WARNINGS AND PRECAUTIONS

- Renal impairment: 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)
- Contains phenylalanine (5.5)

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

- Do not co-administer with antacids (7.1)

INFORMATION FROM OTHER SOURCES

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

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

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>APRISO 1.5 g/day N=367</th>
<th>Placebo N=185</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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

Dermatologic Disorders: alopecia

Gastrointestinal: abdominal pain, lower rectal hemorrhage

Laboratory Abnormalities: increased triglycerides, decreased hematocrit and hemoglobin

General Disorders: anorexia, and weight gain

Hepatic: chronic hepatitis, 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: lumps-like syndrome, drug fever

Cardiovascular: pericarditis, pericardial effusion, myocarditis

Gastrointestinal: pancreatitis, cholecystitis, gastritis, gastrointestinal bleeding, perforated pyloric ulcer

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

Hematologic: agranulocytosis, aplastic anemia

Nervous System: intracranial hypertension

NeuroOPsychiatric: peripheral neuropathy, Guillain-Barré syndrome, transverse myelitis

Renal and Urinary: nephrotic syndrome, diabetes, diabetes insipidus

Respiratory/Dermatologic: eosinophilic pneumonia, interstitial pneumonitis

Skin: psoriasis, pustular gangrenosum, erythema nodosum

APRISO: anaphylactic reactions

7 DRUG INTERACTIONS

Based on in vitro studies, APRISO is not expected to inhibit the metabolism of drugs that are substrates of CYP1A2, CYP2C8, CYP2C9, CYP3A4, or CYP2D6.

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 125 mg/kg/day (about 7.7 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 acetylated metabolites 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 from younger patients. 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.
After single and multiple doses of APRISO, peak plasma concentrations were observed at about 1.5 g (4 x 0.375 g capsules) every 24 hours (QD) for 7 consecutive days. Steady state Pharmacokinetics of arachidonic acid metabolites.

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 cytochrome P450 pathways, i.e., prostaglandins, and through the lipoygenase 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.

12.2 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)) 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 conditions are shown in Table 2.

12.3 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, based on body surface area) induced tubular injury, 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 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.

Overdose

Single oral doses of 800 mg/kg (about 2.2 times the recommended human dose, on the basis of body surface area) induced nonrenal lesions including tubal atrophy, interstitial cell infiltration, chronic nephritis, and papillary necrosis.

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 APRISO capsules when expressed on the basis of body weight (about 110 mg/kg/day, or about 2.7% increase in the cumulative urinary excretion of 5-ASA was observed with a high fat meal. The overall effect of absorption of N-Ac-5-ASA was not affected by a high fat meal. As APRISO and mesalamine gastrografin, equilibrium, APRISO can be taken without regard to food.

Distribution

In an in vitro study, at 2.5 mcg/mL, mesalamine and N-Ac-5-ASA were 43±6% and 78±1% bound, respectively, to plasma proteins. Protein binding of N-acetyl-5-ASA does not appear to be concentration dependent at concentrations ranging from 1 to 10 mcg/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, and CYP3A4.

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.

StORAGE:

Store: 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).

Distributed by: Salix Pharmaceuticals, a division of Bausch Health US LLC, Bridgewater, NJ 08807 USA

Manufactured by: Bausch Health Companies Inc. Steinhach, MB R5G 1Z7, Canada

U.S. Patent Number: 8,860,688

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

<table>
<thead>
<tr>
<th></th>
<th>APRISO 1.5 g/day (% who relapse/N)</th>
<th>Placebo (% who relapse/N)</th>
<th>Difference (90% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>68% (17/25)</td>
<td>51% (49/96)</td>
<td>17% (5.29, 28.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study 2</td>
<td>71% (17/24)</td>
<td>59% (55/93)</td>
<td>12% (0, 24.5)</td>
<td>0.046</td>
</tr>
</tbody>
</table>