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. An evaluation of renal function is recommended before initiating therapy with APRISO.

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.

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 Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 NONCLINICAL TOXICOLOGY
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>APRISO 1.5 g/day (N=376)</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>Nasopharyngitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza &amp; Influenza-like illness</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.

Eard 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 cholestasis, 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, 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
Respiratory/Pulmonary: eosinophilic pneumonia, interstitial pneumonitis
Skin: psoriasis, pyoderma gangrenosum, erythema nodosum
Renal/Urogenital: reversible oligospermia

DRUG INTERACTIONS

7.0 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 485 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 Warnings and Precautions (5.1)].

OVERDOSAGE
APRISO is an aminosalicylate, and symptoms of salicylate toxicity include hematemesis, tachycardia, hyperventilation, 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 overdose. 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:

![Chemical Structure of Mesalamine](image)

Molecular Weight: 153.14
Molecular Formula: C₁₅H₁₄NO₃

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 ethyl acrylate/methyl methacrylate 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.

12.2 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 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 Administration in Healthy Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mesalamine (5-ASA)</th>
<th>N-Ac-5-ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Dose</td>
<td>Multiple Dose</td>
</tr>
<tr>
<td></td>
<td>(n=24)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>AUC:&lt;sub&gt;0-inf&lt;/sub&gt; (µg*h/mL)</td>
<td>11 ± 5</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>AUC:&lt;sub&gt;0-24&lt;/sub&gt; (µg*h/mL)</td>
<td>14 ± 5</td>
<td>-</td>
</tr>
<tr>
<td>C:&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>2.1 ± 1.1</td>
<td>2.7 ± 1.1</td>
</tr>
<tr>
<td>T:&lt;sub&gt;Cmax&lt;/sub&gt; (h)</td>
<td>4 (2, 16)</td>
<td>4 (2, 8)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>9 ± 7</td>
<td>10 ± 8</td>
</tr>
</tbody>
</table>

N-Ac-5-ASA

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N-Ac-5-ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC:&lt;sub&gt;0-inf&lt;/sub&gt; (µg*h/mL)</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>AUC:&lt;sub&gt;0-24&lt;/sub&gt; (µg*h/mL)</td>
<td>51 ± 23</td>
</tr>
<tr>
<td>C:&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>2.4 ± 0.8</td>
</tr>
<tr>
<td>T:&lt;sub&gt;Cmax&lt;/sub&gt; (h)</td>
<td>4 (4, 12)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>12 ± 11</td>
</tr>
</tbody>
</table>

* Median (range); † Harmonic mean (pseudo SD); ‡ 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. Under fed conditions, tmax for both 5-ASA and N-Ac-5-ASA was prolonged by 4 and 2 hours, respectively. A high fat meal did not affect Cmax 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**

The mean age of 46 years (11% age 65 years or older), were 53% female, 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.

**CLINICAL STUDIES**

**14 Ulcerative Colitis**

**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 (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. 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 0 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**

<table>
<thead>
<tr>
<th></th>
<th>APRISO 1.5 g/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (# no relapse/N)</td>
<td>% (# no relapse/N)</td>
<td>Difference (95% C.I.)</td>
</tr>
<tr>
<td>Study 1</td>
<td>68% (143/209)</td>
<td>51% (49/96)</td>
</tr>
<tr>
<td>Study 2</td>
<td>71% (171/243)</td>
<td>59% (55/93)</td>
</tr>
</tbody>
</table>

* 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**


**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 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**

**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.

**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 for:

Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC

Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,551,620; 7,547,451; 8,337,886; 8,496,965; 8,865,688; 8,911,778; 8,940,328; and 8,956,647

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Please see www.salix.com for patient information.

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