HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APRISO safely and effectively. See full prescribing information for APRISO.

APRISO® (mesalamine) extended-release capsules
Initial U.S. Approval: 1987

---------- RECENT MAJOR CHANGES ----------

- Warnings and Precautions
  Severe Cutaneous Adverse Reactions (5.5) 11/2021

---------- INDICATIONS AND USAGE ----------

APRISO is an aminosalicylate indicated for the maintenance of remission of ulcerative colitis in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

Dosage

The recommended dosage is 1.5 g (four 0.375 g capsules) once daily in the morning. (2)

Administration Instructions

- Evaluate renal function before initiating therapy with APRISO. (2)
- Swallow the capsules whole. Do not cut, break, crush or chew the capsules. (2)
- Avoid co-administration with antacids. (2, 7.1)
- Drink an adequate amount of fluids. (2, 5.6)
- Take APRISO without regard to meals. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Extended-release capsules: 0.375 g (3)

---------- CONTRAINDICATIONS ----------

Known or suspected hypersensitivity to salicylates, aminosalicylates, or any component of APRISO capsules. (4, 5.3)

---------- WARNINGS AND PRECAUTIONS ----------

- Renal Impairment: Assess renal function at the beginning of treatment and periodically during treatment. Evaluate the risks and benefits in patients with known renal impairment or taking nephrotoxic drugs; monitor renal function. (5.1, 7.2, 8.6)
- Mesalamine-Induced Acute Intolerance Syndrome: Symptoms may be difficult to distinguish from an exacerbation of ulcerative colitis; monitor for worsening symptoms; discontinue treatment if acute intolerance syndrome is suspected. (5.2)
- Hypersensitivity Reactions, including Myocarditis and Pericarditis: Evaluate patients immediately and discontinue if a hypersensitivity reaction is suspected. (5.3)
- Hepatic Failure: Evaluate the risks and benefits in patients with known liver impairment. (5.4)
- Severe Cutaneous Adverse Reactions: Discontinue at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation. (5.5)
- Photosensitivity: Advise patients with pre-existing skin conditions to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors. (5.6)
- Nephrolithiasis: Mesalamine-containing stones are undetectable by standard radiography or computed tomography (CT). Ensure adequate fluid intake during treatment. (5.7)
- Risks in Patients with Phenylketonuria: Contains phenylalanine. Before prescribing APRISO to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including APRISO. (5.8)
- Interference with Laboratory Tests: Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. (5.9)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥3%) are: headache, diarrhea, upper abdominal pain, nausea, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Nephrotoxic Agents including NSAIDs: Increased risk of nephrotoxicity; monitor for changes in renal function and mesalamine-related adverse reactions. (7.2)
- Azathioprine or 6-Mercaptopurine: Increased risk of blood disorders; monitor complete blood cell counts and platelet counts. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

Geriatric Patients: Increased risk of blood dyscrasias; monitor blood cell counts and platelet counts. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APRISO is indicated for the maintenance of remission of ulcerative colitis in adults.

2 DOSAGE AND ADMINISTRATION

Dosage

The recommended dosage in adults is 1.5 g (four 0.375 g capsules) orally once daily in the morning.

Administration Instructions

- Evaluate renal function before initiating therapy with APRISO *[see Warnings and Precautions (5.1)]*.
- Swallow APRISO capsules whole. Do not cut, break, crush or chew the capsules.
- Avoid co-administration of APRISO with antacids *[see Drug Interactions (7.1)]*.
- Drink an adequate amount of fluids *[see Warnings and Precautions (5.6)]*.
- Take APRISO without regard to meals *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 0.375 g mesalamine in a light blue opaque gelatin capsule with the letters “G” and “M” imprinted on either side of a black band.

4 CONTRAINDICATIONS

APRISO is contraindicated in patients with hypersensitivity to salicylates or aminosalicylates or to any of the components of APRISO capsules *[see Warnings and Precautions (5.3), Adverse Reactions (6.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change disease, acute and chronic interstitial nephritis, and renal failure, has been reported in patients given products such as APRISO that contain mesalamine or are converted to mesalamine. In animal studies, the kidney was the principal organ of mesalamine toxicity *[see Adverse Reactions (6.2), Nonclinical Toxicology (13.2)]*.

Evaluate renal function prior to initiation of APRISO therapy and periodically while on therapy. Evaluate the risks and benefits of using APRISO in patients with known renal impairment or a history of renal disease or taking concomitant nephrotoxic drugs *[see Drug Interactions (7.2), Use in Specific Populations (8.6)]*.

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with APRISO.

5.3 Hypersensitivity Reactions

Some patients have experienced a hypersensitivity reaction to sulfasalazine. Some patients may have a similar reaction to APRISO or to other compounds that contain or are converted to mesalamine.

As with sulfasalazine, mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue APRISO if an alternative etiology for the signs and symptoms cannot be established.

5.4 Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Evaluate the risks and benefits of using APRISO in patients with known liver impairment.

5.5 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with the use of mesalamine *[see Adverse Reactions (6.2)]*. Discontinue APRISO at the first signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

5.6 Photosensitivity

Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors.

5.7 Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalamine, including stones with 100% mesalamine content. Mesalamine-containing stones are radiotransparent and undetectable by standard radiography or computed tomography (CT). Ensure adequate fluid intake during treatment with APRISO.

5.8 Risks in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). APRISO contains phenylalanine, a component of aspartame. Each APRISO 0.375 g capsule contains 0.56 mg of phenylalanine. Before prescribing APRISO to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including APRISO.

5.9 Interference with Laboratory Tests

Use of APRISO may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection because of the similarity in the chromatograms of normetanephrine and the main metabolite of mesalamine, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). Consider an alternative, selective assay for normetanephrine.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Renal Impairment *[see Warnings and Precautions (5.1)]*
- Mesalamine-Induced Acute Intolerance Syndrome *[see Warnings and Precautions (5.2)]*

- Hepatic Failure *[see Warnings and Precautions (5.4)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Photosensitivity *[see Warnings and Precautions (5.6)]*
- Nephrolithiasis *[see Warnings and Precautions (5.7)]*
- Risks in Patients with Phenylketonuria *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to APRISO in 557 patients, including 354 exposed for at least 6 months and 250 exposed for greater than one year. APRISO was studied in two placebo-controlled trials (n=367 treated with APRISO) and in one open-label, long-term study (n=190 additional patients). The population consisted of patients with ulcerative colitis; the mean age was 47 years, 54% were female, and 93% were white. Patients received doses of APRISO 1.5 g administered orally once per day for six months in the placebo-controlled trials and for up to 24 months in the open-label study.

In the two placebo-controlled trials, the most common reactions reported in at least 3% of APRISO-treated patients and at a greater rate than placebo are shown in Table 1 below.

Table 1: Common Adverse Reactions* in Clinical Trials of Adults with Ulcerative Colitis

	APRISO 1.5 g once daily N=367	**Placebo N=185**
Headache	11%	8%
Diarrhea	8%	7%
Upper Abdominal Pain	5%	3%
Nausea	4%	3%
Nasopharyngitis	4%	3%

* Reported in at least 3% of APRISO-treated patients and at a greater rate than with placebo

The following adverse reactions, presented by body system, were reported at a frequency less than 3% in patients treated with APRISO for up to 24 months in controlled and open-label trials.

Ear and Labyrinth Disorders: tinnitus, vertigo

Dermatological Disorder: alopecia

Gastrointestinal: lower abdominal pain, rectal hemorrhage

Laboratory Abnormalities: increased triglycerides, decreased hematocrit and hemoglobin

General Disorders and Administration Site Disorders: fatigue

Hepatic: hepatitis cholestatic, transaminases increased

Renal Disorders: creatinine clearance decreased, hematuria

Musculoskeletal: pain, arthralgia

Respiratory: dyspnea

6.2 Postmarketing Experience

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

Body as a Whole: lupus-like syndrome, drug fever

Cardiovascular: pericarditis, pericardial effusion, myocarditis *[see Warnings and Precautions (5.3)]*

Gastrointestinal: pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer

Hepatic: jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes

Hematologic: agranulocytosis, aplastic anemia

Nervous System: intracranial hypertension

Neurological/Psychiatric: peripheral neuropathy, Guillain-Barré syndrome, transverse myelitis

Renal and Urinary: nephrogenic diabetes insipidus, interstitial nephritis, renal failure, minimal change disease, nephrolithiasis *[see Warnings and Precautions (5.1, 5.7)]*

Respiratory/Pulmonary: eosinophilic pneumonia, interstitial pneumonitis, pleurisy/pleuritis

Skin: psoriasis, pyoderma gangrenosum, erythema nodosum, SJS/TEN, DRESS, and AGEP *[see Warnings and Precautions (5.5)]*

Renal/Urogenital: reversible oligospermia

7 DRUG INTERACTIONS

7.1 Antacids

Because the dissolution of the coating of the granules in APRISO capsules depends on pH, avoid co-administration of APRISO capsules with antacids *[see Dosage and Administration (2)]*.

7.2 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal 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 *[see Warnings and Precautions (5.1)]*.

7.3 Azathioprine or 6-Mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine and/or other drugs known to cause myelotoxicity may increase the risk for blood disorders, bone marrow failure, and associated complications. If concomitant use of APRISO and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

7.4 Interference with Urinary Normetanephrine Measurements

Use of APRISO may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection *[see Warnings and Precautions (5.9)]*. Consider an alternative, selective assay for normetanephrine.

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