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

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

- APRISO is a locally-acting aminosalicylate indicated for the maintenance of remission of ulcerative colitis in adults (1)

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

- Four APRISO capsules once daily (1.5 g/day) in the morning with or without food. Do not co-administer with antacids (2)

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

- Extended-release capsules: 0.375 g (3)

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

- Hypersensitivity to salicylates, aminosalicylates, or any component of APRISO capsules (4)

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

- Renal impairment may occur. Assess renal function at the beginning of treatment and periodically during therapy (5.1)
- Acute exacerbation of colitis symptoms can occur (5.2)
- Use caution with pre-existing liver disease (5.4)

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

- The most common adverse reactions (incidence ≥3%) are headache, diarrhea, upper abdominal pain, nausea, nasopharyngitis, flu or flu-like illness, sinusitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals, Inc. at 1-800-508-0024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Do not co-administer with antacids (7.1)

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

- Use with caution in patients with renal disease (5.1)
- Monitor blood cell counts in geriatric patients (8.5)
- Advise patients with phenylketonuria that APRISO contains aspartame (17.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APRISO capsules are indicated for the maintenance of remission of ulcerative colitis in patients 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

The recommended dose for maintenance of remission of ulcerative colitis in adult patients is 1.5 g (four APRISO capsules) orally once daily in the morning. APRISO may be taken without regard to meals. APRISO should not be co-administered with antacids. An evaluation of renal function is recommended before initiating therapy with APRISO.

3 DOSAGE FORMS AND STRENGTHS

Extended-release capsules containing 0.375 g mesalamine.

4 CONTRAINDICATIONS

APRISO is contraindicated in patients with hypersensitivity to salicylates or aminosalicylates or to any of the components of APRISO capsules.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products such as APRISO that contain mesalamine or are converted to mesalamine.

It is recommended that patients have an evaluation of renal function prior to initiation of APRISO therapy and periodically while on therapy. Exercise caution when using APRISO in patients with known renal dysfunction or a history of renal disease.

In animal studies, the kidney was the principal organ for toxicity *[See Nonclinical Toxicology (13.2)]*

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is suspected, promptly discontinue treatment with APRISO.

5.3 Hypersensitivity

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

5.4 Hepatic Impairment

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Caution should be exercised when administering APRISO to patients with liver disease.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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.

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.

In the two placebo-controlled trials, 59% of APRISO-treated patients experienced an adverse reaction compared with 64% of placebo patients. Most adverse reactions with APRISO were mild or moderate in severity. Severe adverse reactions occurred in 6% of APRISO-treated patients and 5% of placebo-treated patients. Discontinuations due to adverse reactions occurred in 11% of APRISO-treated patients and 17% of placebo-treated patients; the most common adverse reaction resulting in study discontinuation was recurrence of ulcerative colitis (APRISO 6%, placebo 14%). The most common reactions reported with APRISO (≥3%) are shown in Table 1 below.

Table 1: Treatment-Emergent Adverse Reactions during Clinical Trials Occurring in at Least 3% of APRISO-Treated Patients and at a Greater Rate than with Placebo

MedDRA Preferred Term	APRISO 1.5 g/day N=367	Placebo N=185
Headache	11%	8%
Diarrhea	8%	7%
Abdominal Pain Upper	5%	3%
Nausea	4%	3%
Nasopharyngitis	4%	3%
Influenza & Influenza-like illness	4%	4%
Sinusitis	3%	3%

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: abdominal pain lower, 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 Adverse Reaction Information from Other Sources

The following adverse reactions have been identified during clinical trials of a product similar to APRISO and post approval use of other mesalamine-containing products such as APRISO. 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

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

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

Respiratory/Pulmonary: eosinophilic pneumonia, interstitial pneumonitis

Skin: psoriasis, pyoderma gangrenosum, erythema nodosum

Renal/Urogenital: reversible oligospermia

7 DRUG INTERACTIONS

Based on in vitro studies, APRISO is not expected to inhibit the metabolism of drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

7.1 Antacids

Because the dissolution of the coating of the granules in APRISO capsules depends on pH, APRISO capsules should not be co-administered with antacids.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies with mesalamine have been performed in rats at oral doses up to 320 mg/kg/day (about 1.7 times the recommended human dose based on a body surface area comparison) and rabbits at doses up to 495 mg/kg/day (about 5.4 times the recommended human dose based on a body surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Mesalamine is known to cross the placental barrier.

8.3 Nursing Mothers

Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine. Caution should be exercised when APRISO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of APRISO capsules in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of APRISO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing APRISO.

Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias, i.e., neutropenia, pancytopenia, in patients who were 65 years or older who were taking mesalamine-containing products such as APRISO. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

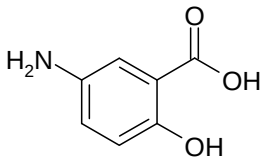
Mesalamine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. *[see Warning and Precautions (5.1)]*.

10 OVERDOSAGE

APRISO is an aminosalicylate, and symptoms of salicylate toxicity include hematemesis, tachypnea, hyperpnea, tinnitus, deafness, lethargy, seizures, confusion, or dyspnea. Severe intoxication may lead to electrolyte and blood pH imbalance and potentially to other organ (e.g., renal and liver) involvement. There is no specific antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. This includes prevention of further gastrointestinal tract absorption by emesis and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained. APRISO is a pH-dependent delayed-release product and this factor should be considered when treating a suspected overdose.

11 DESCRIPTION

Each APRISO capsule is a delayed- and extended-release dosage form for oral administration. Each capsule contains 0.375 g of mesalamine USP (5-aminosalicylic acid, 5-ASA), an anti-inflammatory drug. The structural formula of mesalamine is:



Molecular Weight: 153.14
Molecular Formula: $C_7H_7NO_3$

Each APRISO capsule contains granules composed of mesalamine in a polymer matrix with an enteric coating that dissolves at pH 6 and above.

The inactive ingredients of APRISO capsules are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, simethicone emulsion, ethylacrylate/methylmethacrylate copolymer nonoxynol 100 dispersion, hypromellose, methacrylic acid copolymer, talc, titanium dioxide, triethyl citrate, aspartame, anhydrous citric acid, povidone, vanilla flavor, and edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of mesalamine (5-ASA) is unknown, but appears to be local to the intestinal mucosa rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with ulcerative colitis, and it is possible that 5-ASA diminishes inflammation by blocking production of arachidonic acid metabolites.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of 5-ASA and its metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), were studied after a single and multiple oral doses of 1.5 g APRISO in a crossover study in healthy subjects under fasting conditions. In the multiple-dose period, each subject received APRISO 1.5 g (4 x 0.375 g capsules) every 24 hours (QD) for 7 consecutive days. Steady state was reached on Day 6 of QD dosing based on trough concentrations.

After single and multiple doses of APRISO, peak plasma concentrations were observed at about 4 hours post dose. At steady state, moderate increases (1.5-fold and 1.7-fold) in systemic exposure (AUC_{0-24}) to 5-ASA and N-Ac-5-ASA were observed when compared with a single-dose of APRISO.

Pharmacokinetic parameters after a single dose of 1.5 g APRISO and at steady state in healthy subjects under fasting condition are shown in Table 2.

Table 2: Single Dose and Multiple Dose Mean (±SD) Plasma Pharmacokinetic Parameters of Mesalamine (5-ASA) and N-Ac-5-ASA after 1.5 g APRISO Administration in Healthy Subjects

Mesalamine (5-ASA)	Single Dose (n=24)	Multiple Dose[c] (n=24)
AUC_{0-24} (µg*h/mL)	11 ± 5	17 ± 6
AUC_{0-inf} (µg*h/mL)	14 ± 5	-
C_{max} (µg/mL)	2.1 ± 1.1	2.7 ± 1.1
T_{max} (h) [a]	4 (2, 16)	4 (2, 8)
$t_{½}$ (h)[b]	9 ± 7	10 ± 8
N-Ac-5-ASA		
AUC_{0-24} (µg*h/mL)	26 ± 6	37 ± 9
AUC_{0-inf} (µg*h/mL)	51 ± 23	-
C_{max} (µg/mL)	2.8 ± 0.8	3.4 ± 0.9
T_{max} (h)[a]	4 (4, 12)	5 (2, 8)
$t_{½}$ (h)[b]	12 ± 11	14 ± 10

[a] Median (range); [b] Harmonic mean (pseudo SD); [c] after 7 days of treatment

In a separate study (n = 30), it was observed that under fasting conditions about 32% ± 11% (mean ± SD) of the administered dose was systemically absorbed based on the combined cumulative urinary excretion of 5-ASA and N-Ac-5-ASA over 96 hours post-dose.

The effect of a high fat meal intake on absorption of mesalamine granules (the same granules contained in APRISO capsules) was evaluated in 30 healthy subjects. Subjects received 1.6 g of mesalamine granules in sachet (2 x 0.8 g) following an overnight fast or a high-fat meal in a crossover study. Under fed conditions, t_{max} for both 5-ASA and N-Ac-5-ASA was prolonged by 4 and 2 hours, respectively. A high fat meal did not affect C_{max} for 5-ASA, but a 27% increase in the cumulative urinary excretion of 5-ASA was observed with a high fat meal. The overall extent of absorption of N-Ac-5-ASA was not affected by a high fat meal. As APRISO and mesalamine granules in sachet were bioequivalent, APRISO can be taken without regard to food.

Distribution

In an *in vitro* study, at 2.5 µg/mL, mesalamine and N-Ac-5-ASA are 43 ± 6% and 78 ± 1% bound, respectively, to plasma proteins. Protein binding of N-Ac-5-ASA does not appear to be concentration dependent at concentrations ranging from 1 to 10 µg/mL.

Metabolism

The major metabolite of mesalamine is N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). It is formed by N-acetyltransferase activity in the liver and intestinal mucosa.

Elimination

Following single and multiple doses of APRISO, the mean half-lives were 9 to 10 hours for 5-ASA, and 12 to 14 hours for N-Ac-5-ASA. Of the approximately 32% of the dose absorbed, about 2% of the dose was excreted unchanged in the urine, compared with about 30% of the dose excreted as N-Ac-5-ASA.

In Vitro Drug-Drug Interaction Study

In an *in vitro* study using human liver microsomes, 5-ASA and its metabolite, N-Ac-5-ASA, were shown not to inhibit the major CYP enzymes evaluated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Therefore, mesalamine and its metabolite are not expected to inhibit the metabolism of other drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. These doses are about 2.6 and 5.4 times the recommended human dose of granulated mesalamine capsules of 1.5 g/day (30 mg/kg if 50 kg body weight assumed or 1110 mg/m^2), respectively, based on body surface area. Mesalamine was negative in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, the sister chromatid exchange assay in the Chinese hamster bone marrow test, and the mouse bone marrow micronucleus test. Mesalamine at oral doses up to 320 mg/kg (about 1.7 times the recommended human dose based on body surface area) was found to have no effect on fertility or reproductive performance in rats.

13.2 Animal Toxicology and/or Pharmacology

Renal Toxicity

Animal studies with mesalamine (13-week and 26-week oral toxicity studies in rats, and 26-week and 52-week oral toxicity studies in dogs) have shown the kidney to be the major target organ of mesalamine toxicity. Oral doses of 40 mg/kg/day (about 0.20 times the human dose, on the basis of body surface area) produced minimal to slight tubular injury, and doses of 160 mg/kg/day (about 0.90 times the human dose, on the basis of body surface area) or higher in rats produced renal lesions including tubular degeneration, tubular mineralization, and papillary necrosis. Oral doses of 60 mg/kg/day (about 1.1 times the human dose, on the basis of body surface area) or higher in dogs also produced renal lesions including tubular atrophy, interstitial cell infiltration, chronic nephritis, and papillary necrosis.

Overdosage

Single oral doses of 800 mg/kg (about 2.2 times the recommended human dose, on the basis of body surface area) and 1800 mg/kg (about 9.7 times the recommended human dose, on the basis of body surface area) of mesalamine were lethal to mice and rats, respectively, and resulted in gastrointestinal and renal toxicity.

14 CLINICAL STUDIES

14.1 Ulcerative Colitis

Two similar, randomized, double-blind, placebo-controlled, multi-center studies were conducted in a total of 562 adult patients in remission from ulcerative colitis. The study

populations had a mean age of 46 years (11% age 65 years or older), were 53% female, and were primarily white (92%).

Ulcerative colitis disease activity was assessed using a modified Sutherland Disease Activity Index[1] (DAI), which is a sum of four subscores based on stool frequency, rectal bleeding, mucosal appearance on endoscopy, and physician's rating of disease activity. Each subscore can range from 0 to 3, for a total possible DAI score of 12.

At baseline, approximately 80% of patients had a total DAI score of 0 or 1.0. Patients were randomized 2:1 to receive either APRISO 1.5 g or placebo once daily in the morning for six months. Patients were assessed at baseline, 1 month, 3 months, and 6 months in the clinic, with endoscopy performed at baseline, at end of study, or if clinical symptoms developed. Relapse was defined as a rectal bleeding subscale score of 1 or more and a mucosal appearance subscale score of 2 or more using the DAI. The analysis of the intent-to-treat population was a comparison of the proportions of patients who remained relapse-free at the end of six months of treatment. For the table below (Table 3) all patients who prematurely withdrew from the study for any reason were counted as relapses.

In both studies, the proportion of patients who remained relapse-free at six months was greater for APRISO than for placebo.

Table 3: Percentage of Patients Relapse-Free* through 6 Months in APRISO Maintenance Studies

	APRISO 1.5 g/day % (# no relapse/N)	Placebo % (# no relapse/N)	Difference (95% C.I.)	P-value
Study 1	68% (143/209)	51% (49/96)	17% (5.5, 29.2)	<0.001
Study 2	71% (117/164)	59% (55/93)	12% (0, 24.5)	0.046

* Relapse counted as rectal bleeding score ≥ 1 and mucosal appearance score ≥ 2, or premature withdrawal from study.

Examination of gender subgroups did not identify difference in response to APRISO among these subgroups. There were too few elderly and too few African-American patients to adequately assess difference in effects in those populations.

The use of APRISO for treating ulcerative colitis beyond six months has not been evaluated in controlled clinical trials.

15 REFERENCES

1. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, *et al.* 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology 1987;92(6):1894-1898.

16 HOW SUPPLIED/STORAGE AND HANDLING

APRISO is available as light blue opaque hard gelatin capsules containing 0.375 g mesalamine and with the letters “G” and “M” on either side of a black band imprinted on the capsule.

NDC 65649-103-02 Bottles of 120 capsules
NDC 65649-103-01 Bottles of 4 capsules

Storage:
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

17.1 Patients with Phenylketonuria

- Inform patients with phenylketonuria (PKU) or their caregivers that each APRISO capsule contains aspartame equivalent to 0.56 mg of phenylalanine, so that the recommended adult dosing provides an equivalent of 2.24 mg of phenylalanine per day.

17.2 General Counseling Information

- Instruct patients not to take APRISO capsules with antacids, because it could affect the way APRISO dissolves.

- Instruct patients to contact a health care provider if they experience a worsening of ulcerative colitis symptoms, because it could be due to a reaction to APRISO.

Manufactured by Catalent Pharma Solutions for Salix Pharmaceuticals, Inc., Morrisville, NC 27560
* APRISO™ is a trademark of Salix Pharmaceuticals, Inc.

Product protected by U.S. Patent No. 6,551,620

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