trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of Mesalamine has been associated with an acute intolerance syndrome that may be difficult...

5.2 Mesalamine-Induced Acute Intolerance Syndrome

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

CONTRAINDICATIONS

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

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 any component 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.

5.5 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The data described below reflect exposure to APRISO in 557 patients, including 354 exposed for at least 6 months and 230 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.

Revised: 09/2019
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

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>APRISO 1.5 g/day</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>Nauseopharyngitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza and 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.

- **Eyes**
  - Conjunctivitis

- **Skin**
  - psoriasis
  - pyoderma gangrenosum
  - erythema nodosum

- **Respiratory/Pulmonary**
  - eosinophilic pneumonia
  - interstitial pneumonitis

- **Renal and Urinary**
  - nephrogenic diabetes insipidus

- **Neurological/Psychiatric**
  - peripheral neuropathy
  - Guillain-Barré syndrome
  - transverse myelitis

- **Hematologic**
  - agranulocytosis
  - aplastic anemia

- **Gastrointestinal**
  - jaundice
  - liver necrosis
  - liver failure

- **Body as a Whole**
  - lupus-like syndrome
  - drug fever

- **Cardiovascular**
  - pericarditis
  - pericardial effusion

- **Gastrointestinal**
  - pancreatitis
  - cholecystitis
  - gastritis
  - gastroenteritis

- **Dermatological Disorder**
  - alopecia

- **Hepatic**
  - hepatitis cholestatic
  - transaminases increased

- **Renal Disorders**
  - creatinine clearance decreased
  - hematuria

- **Musculoskeletal**
  - pain

- **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

- **Gastrointestinal**
  - pancreatitis
  - cholecystitis
  - gastritis
  - gastroenteritis

- **Dermatological Disorder**
  - alopecia

- **Hepatic**
  - hepatitis cholestatic
  - transaminases increased

- **Renal Disorders**
  - creatinine clearance decreased
  - hematuria

- **Musculoskeletal**
  - pain

- **Respiratory**
  - dyspnea

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 is a pH-dependent delayed-release product and this factor should be considered when treating a suspected overdose.

11 **DESCRIPTION**

Each APRISO capsule contains 0.375 g of mesalamine USP (5-aminosalicylic acid, 5-ASA), an anti-inflammatory drug. The structural formula of mesalamine is:

\[
\begin{align*}
H & N \\
& OH \\
& OH
\end{align*}
\]

Molecular Weight: 153.14

Molecular Formula: C\textsubscript{4}H\textsubscript{8}N\textsubscript{2}O\textsubscript{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 ethyl acrylate/methyl methacrylate copolymer nonoxynol 10 dispersion, hypromellose, methacrylic acid copolymer, talc, titanium dioxide, triethyl citrate, aspartame, anhydrous citric acid, povidone, vanilla flavor, and edible black ink. Each APRISO 0.375 g capsule contains 0.56 mg of phenylalanine.

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 peroxidase 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\textsubscript{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.
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 following an overnight fast or a high fat meal in a crossover study. After 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 absorption, about 2% of the dose was excreted unchanged in the urine, compared with about 30% of the dose excreted as N-Ac-5-ASA. 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 mcg/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 from 1 to 10 mcg/mL.

**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 Vivo 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/m²), 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.

**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**

<table>
<thead>
<tr>
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<th>Multiple Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-ASA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>2.8±1.1</td>
<td>3.4±0.9</td>
</tr>
<tr>
<td>Cmin (mcg/mL)</td>
<td>2.1±1.1</td>
<td>2.7±1.1</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>4 (2.16)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>12±11</td>
<td>14±10</td>
</tr>
<tr>
<td><strong>N-Ac-5-ASA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>26±6</td>
<td>37±9</td>
</tr>
<tr>
<td>Cmin (mcg/mL)</td>
<td>51±23</td>
<td>52±22</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>4 (12)</td>
<td>5 (2.8)</td>
</tr>
<tr>
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* Median (range); † Harmonic mean (pseudo SD); a after 7 days of treatment

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