CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-301

LABELING

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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

---

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.