

## **PRODUCT MONOGRAPH**

**PrTEVA-5 ASA**

5-aminosalicylic Acid  
400 mg Enteric Coated Tablets,

Teva Standard

Lower Gastrointestinal Anti-inflammatory

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## PRODUCT MONOGRAPH

### <sup>Pr</sup>TEVA-5 ASA (5-aminosalicylic acid)

400 mg Enteric Coated Tablets

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	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.

### INDICATIONS AND CLINICAL USE

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.

#### **Pediatrics:**

Safety and effectiveness of 5-aminosalicylic acid therapy in children have not been established.

### CONTRAINDICATIONS

TEVA-5-ASA is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS,

COMPOSITION AND PACKAGING section of this product monograph

- ❑ Patients with a history of sensitivity to salicylates
- ❑ Patients with severe renal impairment ( $\text{GFR} < 30 \text{ ml/min/1.73m}^2$ ) 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
- ❑ Infants under 2 years of age

## WARNINGS AND PRECAUTIONS

### 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.

### 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.

### 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**

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.

### **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, 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.

### **Special Populations**

**Pregnancy:** 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.

**Nursing Women:** 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.

### **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.

## **ADVERSE REACTIONS**

### **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.

### **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 of occurrence.*

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	Placebo (n=87)	Teva-5-ASA 0.8 g/day (n=90)	Teva-5-ASA 1.6 g/day (n=87)
Headache	49	52	47
Rhinitis	36	43	40
Diarrhea	49	30	40
Abdominal Pain	44	30	33
Flatulence	30	21	28
Pain	11	19	23
Pharyngitis	15	22	21
Asthenia	16	10	20
Nausea	15	19	17
Fever	13	12	14
Constipation	13	4	13
Back Pain	11	21	10
Flu Syndrome	20	14	10
Colitis Flare	8	8	10
Gastrointestinal Bleeding	8	8	10
Stool Abnormality	8	7	10
Infection	3	7	9
Dizziness	7	8	8
Chest Pain	6	8	8
Arthralgia	9	7	8
Myalgia	5	7	8
Increased Cough	16	12	7
Sinusitis	6	7	7
Tenesmus	5	6	7
Rectal Disorder	2	1	7
Vomiting	7	6	6
Nervousness	2	6	6
Dyspepsia	9	9	5
Insomnia	5	4	5
Hypertonia	3	4	5
Gastroenteritis	1	2	5
Malaise	3	1	5
Dysmenorrhea	2	1	5
Paresthesia	5	0	5
Pruritus	7	2	3
Joint Disorder	0	2	3

Event	Placebo (n=87)	Teva-5-ASA 0.8 g/day (n=90)	Teva-5-ASA 1.6 g/day (n=87)
Increased Urination	0	2	3
Vision Abnormality	0	1	3
Hematuria	1	0	3
Lung Disorder	0	0	3
Rectal Bleeding	5	4	2
Anxiety	2	3	2
Bronchitis	2	3	2
Abdomen Enlargement	0	3	2
Arthritis	2	1	2
Dysuria	1	1	2
Monilia Vagina	1	1	2
Amblyopia	0	1	2
Dry Mouth	0	1	2
Epistaxis	0	1	2
Lacrimation Disorder	0	1	2
Prostate Disorder	0	1	2
Somnolence	3	0	2
Urticaria	1	0	2
Asthma	0	0	2
Cystitis	0	0	2
Deaf	0	0	2
Vaginitis	0	0	2

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.

**Abnormal Hematologic and Clinical Chemistry Findings:** Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated serum creatinine and BUN.

#### **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.

**Body as a Whole:** Neck pain, abdominal enlargement, facial edema, edema, lupus-like syndrome, drug fever (rare).

**Cardiovascular:** Pericarditis (rare), myocarditis (rare), vasodilation, migraine.

**Digestive:** Anorexia, pancreatitis, gastroenteritis, gastritis, increased appetite, dry mouth, oral



ulcers, perforated peptic ulcer (rare), bloody diarrhea, tenesmus.

**Hematologic:** Agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

**Immunological:** Anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS).

**Musculoskeletal:** Gout.

**Nervous:** Anxiety, depression, somnolence, emotional lability, hyperesthesia, vertigo, nervousness, confusion, paresthesia, tremor, peripheral neuropathy (rare), Guillain-Barré syndrome (rare), and transverse myelitis (rare).

**Respiratory/Pulmonary:** Sinusitis, eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis.

**Skin:** Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, urticaria.

**Special Senses:** Ear pain, eye pain, taste perversion, blurred vision, tinnitus.

**Urogenital:** Interstitial nephritis (rare), minimal change nephropathy (rare), nephrolithiasis, renal failure (rare) (see WARNINGS AND PRECAUTIONS), dysuria, urinary urgency, hematuria, epididymitis, menorrhagia.

**Hepatic:** 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.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

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<sub>2</sub>-antagonist, and 5-aminosalicylic acid tablets does not influence the absorption and urinary excretion of mesalamine.

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.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **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.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Patients with ulcerative colitis should be made aware that 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.

### **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.

### **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.

### **Administration**

1. 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.
2. 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.

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

## **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 immediately.

## **ACTION AND CLINICAL PHARMACOLOGY**

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.

TEVA-5 ASA tablets have a special acrylic-based resin coating, which does not allow the drug to be released below pH 5.5. The coating delays release of mesalamine until the tablets reach the terminal ileum and colon. Once released in the colon, mesalamine is minimally absorbed and plasma levels are similar to those found following rectal administration of mesalamine. Approximately 20% of the administered dose released in the colon is absorbed, the remainder is available for colon therapeutic activity and excretion in the feces. Absorption of mesalamine is similar in fasted and fed subjects. The absorbed mesalamine is rapidly acetylated through the gut mucosal wall and by the liver. It is mainly excreted by the kidney, as N-acetyl-5-aminosalicylic acid.

## **STABILITY AND STORAGE RECOMMENDATIONS**

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

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

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 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.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

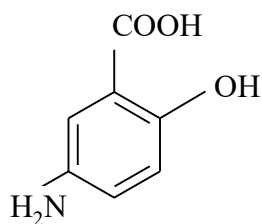
#### Drug Substance

INN: mesalazine

USAN: mesalamine

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

#### **Structural Formula:**



**Molecular Formula:** C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>

**Molecular Weight:** 153.1 g/mol

**Description:** 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.

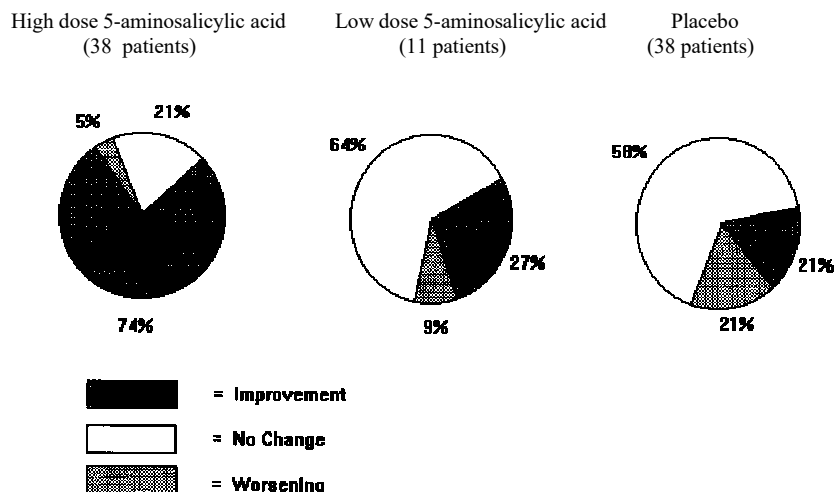
pK<sub>a</sub> Values: pK<sub>1</sub> = 2.74, pK<sub>2</sub> = 5.80.

## CLINICAL TRIALS

### 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



### 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). 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.

## DETAILED PHARMACOLOGY

**Pharmacokinetics:** Mesalamine release from 5-aminosalicylic acid is delayed until the terminal ileum as reflected by  $t_{\max}$ 's of about 7 hours for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid. The  $t_{1/2_{\text{elm}}}$ 's were about 3 hours for mesalamine and 10 hours for N-acetyl-5-aminosalicylic acid.

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. 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. The absorbed mesalamine was rapidly acetylated through the gut mucosal wall and by the liver. It was mainly excreted by the kidney as N-acetyl-5-aminosalicylic acid.

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.

## 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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** 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.)

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

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.



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**PART III CONSUMER INFORMATION**  
**PrTEVA-5 ASA®**  
**5-aminosalicylic acid Enteric-Coated Tablets,**  
**400 mg**

**This leaflet is part III of a three-part “Product Monograph” published when Teva-5 ASA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Teva-5 ASA. Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION**

**What the medication is used for:**

Teva-5 ASA is used for the treatment of mild to moderate ulcerative colitis and the maintenance of remission of mild to moderate ulcerative colitis.

**What it does:**

Ulcerative colitis involves chronic inflammation of the inner lining of the colon and rectum. Teva-5 ASA reduces inflammation right at the site.

**When it should not be used:**

Teva-5 ASA is not suitable for everyone. It should not be used if:

- You are allergic to this drug or to any ingredient in the formulation or component of the container (see below for ingredient listing)
- 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 stomach or intestinal ulcer
- You have urinary tract obstruction
- You are unable to swallow the intact tablet
- The patient in question is an infant under 2 years of age

**What the medicinal ingredient is:**

Mesalazine or 5-aminosalicylic acid (5-ASA)

**What the nonmedicinal ingredients are:**

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.

**What dosage forms it comes in:**

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.

**WARNINGS AND PRECAUTIONS**

Some patients who have experienced an allergic reaction to sulfasalazine may have a similar reaction to Teva-5 ASA or to other products that contain, or are converted to, 5-ASA. Teva-5 ASA does not contain sulfa.

The development of some cases of liver function problems, including liver failure, have been reported in patients who were using medication similar to or the same as that contained in Teva-5 ASA.

**Serious Warnings and Precautions**

If you have an allergic reaction to Teva-5 ASA, stop taking the medication and either consult your doctor 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.

Kidney failure has been reported in patients taking products with mesalamine, the active ingredient in Teva-5 ASA. If you have a history of kidney problems, you should tell your doctor before using Teva-5 ASA, as it may worsen your kidney condition. Your doctor may require certain tests to check your kidney function before starting Teva-5 ASA therapy and periodically while you continue Teva-5 ASA therapy.

*Talk with your doctor about your medical history and if you have any questions about your medication. It's also important to visit your doctor periodically to monitor your condition and discuss how your treatment plan is working for you*

**BEFORE you use Teva-5 ASA talk to your doctor or pharmacist if:**

- You have any liver or kidney problems
- You are pregnant, become pregnant, or are a nursing mother. Small amounts of 5-aminosalicylic acid and its metabolite have been found in human breast milk. Caution should be taken when using Teva-5 ASA while you are nursing. Discuss with your doctor.
- 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). Pyloric stenosis may keep the Teva-5 ASA tablet from reaching the colon as quickly as it normally would.

Kidney stones may develop with use of mesalazine. Symptoms may include blood in urine, urinating more often, pain in your back, side, belly or groin. Be sure to drink enough liquids while you are taking TEVA-5 ASA. Talk to your doctor about how much water or other liquids you should be drinking.

**INTERACTIONS WITH THIS MEDICATION**

If taken with some other medicines, the effects of Teva-5 ASA or the effects of other medicines may be changed. Please check with your doctor or pharmacist before taking other medications with Teva-5 ASA.

Teva-5 ASA tablets should not be taken with drugs that can

## IMPORTANT: PLEASE READ

change the acidity level of the stool, such as lactulose.

Teva-5 ASA can be taken with or without food.

### PROPER USE OF THIS MEDICATION

Ulcerative colitis rarely disappears completely. Therefore it is important to closely follow your doctor's dosage instructions. This can reduce the risk of symptoms re-appearing.

Do not stop taking the medication abruptly.

#### Usual dose:

**Treatment:** The usual daily adult dose is 2 to 8 Teva-5 ASA tablets, taken orally, in divided doses. In severe disease the dose may be increased to 12 Teva-5 ASA tablets daily.

**Maintenance of remission:** The recommended daily dosage in adults is 4 Teva-5 ASA tablets, taken orally, in divided doses.

#### **When taking Teva-5 ASA, you should:**

1. Swallow tablets whole. Take care not to break or chew the tablet, as this breaks the special outer coating.
2. Take Teva-5 ASA tablets only as prescribed. Do not change the number or frequency of tablets ingested without first consulting your doctor.
3. What appears to be intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, consult your doctor.

If you have questions about your medication, please contact your doctor or pharmacist.

#### 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.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Teva-5 ASA is generally well tolerated, however, side effects may occur with its use. The most commonly reported side effects included nausea, diarrhea, abdominal pain and headache. Other common adverse reactions seen with Teva-5 ASA were worsening of ulcerative colitis symptoms, abnormal liver function tests and rash.

Inform your doctor, if you experience worsening of your ulcerative colitis symptoms, fever, rash, chest pain or stomach pain, or difficulty breathing while taking Teva-5 ASA.

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

Symptom / Effect	Talk to your healthcare professional		Stop taking drug and get immediate help
	Only if severe	In all cases	
Common (more than 1 in 100)			
Worsening of your ulcerative colitis symptoms		√	
Uncommon			
Kidney stones (hard little pebbles that form in your kidneys) – symptoms include blood in urine, urinating more often, pain in your back, side, belly or groin.		√	
Rare (less than 1 in 1,000)			
Fever		√	
Allergic reaction which may include symptoms such as: itching; rash, swelling of face or hands, tightness in chest, trouble breathing.			√
Kidney problems which may include symptoms such as: 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 which may include symptoms such as: severe abdominal pain or distension, nausea, vomiting, drop in appetite, and bloating, together with yellowing of the skin and eyes.		√	

*This is not a complete list of side effects. For any unexpected effects while taking Teva-5 ASA, contact your doctor or pharmacist.*

### HOW TO STORE IT

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

#### **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.*

#### **MORE INFORMATION**

##### **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 Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website <http://www.tevacanada.com>; or by calling 1-800-268-4127 ext. 3; or email [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com)

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