations (rapid or irregular heartbeats), changes in blood pressure, painful or bloated stomach, hair loss, indigestion, acne, rash, joint aches or pains, back pain, weakness, increased sensitivity of your skin to sun and ultraviolet light (photosensitivity), swollen face, reduced kidney function, decrease in bile flow, an inflamed pancreas or colon (associated with pain in upper abdomen and back and feeling sick). Rarely- decreased sperm count and motility which may be reversible when treatment is stopped.

The following side effects are associated with other medicines containing mesalazine. These are: low blood cell counts; neuropathy (abnormal or damaged nerves giving a sensation of numbness and tingling), inflammation of the heart and lining around the heart; inflammation of the lung, difficulty in breathing; gall stones, hepatitis (inflammation of the liver giving rise to flu-like symptoms and jaundice), allergic swelling of tongue, lips and around eyes, skin redness, muscular pain, kidney problems (such as inflammation and scarring of the kidney).

If any of the side effects become serious or persist, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	**Blood problems** and symptoms such as unexplained bruising, unusual bleeding (for example, nose bleeds), anemia (feeling weak), fever, sore throat **Pancreatitis** (inflamed or swollen pancreas) and symptoms such as abdominal pain and feeling sick.		√	
	Acute Intolerance Syndrome – symptoms include 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.			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your**
	Allergic reaction – symptoms include swelling of the mouth, throat, difficulty in breathing and rash. **Hepatitis** including liver failure (inflammation of the liver) – symptoms include jaundice (yellowing of the skin and eyes) and flu-like symptoms.		√	

This is not a complete list of side effects. For any unexpected effects while taking PENTASA, contact your doctor or pharmacist.

HOW TO STORE IT

PENTASA (mesalazine) rectal suspension (enema) should be stored at controlled room temperature, preferably below 25°C and dispensed in the original containers.

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be provided by contacting the sponsor, Ferring Inc. at: 1-866-384-1314.

This leaflet was prepared by Ferring Inc.

FERRING PHARMACEUTICALS

Last revised: May 2, 2018

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PART III: CONSUMER INFORMATION (SUPPOSITORY)

PrPENTASA®
Mesalazine suppository 1 g

This leaflet is part III of a three-part "Product Monograph" published when PENTASA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PENTASA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed PENTASA (mesalazine, also known as 5-aminosalicylic acid, 5-ASA or meslamine) suppositories for your acute Ulcerative Proctitis and for long-term maintenance therapy in order to maintain remission and prevent relapse of active disease.

Acute ulcerative proctitis is an inflammation of the lining of the rectum (rectum is the last 6 inches of the large intestine).

Currently there is no cure for Ulcerative Proctitis but medical therapy can bring the bleeding, diarrhea, and/ or cramping under control. Medications such as Pentasa are used to calm the inflamed tissue. To do this, the medication must cover the diseased area.

What it does:
It is believed that PENTASA blocks the production and action of certain substances (cyclo-oxygenase, prostaglandins and others) involved in producing inflammation. PENTASA acts throughout the colon and rectum to treat this inflammation and reduces symptoms, such as bloody stools and diarrhea.

When it should not be used:
- If you are allergic to this drug or its ingredients or parts of the container (see What the nonmedicinal ingredients are)
- If you are allergic to a family of drugs known as salicylates (which includes acetylsalicylic acid (i.e. Aspirin†)
- If you have severe liver problems
- If you have severe kidney problems
- If you have a stomach or intestinal ulcer
- If you have a urinary tract obstruction
- If the patient is an infant under 2 years of age

What the medicinal ingredient is:
Mesalazine, also known as mesalamine, 5-ASA or 5-aminosalicylic acid.

What the important nonmedicinal ingredients are:
magnesium stearate, polyethylene glycol, povidone, talc

Pentasa is phthalate free.

What dosage forms it comes in:
Suppository contains 1 g of mesalazine

WARNINGS AND PRECAUTIONS

BEFORE you use PENTASA, talk to your doctor or pharmacist if:
- You have pyloric stenosis (a narrowing of the outlet from the stomach that causes contents of the stomach to remain there for a longer period of time)
- You have any kidney or liver problems
- You have digestive (peptic) ulcers
- You have had previously inflammation of the heart (which may be the result of an infection of the heart)
- You have chronic lung problems (e.g. asthma, bronchitis)
- You think you might be pregnant or are breast-feeding, since mesalazine crosses the placenta in pregnancy and is excreted in breast milk in small quantities. You should ask your doctor for advice about taking PENTASA in these circumstances.
- You have had previous allergy (hypersensitivity reaction) to sulfasalazine (an ingredient in other medicines used to treat ulcerative colitis)
- You have had any allergies to this drug or its ingredients or components of the container

INTERACTIONS WITH THIS MEDICATION

The simultaneous use of mesalazine with drugs known to affect the kidney, including some anti-inflammatory drugs and azathioprine, may increase the risk of renal reactions.

In patients receiving azathioprine or 6-mercaptopurine, simultaneous use of mesalazine can increase the possibility of having abnormal blood components.

Tell your doctor if you are taking anticoagulants (e.g. coumarin), probenecid, sulfinpyrazone, spironolactone, furosemide, rifampicin and methotrexate.

PROPER USE OF THIS MEDICATION

Directions for Adult Use: One suppository at bedtime for a period determined by your doctor.

SUPPOSITORIES ARE NOT TO BE TAKEN BY MOUTH

1. We recommend that the bowel be emptied, if possible, prior to the suppository being administered.

2. Push the suppository through the foil blister.

3. You may lubricate the suppository with a water based lubricant to aid in the insertion of the suppository.

4. Using a rubber finger protector on your index finger, insert the suppository, either end first, into the rectum.

   NOTE: the inserting of the suppository can be done while in a standing position or laying down with one leg bent. The suppository should be inserted as far into the rectum as possible.

5. For best results, retain the suppository as long as possible.

   NOTE: If the suppository is discharged within the first 10 minutes, a new one can be inserted.

6. Discard the rubber finger protector.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take your dose before bedtime, take the medication as soon as you remember IF you will be able to retain the suppository. If this is not possible administer the next bedtime dose, the next evening.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, PENTASA can cause side effects, although not everybody gets them. The most common side effects are anal discomfort, irritation at the application site, tenesmus (feeling the urge to have a bowel movement), excessive gas, abdominal pain, vomiting, rash, fatigue, fever , back pain, dizziness, headache, itching skin (pruritis), diarrhea and feeling sick (nausea).

Other less common side effects (seen in less than 1 in 100 patients) are dizziness, feeling sleepy or tired, trembling or shaking, ear or throat pain, inflammation of some areas of the heart (myocarditis and pericarditis) which can cause shortness of breath and chest pain or palpitations (rapid or irregular heartbeats), changes in blood pressure, painful or bloated stomach, hair loss, indigestion, acne, rash, joint aches or pains, back pain, weakness, increased sensitivity of your skin to sun and ultraviolet light (photosensitivity), swollen face, reduced kidney function, decrease in bile flow, an inflamed pancreas or colon (associated with pain in upper abdomen and back and feeling sick). Rarely-decreased sperm count and motility which may be reversible when treatment is stopped.

The following side effects are associated with other medicines containing mesalazine. These are: low blood cell counts; neuropathy (abnormal or damaged nerves giving a sensation of numbness and tingling), inflammation of the heart and lining around the heart; inflammation of the lung, difficulty in breathing; gall stones, hepatitis (inflammation of the liver giving rise to flu-like symptoms and jaundice), allergic swelling of tongue, lips and around eyes, skin redness, muscular pain, kidney problems (such as inflammation and scarring of the kidney).

If any of the side effects become serious or persist, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	**Blood problems** and symptoms such as unexplained bruising, unusual bleeding (for example, nose bleeds), anemia (feeling weak), fever, sore throat **Pancreatitis** (inflamed or swollen pancreas) and symptoms such as abdominal pain and feeling sick.		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or**
	Acute Intolerance Syndrome – symptoms include 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.			√
	Allergic reaction – symptoms include swelling of the mouth, throat, difficulty in breathing and rash. **Hepatitis** including liver failure (inflammation of the liver) – symptoms include jaundice (yellowing of the skin and eyes) and flu-like symptoms.		√	

This is not a complete list of side effects. For any unexpected effects while taking PENTASA, contact your doctor or pharmacist.

HOW TO STORE IT

PENTASA suppositories should be stored at
15 – 25 °C and dispensed in the original containers.

Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be provided by contacting the sponsor, Ferring Inc. at: 1-866-384-1314.

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