PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr TEVA-5 ASA

5-aminosalicylic Acid Tablets
Enteric Coated Tablets, 400 mg, Oral

Teva Standard

Lower Gastrointestinal Anti-inflammatory

Teva Canada Limited
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M1B 2K9

Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Renal	11/2021
7 WARNINGS AND PRECAUTIONS, Acute Intolerance Syndrome	11/2021
7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast- Feeding	11/2021

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-5 ASA (5-aminosalicylic acid) is indicated for:

- the treatment of mild to moderate active ulcerative colitis
- the maintenance of remission of mild to moderate ulcerative colitis. TEVA-5 ASA at the dosage tested of 1.6 g/day may not be effective for the maintenance of remission when the underlying disease is severe.

Abrupt discontinuation may result in relapse.

1.1 Pediatrics

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

1.2 Geriatrics

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

2 CONTRAINDICATIONS

TEVA-5-ASA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

TEVA-5-ASA is contraindicated in:

- Patients with a history of sensitivity to salicylates
- Patients with severe renal impairment (GFR<30ml/min/1.73m^2) and/or severe hepatic impairment (see WARNINGS & PRECAUTIONS – Renal and Hepatic/Biliary/Pancreatic)
- Patients with existing gastric or duodenal ulcer
- Patients with urinary tract obstruction
- Patients unable to swallow the intact tablets

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Hypersensitivity:** If toxic or hypersensitivity reactions occur, the drug should be discontinued. In assessing liver and joint complications, it should be kept in mind that these are frequently associated with ulcerative colitis.

- **Renal:** Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and renal failure has been reported in patients taking 5-aminosalicylic acid tablets as well as in patients taking other mesalamine products**.** 5-aminosalicylic acid is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS). It is recommended that all patients have an evaluation of renal function prior to initiation of 5-aminosalicylic acid tablets and periodically while on 5-aminosalicylic acid therapy. For patients with moderate or mild renal impairment, see WARNINGS AND PRECAUTIONS.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

For the treatment of mildly to moderately active ulcerative colitis: Usual daily adult dose is 2 to 8 TEVA-5 ASA 400 mg tablets, taken orally in divided doses. In patients with severe active disease, the dose may be increased to 12 tablets daily.

For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 4 tablets, taken orally in divided doses. The treatment duration in a well-controlled clinical trial was 6 months.

Abrupt discontinuation is not recommended.

Ulcerative colitis rarely remits completely. Thus, it is important for patients to closely comply with the maintenance dosage prescribed by their doctors. By doing so, the risk of relapse can be substantially reduced.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Tablets should be swallowed whole, taking care not to break the outer coating. The outer coating is designed to remain intact, to protect the active ingredient until it reaches the terminal ileum, where the tablet coating dissolves and the contents of the tablet are released into the terminal ileum and colon.

Patients should be advised to take TEVA-5 ASA tablets only as prescribed. The number or frequency of tablets ingested should not be changed without first consulting their physician.

Intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, the patient should be advised to consult their physician.

4.5 Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take double the dose.

5 OVERDOSAGE

There are no documented reports of serious human toxicity following overdose with mesalamine. Based on the adverse effect profile, symptoms that might be observed following acute overdose include headache, abdominal pain, nausea, vomiting, and diarrhea. Mesalamine is not metabolized to salicylate. There is no specific antidote and treatment is symptomatic and supportive. In treatment of acute overdose, activated charcoal and/or gastric lavage may be indicated if implemented within sixty minutes from the time of ingestion.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	All Nonmedicinal Ingredients
oral	Enteric coated tablet 400 mg	Ethyl acrylate, hypromellose, iron oxide black, iron oxide red, magnesium stearate, mannitol, methacrylic acid copolymer (Type C), potassium sorbate, povidone, propylene glycol, purified water, and sodium citrate, sodium starch glycolate, talc, triethyl citrate, titanium dioxide and xanthan gum.

TEVA-5 ASA (5-aminosalicylic acid) is available as brown-red capsule shaped enteric-coated tablets each containing 400 mg of 5-aminosalicylic acid coated with an acrylic based resin supplied in bottles of 100 and 500.

Each tablet contains the following non-medicinal ingredients: ethyl acrylate, hypromellose, iron oxide black, iron oxide red, magnesium stearate, mannitol, methacrylic acid copolymer (Type C), potassium sorbate, povidone, propylene glycol, purified water, and sodium citrate, sodium starch glycolate, talc, triethyl citrate, titanium dioxide and xanthan gum.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

5-aminosalicylic acid and other mesalamine-containing products have differences in formulation and release characteristics that may lead to differences in concentrations of mesalamine delivered to the colon. If it is deemed necessary to switch from one mesalamine-containing product to another mesalamine-containing product, the prescriber should carefully assess the overall benefit-risk analysis based on the patient's clinical conditions and on all available information for the various mesalamine-containing products.

Acute Intolerance Syndrome

Mesalamine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's history of sulfasalazine intolerance, if any, should be re-evaluated. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. The possibility of increased absorption of mesalamine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on concurrent mesalamine and those with pre-existing renal disease, should be carefully monitored with urinalysis, blood urea nitrogen (BUN) and creatinine testing.

Driving and Operating Machinery

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

Gastrointestinal

Exacerbation of the symptoms of colitis, thought to have been caused by mesalamine or sulfasalazine, has been reported in 3% of patients in controlled clinical trials. This acute reaction, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported after the initiation of 5-aminosalicylic acid tablets as well as other mesalamine products. Symptoms usually abate when 5-aminosalicylic acid tablets are discontinued.

Patients with pyloric stenosis may have prolonged gastric retention of 5-aminosalicylic acid tablets which could delay release of mesalamine in the colon.

What appears to be intact or partially intact tablets may be observed in the stool.

Hepatic / Biliary / Pancreatic

Caution should be exercised when using TEVA-5 ASA (or other compounds which contain or are converted to mesalamine or its metabolites) in patients with hepatic dysfunction.

In assessing liver complications, it should be kept in mind that these are frequently associated with ulcerative colitis.

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with Mesalazine products. Therefore, TEVA-5 ASA is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised and TEVA-5 ASA should only be used if the expected benefit clearly outweighs the risks to the patients. Appropriate assessment and monitoring of liver function should be performed.

Immune

Hypersensitivity

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to TEVA-5 ASA tablets or to other compounds that contain, or are converted to, mesalamine. 5-aminosalicylic acid does not contain a sulfa moiety, thus sulfa-related side effects are avoided. Many patients with a history of sulfasalazine intolerance are able to tolerate 5-aminosalicylic acid tablets as demonstrated in open-label clinical trials. These patients should be instructed to discontinue therapy if signs of rash or fever become apparent. In case of an allergic reaction, appropriate measures (standard of care) should be taken.

Monitoring and Laboratory Tests

It is recommended that all patients have an evaluation of renal function prior to initiation of TEVA-5 ASA tablets and periodically while on TEVA-5 ASA therapy.

It is recommended that appropriate assessment and monitoring of liver function should be performed.

Renal

Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine products and pro-drugs of mesalamine. Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment. TEVA-5 ASA is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction history of renal disease or taking concomitant nephrotoxic drugs, caution should be exercised and TEVA-5 ASA should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies of 5-aminosalicylic acid use in pregnant women. 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. Mesalamine crosses the placenta. Animal reproduction studies of mesalamine found no evidence of fetal harm. Mesalamine should be used during pregnancy only if the benefits clearly outweigh the risks to the fetus.

7.1.2 Breast-feeding

It has been reported that small amounts of 5-ASA and higher concentrations of acetyl-5-ASA are found in breast milk. While the clinical significance of this has not been determined, caution should be exercised when TEVA-5 ASA tablets are administered to a nursing woman.

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

Isolated weight decrease in nursing infant has been reported during post-marketing experience with mesalamine.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

5-aminosalicylic acid is generally well tolerated. The most commonly reported adverse reactions were nausea, diarrhea, abdominal pain and headache. Other common adverse reactions seen in clinical trials with 5-aminosalicylic acid were acute exacerbation of ulcerative colitis symptoms, abnormal hepatic functions tests and rash. Adverse events seen in clinical trials with 5-aminosalicylic acid tablets have generally been mild and reversible, and have seldom resulted in discontinuation of treatment.

8.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two short-term (6 weeks), double-blind, placebo-controlled clinical studies involving 245 patients, 155 of whom were randomized to 5-aminosalicylic acid tablets, five (3.2%) of the 5-aminosalicylic acid patients discontinued 5-aminosalicylic acid therapy because of adverse events as compared to two (2.2%) of the placebo patients. Adverse reactions leading to withdrawal from 5-aminosalicylic acid tablets included (each in one patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache; rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild indigestion and cramping; headache, nausea, malaise, aching, vomiting, muscle cramps, a stuffy head, plugged ears, and fever.

Adverse events occurring at a frequency of greater than 2% in these clinical trials are listed below. Overall, the incidence of adverse events seen with 5-aminosalicylic acid tablets was similar to placebo.

Headache, abdominal pain, eructation, pain, nausea, pharyngitis, dizziness, asthenia, diarrhea, back pain, fever, rash, dyspepsia, rhinitis, arthralgia, vomiting, constipation, hypertonia, flatulence, flu syndrome, chills, colitis exacerbation, chest pain, peripheral edema, myalgia, pruritus, sweating, dysmenorrhea.

Of these adverse events, only rash showed a consistently higher frequency with increasing 5-aminosalicylic acid dose in these studies.

The following adverse reactions were seen in 2% of the patients in the controlled studies: malaise, arthritis, insomnia, increased cough, acne, and conjunctivitis.

In a 6 month placebo-controlled maintenance trial involving 264 patients, 177 of whom were randomized to 5-aminosalicylic acid tablets, six (3.4%) of the 5-aminosalicylic acid patients discontinued 5-aminosalicylic acid therapy because of adverse events, as compared to four

(4.6%) of the placebo patients. Adverse reactions leading to withdrawal from 5-aminosalicylic acid tablets included (each in one patient): anxiety; headache; pruritus, decreased libido; rheumatoid arthritis; and stomatitis and asthenia.

In the 6 month placebo-controlled maintenance trial, the incidence of adverse events seen with 5-aminosalicylic acid tablets was similar to that seen with placebo. Adverse events occurring in 5-aminosalicylic acid 1.6 g/day group at a frequency of 2% or greater are listed in Table 1 below.

Table 1 Frequency (%) of Adverse Events Reported in the Long-Term (6 months) Double-Blind Controlled Study

Event	Teva-5-ASA 0.8 g/day (n=90)	Teva-5-ASA 1.6 g/day (n=87)	Placebo (n=87)
Cardiac disorders			
Chest Pain	8	8	6
Ear and labyrinth disorders			
Deaf	0	2	0
Eye disorders			
Amblyopia	1	2	0
Lacrimation Disorder	1	2	0
Vision Abnormality	1	3	0
Gastrointestinal disorders			
Abdomen Enlargement	3	2	0
Abdominal Pain	30	33	44
Colitis Flare	8	10	8
Constipation	4	13	13
Diarrhea	30	40	49
Dry Mouth	1	2	2
Dyspepsia	9	5	9
Flatulence	21	28	30
Gastroenteritis	2	5	1
Gastrointestinal Bleeding	8	10	8
Nausea	19	17	15
Rectal Bleeding	4	2	5
Rectal Disorder	1	7	2
Stool Abnormality	7	10	8
Tenesmus	6	7	5
Vomiting	6	6	7
General disorders and administration site conditions			
Asthenia	10	20	16
Fever	12	14	13
Flu Syndrome	14	10	20
Malaise	1	5	5
Pain	19	23	11
Infections and infestations			
Infection	7	9	3
Monilia Vagina	1	2	1
Pharyngitis	22	21	15
Sinusitis	7	7	6
Musculoskeletal and connective tissue disorders			
Arthralgia	7	8	9
Arthritis	1	2	2
Back Pain	21	10	11
Hypertonia	4	5	3

Joint Disorder	2	3	0
Myalgia	7	8	5
Nervous system disorders			
Dizziness	8	8	7
Headache	52	47	49
Nervousness	6	6	2
Paresthesia	0	5	5
Somnolence	0	2	3
Psychiatric disorders			
Anxiety	3	2	2
Insomnia	4	5	5
Renal and urinary disorders			
Cystitis	0	2	0
Dysuria	1	2	1
Hematuria	0	3	1
Increased Urination	2	3	0
Reproductive system and breast disorders			
Dysmenorrhea	1	5	2
Prostate Disorder	1	2	0
Vaginitis	0	2	0
Respiratory, thoracic and mediastinal disorders			
Asthma	0	2	0
Bronchitis	3	2	2
Epistaxis	1	2	0
Increased Cough	2	7	16
Lung Disorder	0	3	0
Rhinitis	43	40	36
Skin and subcutaneous tissue disorders			
Pruritus	2	3	7
Urticaria	0	2	1

8.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse reactions were seen in 1% of patients receiving 5-aminosalicylic acid 1.6 g/day in the maintenance study: migraine, ear disorder, rash, vasodilation, allergic reaction, dyspnea, chills, pneumonia, urine abnormality, peripheral edema, palpitations, anorexia, depression, urinary tract infection, leg cramps, alopecia and sweating.

In uncontrolled clinical studies, the following adverse events occurred at a frequency of 5% or greater and appeared to increase in frequency with increasing dose: Asthenia, flu syndrome, back pain, arthralgia, and rhinitis.

8.4 Abnormal Hematologic and Clinical Chemistry and Other Quantitative data

Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated serum creatinine and BUN.

8.5 Post-Market Adverse Drug Reactions

In addition to the adverse events listed above, the following adverse events have also been reported in controlled clinical trials, open-label studies, literature reports, or foreign and domestic marketing experience. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The relationship of the reported events to 5-aminosalicylic acid is unclear in many cases, some, including anorexia, joint pain, pyoderma gangrenosum, oral ulcers, and anemia, are sometimes part of the clinical presentation of ulcerative colitis.

Blood and lymphatic system disorders: agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy
Cardiac disorders: pericarditis (rare), myocarditis (rare)
Ear and labyrinth disorders: ear pain, tinnitus, vertigo
Eye disorders: eye pain, blurred vision
Gastrointestinal disorders: pancreatitis, gastroenteritis, gastritis, dry mouth, abdominal enlargement, oral ulcers, perforated peptic ulcer (rare), bloody diarrhea, tenesmus
General disorders and administration site conditions: facial edema, edema, drug fever (rare), mesalamine-induced acute intolerance syndrome
Hepatobiliary disorders: hepatic impairment, including hepatic failure or hepatitis (rare), cholecystitis. Asymptomatic elevations of liver function tests have occurred in patients taking 5-aminosalicylic acid tablets. These elevations usually resolve during continued therapy or with discontinuation of 5-aminosalicylic acid. When any elevations in liver enzymes are assessed, it should be kept in mind that hepatic complications are frequently associated with inflammatory bowel disease.
Immune system disorders: anaphylactic reaction, lupus-like syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Infections and infestations: sinusitis
Metabolism and nutrition disorders: anorexia, increased appetite
Musculoskeletal and connective tissue disorders: gout, neck pain
Nervous system disorders: somnolence, migraine, paresthesia, tremor, taste perversion, peripheral neuropathy (rare), Guillain-Barré syndrome (rare), transverse myelitis (rare)
Psychiatric disorders: anxiety, confusion, depression, emotional lability, hyperesthesia, nervousness
Respiratory, thoracic and mediastinal disorders: allergic and interstitial lung disease, eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis
Skin and subcutaneous tissue disorders: alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, Stevens-Johnson Syndrome (SJS), urticaria.
Renal and urinary disorders: interstitial nephritis (rare), minimal change nephropathy (rare), nephrolithiasis, renal failure (rare) (see WARNINGS AND PRECAUTIONS), dysuria, urinary urgency, hematuria, epididymitis
Reproductive system and breast disorders: menorrhagia
Vascular disorders: vasodilation

9 DRUG INTERACTIONS

9.2 Overview

There are no known drug interactions. The effects of co-administration of 5-aminosalicylic acid tablets with cimetidine, with an antacid containing activated dimethicone and aluminum hydroxide, or with an antacid accompanied by a high fat meal were addressed in a clinical study. There were no significant *in vivo* effects on mesalamine release or the extent of drug absorption from 5-aminosalicylic acid tablets by any of the three treatments. It has been reported that simultaneous administration of famotidine, a potent H_2-antagonist, and 5-aminosalicylic acid tablets does not influence the absorption and urinary excretion of mesalamine.

9.4 Drug-Drug Interactions

TEVA-5 ASA tablets should not be administered with preparations which lower the stool pH, such as lactulose.

Interactions similar to acetylsalicylic acid cannot be excluded.

The hypoglycaemic effect of sulfonylureas may be enhanced when administered with aminosalicylates (oral antidiabetics may be displaced from the binding sites of plasma proteins). 5- ASA was reported to inhibit coumarin anticoagulants, resulting in thrombosis.

Concomitant treatment with mesalamine may increase the risk of myelosuppression in patients receiving azathioprine or 6-mercaptopurine. The concurrent use of mesalamine with azathioprine or 6-mercaptopurine may increase the risk for blood dyscrasia. If concomitant use including complete blood cell counts and platelet counts.

The concurrent use of mesalamine with known nephrotoxic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of nephrotoxicity. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions.

9.5 Drug-Food Interactions

Interactions with food products have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Interactions

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients

exposed to sulfasalazine or its metabolite, mesalamine/mesalazine.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The active ingredient in TEVA-5 ASA, mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), is the major active component of sulfasalazine for the treatment of inflammatory bowel disease. The available evidence suggests that mesalamine has a topical anti-inflammatory effect on the colon, where it inhibits prostaglandin and leukotriene synthesis.

10.3 Pharmacokinetics

Absorption
Human studies conducted using radiological and serum markers showed that the 5-aminosalicylic acid coating delayed release of mesalamine until the terminal ileum was reached. Other studies compared mesalamine absorption when administered as an enema (a readily available dosage form) and when released for absorption in the stomach, small intestine, and colon relative to an intravenous dose. Mesalamine release from 5-aminosalicylic acid is delayed until the terminal ileum as reflected by tmax's of about 7 hours for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid. The $t_{1/2}$elm's were about 3 hours for mesalamine and 10 hours for N-acetyl-5-aminosalicylic acid. Once released in the colon, mesalamine was minimally absorbed and plasma levels were similar to those found following rectal administration. Approximately 20% of the administered dose released was absorbed, with about 80% available for topical activity in the colon. Absorption of mesalamine is similar in fasted and fed subjects.

Serum levels and urinary excretion of mesalamine and N-acetyl-5-aminosalicylic acid following single and multiple equimolar 5-aminosalicylic acid and sulfasalazine doses to healthy subjects and to patients were compared. There was no consistent trend for greater serum mesalamine or metabolite levels following 5-aminosalicylic acid dosage. Based on urinary dose recoveries, the extent of mesalamine absorption for 5-aminosalicylic acid was no greater than that for sulfasalazine. Overall, there were no meaningful differences in the extents of mesalamine absorption following equimolar 5-aminosalicylic acid and sulfasalazine doses.

In another study, there was a dose response in serum mesalamine and metabolite levels at 5-aminosalicylic acid doses of 1.2 and 2.4 g/day. In other studies when 5-aminosalicylic acid was administered at higher or lower doses than 1.2 and 2.4 g/day, serum mesalamine and N-acetyl-5-aminosalicylic acid concentrations differed from those for the 1.2 and 2.4 g/day doses as would be expected following a linear dose response relationship. The effects of co-administration of 5-aminosalicylic acid with cimetidine, an antacid containing activated simethicone and aluminum hydroxide, and antacid with a high fat meal were addressed in another study. There were no significant in vivo effects on mesalamine release or the extent of drug absorption from 5-aminosalicylic acid by any of the three treatments.

Metabolism
Mesalamine, once absorbed, is rapidly acetylated through the gut mucosal wall and by the liver.

Elimination
Mesalamine is mainly excreted by the kidney as N-acetyl-5-aminosalicylic acid.

11 STABILITY AND STORAGE RECOMMENDATIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

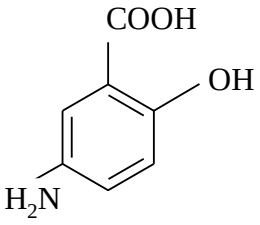
INN: mesalazine

USAN: mesalamine

Chemical name**:** 5-amino-2-hydroxybenzoic acid, also referred to as 5-aminosalicylic acid or 5-ASA.

Molecular formula and molecular mass: $C_7H_7NO_3$ and 153.1 g/mol

Structural formula:



Physicochemical properties**:** Mesalamine is an off-white to light-brown powder that decomposes at 280°C and is slightly soluble in water. It darkens upon exposure to air, high humidity or light over a period of several months.
pK_a Values: $pK_1 = 2.74$, $pK_2 = 5.80$.

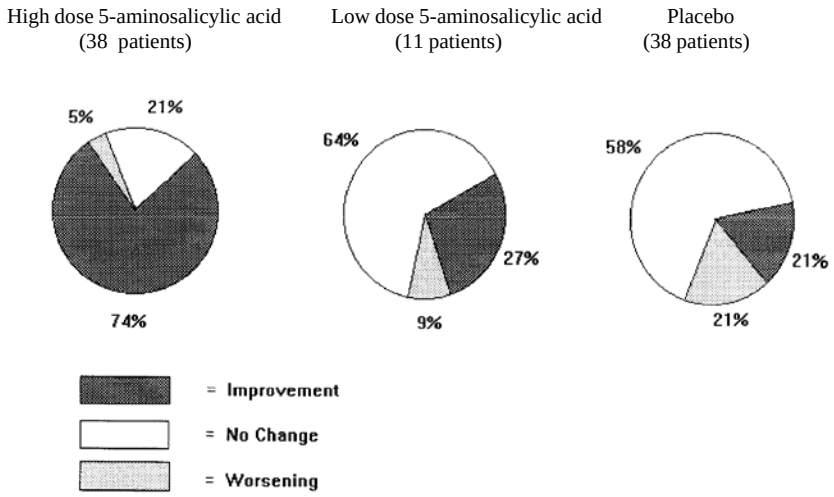
14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Mildly to moderately active ulcerative colitis:

In a randomized, double-blind, placebo-controlled clinical trial it was shown (see chart below) that 5-aminosalicylic acid (4.8 g/day of mesalamine in divided doses) was highly effective in inducing remission in ulcerative colitis patients with active disease.

OVERALL OUTCOME OF PHYSICIANS GLOBAL ASSESSMENT



14.1.1 Trial Design and Study Demographics

Maintenance of remission of ulcerative colitis:

A 6 month, randomized, double-blind, placebo-controlled, multi-centre study involved 264 patients treated with 5-aminosalicylic acid 0.8 g/day (n=90), 1.6 g/day (n=87), or placebo (n=87).

Table 2 Summary of patient demographics for clinical trials in the maintenance of remission of ulcerative colitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N=number)
Study 1	6 month, randomized, double-blind, placebo-controlled, multi-centre	5-aminosalicylic acid 0.8 g/day, 1.6 g/day (n=87), or placebo	N=264 0.8 g: n=84 1.6 g: n=87

	study	(n=87)	Placebo: n =87

14.1.2 Study Results

The proportion of patients treated with 0.8 g/day who maintained endoscopic remission was not statistically significant compared to placebo. In the ITT analysis of patients treated with 5-aminosalicylic acid 1.6 g/day, 5-aminosalicylic acid maintained endoscopic remission of ulcerative colitis in 61 of 87 (70.1%) of patients, compared to 42 of 87 (48.3%) of placebo recipients (p=0.005).

A pooled efficacy analysis of 4 maintenance trials compared 5-aminosalicylic acid (0.8 to 2.8 g/day) with sulfasalazine (2 to 4 g/day). Treatment success was 58 of 98 (59%) for 5-aminosalicylic acid and 70 of 102 (69%) for sulfasalazine, a non-significant difference.

Additional double-blind clinical trials of 16, 24, and 52 weeks duration have shown 5-aminosalicylic acid in doses ranging from 0.8 to 4.4 g/day to be as effective as sulfasalazine for maintenance of remission. It is particularly noteworthy that most patients intolerant or allergic to sulfasalazine can be effectively maintained in remission on 5-aminosalicylic acid as demonstrated in open-labeled clinical trials. In addition, male infertility resulting from sulfasalazine therapy has been shown to be reversible upon treatment with 5-aminosalicylic acid.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity Studies: The acute peroral LD_{50} value for mesalamine is reported to be 5000 mg/kg in mice and 4594 mg/kg in rats.

Subacute Toxicity Studies: Rats (2/sex/group) were administered mesalamine orally at dosages of 0, 40, 120, 360, and 1080 mg/kg/day for 14 days. One female rat (1080 mg/kg/day) died, most probably of renal failure complicated by gastric mucosal injury. Drug-related changes in the clinical chemistry assays (increased serum urea nitrogen, serum creatinine and serum total proteins, and decreased albumin/globulin ratios) occurred only at the 1080 mg/kg/day level. Drug-related histomorphologic effects were present in the kidneys (1080 mg/kg/day) and gastrointestinal tracts (360 and 1080 mg/kg/day) of treated rats.

A similar study in rabbits resulted in diarrhea during the first week (males, 1080 mg/kg/day). Urinalysis revealed slight increases in proteinuria, bilirubinuria, and urinary acetone in the high dose group.

No drug-related effects were observed when rabbits were given 227.3 mg/kg/day rectally (suppository) for 12 days.

Chronic Toxicity Study: Dogs (2/sex/group) were administered 5-aminosalicylic acid tablets at oral dosages of 40, 120, and 200 mg/kg/day for one year. Control dogs received placebo tablets. Histopathology and clinical chemistry assessment showed no evidence of drug-related effects.

Teratology Studies: No evidence of teratogenicity was observed when mesalamine was administered orally at a dosage of 480 mg/kg/day to pregnant rats and rabbits.

Carcinogenicity: Dietary mesalamine was determined not to be carcinogenic in rats at doses as high as 480 mg/kg/day in one two year study, and 840 mg/kg/day in a second two year study. Similarly, dietary mesalamine was not carcinogenic in mice at 2000 mg/kg/day. These doses are 15, 26 and 62.5 times the maximum recommended human maintenance dose of 5-aminosalicylic acid of 1.6 g/day (32 mg/kg/day if 50 kg body weight assumed.)

Genotoxicity: Mesalamine was not mutagenic in two bacterial test systems (Ames assay and K. pneumoniae test) with and without metabolic activation.

Reproductive and Developmental Toxicology: The effects of oral mesalamine on fertility and gestation indices were investigated in rats at doses up to 480 mg/kg/day. No effects on fertility or gestation parameters were noted in these studies.

Special Studies: Two studies to assess the potential renal toxicity of mesalamine in a rat model have been reported in the literature. In an acute study, rats were given a single massive intravenous injection, at dose levels between 214 and 872 mg/kg. The animals killed 24-96 hours after the injection presented lesions in the proximal cortical tubules as well as renal papillary necrosis. The former lesion was reversible by one week post-administration. In a second study, using a more clinically relevant dosing regimen, rats were dosed up to 200 mg/kg p.o. for 4 weeks. No drug-related effects were observed.

17 SUPPORTING PRODUCT MONOGRAPH

1. Asacol Tablets, 400 mg, submission control # 245536, Product Monograph, Allergan Inc. MAR. 18, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEVA-5 ASA®
5-aminosalicylic acid Enteric-Coated Tablets

Read this carefully before you start taking **Teva-5 ASA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Teva-5 ASA**.

Serious Warnings and Precautions

- **Stop taking Teva-5 ASA if you have an allergic reaction to this drug. Speak to your doctor immediately or go to the nearest emergency department. Symptoms of allergic reaction may include itching, hives, swelling in face or hands, tightness in chest, trouble breathing.**
- **Teva-5 ASA contains the medicinal ingredient mesalamine. Kidney failure has been reported in patients taking Teva-5 ASA as well with drugs that contain mesalamine.**
- **Speak to your doctor if you have a history of kidney problems before using Teva-5 ASA. Taking Teva-5 ASA may worsen your kidney condition. Your doctor may check your kidney function before you begin Teva-5 ASA and during your treatment**.

What is Teva-5 ASA used for?

- To treat symptoms related to ulcerative colitis when the condition of the disease is mild to moderate. Ulcerative colitis is where the large bowel (colon) and back passage (rectum) becomes red and swollen (inflamed).
- To help prevent a moderate to mild condition of ulcerative colitis from returning.

How does Teva-5 ASA work?
Teva-5 ASA is an anti-inflammatory drug for the bowel. Teva-5 ASA is believed to stop the production of certain substances in your body that cause swelling (inflammation). Teva-5 ASA tablets are designed to prevent the medicine from being released early.

What are the ingredients in Teva-5 ASA?
Medicinal ingredients: Mesalazine or 5-aminosalicylic acid (5-ASA)
Non-medicinal ingredients: Each tablet contains the following inactive ingredients:
ethyl acrylate, hypromellose, iron oxide black, iron oxide red, magnesium stearate, mannitol, methacrylic acid copolymer (Type C), potassium sorbate, povidone, propylene glycol, purified water, and sodium citrate, sodium starch glycolate, talc, triethyl citrate, titanium dioxide and xanthan gum.

Teva-5 ASA comes in the following dosage form:
TEVA-5 ASA (5-aminosalicylic acid) is available as brown-red capsule shaped enteric-coated tablets each containing 400 mg of 5-aminosalicylic acid coated with an acrylic based resin supplied in bottles of 100 and 500.

Do not use Teva-5 ASA if:

- You are allergic to mesalamine (5-ASA) or any of the ingredients in Teva-5 ASA.
- You have a history of sensitivity to salicylates, for example acetylsalicylic acid (i.e. Aspirin®).
- You have severe liver problems.
- You have severe kidney problems.
- You have an ulcer in the stomach or intestines.
- You have a blocked urinary tract.
- You are unable to swallow the whole tablet.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Teva-5 ASA. Talk about any health conditions or problems you may have, including if you:

- have higher than normal blood urea nitrogen (BUN) levels (renal function test)
- have a history of kidney problems
- are taking other ulcerative colitis drugs that contain Mesalamine. Speak to your doctor before switching your treatment to Teva-5 ASA.
- had an allergic reaction to sulfasalazine. Stop taking Teva-5 ASA and speak to your doctor if you experience a rash or a fever.
- have pyloric stenosis. Pyloric Stenosis is a condition in where the passage from the stomach to the small intestine is narrow or blocked. Pyloric stenosis may keep the Teva-5 ASA tablet from reaching the colon as quickly as it normally would.

Other warnings you should know about:
Treatment with Teva-5 ASA can increase your risk of certain side effects, including:

- **Liver problems**: You may develop liver function problems, including liver failure.
- **Kidney Stones**: You may develop kidney stones when using Teva-5 ASA. Be sure to drink enough liquids while you are taking Teva-5 ASA. Speak to your doctor about how much water or other liquids you should be drinking. Symptoms of kidney stones may include:
    - o blood in urine
    - o urinating more often
    - o pain in back, side, stomach and groin
- **Acute Intolerance Syndrome**: Mesalamine, the medicinal ingredient in Teva-5 ASA, can cause acute intolerance syndrome. Your doctor may monitor your kidney function if you have kidney disease while on treatment. Speak to your doctor immediately if you experience any of the following symptoms:
    - o cramping
    - o sudden abdominal pain
    - o bloody diarrhea
    - o fever
    - o headache
    - o rash

- **Colitis (inflamed colon)**: Teva-5 ASA can cause the symptoms of colitis to worsen. Speak to your doctor immediately if you suddenly experience any of the following symptoms:
    - o abdominal pain
    - o bloody diarrhea
    - o fever
    - o headache
    - o rash or itchy skin
    - o eye infection

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

- Tell your doctor right away if you become pregnant or think you are pregnant during treatment with Teva-5 ASA.
- Taking mesalamine during pregnancy have been reported to cause:
    - o early Labor
    - o stillbirth (death of baby)
    - o low birth weight of baby
- If you breastfeed your baby while taking Teva-5 ASA, your baby could develop / start to have diarrhea. It is important to monitor your baby's stool and contact your doctor right away if they have diarrhea. Your doctor may advise you to stop breastfeeding your baby.

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

The following may interact with Teva-5 ASA:

- aminosalicylates. Taking Teva-5 ASA with aminosalicylates may increase your risk of developing a blood clot.
- azathioprine, 6-mercaptopurine. Taking Teva-5 ASA with these drugs may increase your risk of developing a blood disorder.
- medicines that can change the acidity level of the stool, such as lactulose
- medicines to treat ulcers such as cimetidine, famotidine
- nonsteroidal anti-inflammatory drugs (NSAID). Taking Teva-5 ASA with these drugs may increase your risk of side effects to your kidneys.

Treatment with Teva-5 ASA can affect the results of a urine test. Tell your doctor or nurse that you are taking Teva-5 ASA when taking a urine test.

How to take Teva-5 ASA:

- Take Teva-5 ASA exactly as your doctor tells you to take it. Do NOT take more of it than prescribed. Speak to your doctor or pharmacist if you are not sure.
- Take the exact dose your doctor tells you to take during remission. Following your doctor's instructions can reduce the risk of your symptoms returning.
- Do NOT stop using Teva-5 ASA abruptly.
- Swallow tablets whole. Do NOT crush or chew the tablet.
- The whole tablet or a part of it may occasionally appear in your stool. Speak to your doctor if this occurs frequently.

Usual Adult Dose:
Treatment of moderate to mild ulcerative colitis:

- Take two to eight 400 mg tablets daily in divided doses.
- Your doctor may increase your daily dose to twelve 400 mg tablets if your condition is severe.

Treatment for the maintenance of remission of ulcerative colitis:
Take four 400 mg tablets daily in divided doses.

Overdose:

If you think you, or a person you are caring for, have taken too much Teva-5 ASA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take double the dose.

What are possible side effects from using Teva-5 ASA?

These are not all the possible side effects you may feel when taking Teva-5 ASA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- acne
- aches and muscle cramps
- constipation
- coughing
- chills
- diarrhea
- dizziness
- dry mouth
- feelings of confusion, anxiety or nervousness
- hair loss
- headache or migraine
- increased appetite
- joint and groin pain
- lower back discomfort or back pain
- low energy or feeling unwell
- menstrual (period) pain
- nausea and vomiting
- rash
- runny nose

- sore throat
- stuffy head
- sweating

Your doctor may run tests, including a blood test, to check your liver function and blood cell counts.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Worsening of your ulcerative colitis symptoms		√	
UNCOMMON			
Kidney stones (hard little pebbles that form in your kidneys) blood in urine, urinating more often, pain in your back, side, belly or groin.		√	
Eye problems: itchy, red eyes with discharge, pain, swelling and blurred vision		√	
Ear problems: ear pain	√		
Pneumonia (infection in the lungs): chest pain when you breath or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath			√
Fast heartbeat: pounding, fluttering, racing, skipping beats, chest discomfort or shortness of breath			√
Chest pain		√	
Stomach pain		√	
RARE			
Fever (higher than normal body temperature)		√	
Allergic (hypersensitivity) reactions itching; rash, swelling of face or hands, tightness in chest, trouble breathing			√
Lung problems (thickening and scaring of lung tissues): Shortness of breath, fast, shallow breathing, dry cough		√	
Kidney problems changes in urine output, cloudy or tea-coloured urine, blood in the urine, weight gain (from retaining fluid), confusion, swelling of the		√	

eyes, hands, legs, and feet Additional less specific symptoms may include: drowsiness, fatigue, nausea, vomiting, rash, persistent itching, and back pain			
Liver problems severe abdominal pain or distension, nausea, vomiting, drop in appetite, bloating, together with yellowing of the skin and eyes, and abnormal liver function tests		√	
Acute intolerance syndrome cramping, stomach pain, bloody and excessive stools, fever, headache and rash			√
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			√

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

Reporting Side Effects

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

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

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

Storage:
Teva-5 ASA should be stored at controlled room temperature (15°C - 30°C). Protect from light.

Keep out of reach and sight of children.

If you want more information about Teva-5 ASA:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website

http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9.

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