

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-301**

**LABELING**

## 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  $\geq 3\%$ ) 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](http://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

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

1 **FULL PRESCRIBING INFORMATION**

2  
3 **1 INDICATIONS AND USAGE**

4 APRISO capsules are indicated for the maintenance of remission of ulcerative colitis in  
5 patients 18 years of age and older.  
6

7 **2 DOSAGE AND ADMINISTRATION**

8 The recommended dose for maintenance of remission of ulcerative colitis in adult  
9 patients is 1.5 g (four APRISO capsules) orally once daily in the morning. APRISO  
10 may be taken without regard to meals. APRISO should not be co-administered with  
11 antacids. An evaluation of renal function is recommended before initiating therapy  
12 with APRISO.  
13

14 **3 DOSAGE FORMS AND STRENGTHS**

15 Extended-release capsules containing 0.375 g mesalamine.  
16

17 **4 CONTRAINDICATIONS**

18 APRISO is contraindicated in patients with hypersensitivity to salicylates or aminosaliclates  
19 or to any of the components of APRISO capsules.  
20

21 **5 WARNINGS AND PRECAUTIONS**

22 **5.1 Renal Impairment**

23 Renal impairment, including minimal change nephropathy, acute and chronic interstitial  
24 nephritis, and, rarely, renal failure, has been reported in patients given products such as  
25 APRISO that contain mesalamine or are converted to mesalamine.  
26

27 It is recommended that patients have an evaluation of renal function prior to initiation of  
28 APRISO therapy and periodically while on therapy. Exercise caution when using APRISO  
29 in patients with known renal dysfunction or a history of renal disease.  
30

31 In animal studies, the kidney was the principal organ for toxicity [*See Nonclinical Toxicology*  
32 (*13.2*)]  
33

34 **5.2 Mesalamine-Induced Acute Intolerance Syndrome**

35 Mesalamine has been associated with an acute intolerance syndrome that may be difficult to  
36 distinguish from a flare of inflammatory bowel disease. Although the exact frequency of  
37 occurrence has not been determined, it has occurred in 3% of patients in controlled clinical  
38 trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain  
39 and bloody diarrhea, sometimes fever, headache, and rash. If acute intolerance syndrome is  
40 suspected, promptly discontinue treatment with APRISO.  
41

42 **5.3 Hypersensitivity**

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

46  
47 **5.4 Hepatic Impairment**

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

51

52 **6 ADVERSE REACTIONS**

53 **6.1 Clinical Studies Experience**

54 The data described below reflect exposure to APRISO in 557 patients, including 354 exposed  
55 for at least 6 months and 250 exposed for greater than one year. APRISO was studied in two  
56 placebo-controlled trials (n = 367 treated with APRISO) and in one open-label, long-term  
57 study (n = 190 additional patients). The population consisted of patients with ulcerative  
58 colitis; the mean age was 47 years, 54% were female, and 93% were white. Patients received  
59 doses of APRISO 1.5 g administered orally once per day for six months in the placebo-  
60 controlled trials and for up to 24 months in the open-label study.

61

62 Because clinical studies are conducted under widely varying conditions, adverse reaction  
63 rates observed in the clinical trials of a drug cannot be directly compared to rates in the  
64 clinical trials of another drug and may not reflect the rates observed in practice.

65

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

74

75  
76  
77

**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%

78

79 The following adverse reactions, presented by body system, were reported at a frequency less  
80 than 3% in patients treated with APRISO for up to 24 months in controlled and open-label  
81 trials.

82

83 Ear and Labyrinth Disorders: tinnitus, vertigo

84

85 Dermatological Disorder: alopecia

86

87 Gastrointestinal: abdominal pain lower, rectal hemorrhage

88

89 Laboratory Abnormalities: increased triglycerides, decreased hematocrit and hemoglobin

90

91 General Disorders and Administration Site Disorders: fatigue

92

93 Hepatic: hepatitis cholestatic, transaminases increased

94

95 Renal Disorders: creatinine clearance decreased, hematuria

96

97 Musculoskeletal: pain, arthralgia

98

99 Respiratory: dyspnea

100

## 101 **6.2 Adverse Reaction Information from Other Sources**

102 The following adverse reactions have been identified during clinical trials of a product  
103 similar to APRISO and post approval use of other mesalamine-containing products such as  
104 APRISO. Because many of these reactions are reported voluntarily from a population of  
105 unknown size, it is not always possible to reliably estimate their frequency or establish a  
106 causal relationship to drug exposure.

107

108 Body as a Whole: lupus-like syndrome, drug fever

109

Cardiovascular: pericarditis, pericardial effusion, myocarditis

- 110 Gastrointestinal: pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding,  
111 perforated peptic ulcer
- 112 Hepatic: jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like  
113 syndrome including changes in liver enzymes
- 114 Hematologic: agranulocytosis, aplastic anemia
- 115 Neurological/Psychiatric: peripheral neuropathy, Guillain-Barré syndrome, transverse  
116 myelitis
- 117 Respiratory/Pulmonary: eosinophilic pneumonia, interstitial pneumonitis
- 118 Skin: psoriasis, pyoderma gangrenosum, erythema nodosum
- 119 Renal/Urogenital: reversible oligospermia  
120

## 121 7 DRUG INTERACTIONS

122 Based on in vitro studies, APRISO is not expected to inhibit the metabolism of drugs that are  
123 substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.  
124

### 125 7.1 Antacids

126 Because the dissolution of the coating of the granules in APRISO capsules depends on pH,  
127 APRISO capsules should not be co-administered with antacids.  
128

## 129 8 USE IN SPECIFIC POPULATIONS

### 130 8.1 Pregnancy

131 Pregnancy Category B. Reproduction studies with mesalamine have been performed in rats  
132 at oral doses up to 320 mg/kg/day (about 1.7 times the recommended human dose based on a  
133 body surface area comparison) and rabbits at doses up to 495 mg/kg/day (about 5.4 times the  
134 recommended human dose based on a body surface area comparison) and have revealed no  
135 evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however,  
136 no adequate and well-controlled studies in pregnant women. Because animal reproduction  
137 studies are not always predictive of human response, this drug should be used during  
138 pregnancy only if clearly needed.  
139

140 Mesalamine is known to cross the placental barrier.  
141

### 142 8.3 Nursing Mothers

143 Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have  
144 been detected in human breast milk. The clinical significance of this has not been  
145 determined and there is limited experience of nursing women using mesalamine. Caution  
146 should be exercised when APRISO is administered to a nursing woman.  
147

### 148 8.4 Pediatric Use

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

150

151 **8.5 Geriatric Use**

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

158

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

163

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

168

169 **10 OVERDOSAGE**

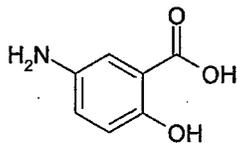
170 APRISO is an aminosalicylate, and symptoms of salicylate toxicity include hematemesis,  
171 tachypnea, hyperpnea, tinnitus, deafness, lethargy, seizures, confusion, or dyspnea. Severe  
172 intoxication may lead to electrolyte and blood pH imbalance and potentially to other organ  
173 (e.g., renal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

180

181 **11 DESCRIPTION**

182 Each APRISO capsule is a delayed- and extended-release dosage form for oral  
183 administration. Each capsule contains 0.375 g of mesalamine USP (5-aminosalicylic acid,  
184 5-ASA), an anti-inflammatory drug. The structural formula of mesalamine is:

185



186

187 Molecular Weight: 153.14

188 Molecular Formula: C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>

189

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

192  
193 The inactive ingredients of APRISO capsules are colloidal silicon dioxide, magnesium  
194 stearate, microcrystalline cellulose, simethicone emulsion, ethylacrylate/methylmethacrylate  
195 copolymer nonoxynol 100 dispersion, hypromellose, methacrylic acid copolymer, talc,  
196 titanium dioxide, triethyl citrate, aspartame, anhydrous citric acid, povidone, vanilla flavor,  
197 and edible black ink.  
198

## 199 **12 CLINICAL PHARMACOLOGY**

### 200 **12.1 Mechanism of Action**

201 The mechanism of action of mesalamine (5-ASA) is unknown, but appears to be local to the  
202 intestinal mucosa rather than systemic. Mucosal production of arachidonic acid metabolites,  
203 both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase  
204 pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with  
205 ulcerative colitis, and it is possible that 5-ASA diminishes inflammation by blocking  
206 production of arachidonic acid metabolites.  
207

### 208 **12.3 Pharmacokinetics**

#### 209 *Absorption*

210 The pharmacokinetics of 5-ASA and its metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-  
211 ASA), were studied after a single and multiple oral doses of 1.5 g APRISO in a crossover  
212 study in healthy subjects under fasting conditions. In the multiple-dose period, each subject  
213 received APRISO 1.5 g (4 x 0.375 g capsules) every 24 hours (QD) for 7 consecutive days.  
214 Steady state was reached on Day 6 of QD dosing based on trough concentrations.  
215

216 After single and multiple doses of APRISO, peak plasma concentrations were observed at  
217 about 4 hours post dose. At steady state, moderate increases (1.5-fold and 1.7-fold) in  
218 systemic exposure ( $AUC_{0-24}$ ) to 5-ASA and N-Ac-5-ASA were observed when compared  
219 with a single-dose of APRISO.  
220

221 Pharmacokinetic parameters after a single dose of 1.5 g APRISO and at steady state in  
222 healthy subjects under fasting condition are shown in Table 2.  
223

224  
225  
226

**Table 2: Single Dose and Multiple Dose Mean ( $\pm$ 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 <sup>c</sup> (n=24)
AUC <sub>0-24</sub> ( $\mu$ g*h/mL)	11 $\pm$ 5	17 $\pm$ 6
AUC <sub>0-inf</sub> ( $\mu$ g*h/mL)	14 $\pm$ 5	-
C <sub>max</sub> ( $\mu$ g/mL)	2.1 $\pm$ 1.1	2.7 $\pm$ 1.1
T <sub>max</sub> (h) <sup>a</sup>	4 (2, 16)	4 (2, 8)
t <sub>1/2</sub> (h) <sup>b</sup>	9 $\pm$ 7	10 $\pm$ 8
<b>N-Ac-5-ASA</b>		
AUC <sub>0-24</sub> ( $\mu$ g*h/mL)	26 $\pm$ 6	37 $\pm$ 9
AUC <sub>0-inf</sub> ( $\mu$ g*h/mL)	51 $\pm$ 23	-
C <sub>max</sub> ( $\mu$ g/mL)	2.8 $\pm$ 0.8	3.4 $\pm$ 0.9
T <sub>max</sub> (h) <sup>a</sup>	4 (4, 12)	5 (2, 8)
t <sub>1/2</sub> (h) <sup>b</sup>	12 $\pm$ 11	14 $\pm$ 10

<sup>a</sup> Median (range); <sup>b</sup> Harmonic mean (pseudo SD); <sup>c</sup> after 7 days of treatment

227

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

231

232 The effect of a high fat meal intake on absorption of mesalamine granules (the same granules  
233 contained in APRISO capsules) was evaluated in 30 healthy subjects. Subjects received  
234 1.6 g of mesalamine granules in sachet (2 x 0.8 g) following an overnight fast or a high-fat  
235 meal in a crossover study. Under fed conditions, t<sub>max</sub> for both 5-ASA and N-Ac-5-ASA was  
236 prolonged by 4 and 2 hours, respectively. A high fat meal did not affect C<sub>max</sub> for 5-ASA, but  
237 a 27% increase in the cumulative urinary excretion of 5-ASA was observed with a high fat  
238 meal. The overall extent of absorption of N-Ac-5-ASA was not affected by a high fat meal.  
239 As APRISO and mesalamine granules in sachet were bioequivalent, APRISO can be taken  
240 without regard to food.

#### 241 *Distribution*

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

#### 245 *Metabolism*

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

#### 248 *Elimination*

249 Following single and multiple doses of APRISO, the mean half-lives were 9 to 10 hours for  
250 5-ASA, and 12 to 14 hours for N-Ac-5-ASA. Of the approximately 32% of the dose  
251 absorbed, about 2% of the dose was excreted unchanged in the urine, compared with about  
252 30% of the dose excreted as N-Ac-5-ASA.

253

254 *In Vitro Drug-Drug Interaction Study*

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

260

261 **13 NONCLINICAL TOXICOLOGY**

262 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

272

273 **13.2 Animal Toxicology and/or Pharmacology**

274 *Renal Toxicity*

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

284 *Overdosage*

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

289

290 **14 CLINICAL STUDIES**

291 **14.1 Ulcerative Colitis**

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

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

296  
297 Ulcerative colitis disease activity was assessed using a modified Sutherland Disease Activity  
298 Index<sup>1</sup> (DAI), which is a sum of four subscores based on stool frequency, rectal bleeding,  
299 mucosal appearance on endoscopy, and physician's rating of disease activity. Each subscore  
300 can range from 0 to 3, for a total possible DAI score of 12.

301  
302 At baseline, approximately 80% of patients had a total DAI score of 0 or 1.0. Patients were  
303 randomized 2:1 to receive either APRISO 1.5 g or placebo once daily in the morning for six  
304 months. Patients were assessed at baseline, 1 month, 3 months, and 6 months in the clinic,  
305 with endoscopy performed at baseline, at end of study, or if clinical symptoms developed.  
306 Relapse was defined as a rectal bleeding subscale score of 1 or more and a mucosal  
307 appearance subscale score of 2 or more using the DAI. The analysis of the intent-to-treat  
308 population was a comparison of the proportions of patients who remained relapse-free at the  
309 end of six months of treatment. For the table below (Table 3) all patients who prematurely  
310 withdrew from the study for any reason were counted as relapses.

311  
312 In both studies, the proportion of patients who remained relapse-free at six months was  
313 greater for APRISO than for placebo.

314  
315 **Table 3: Percentage of Patients Relapse-Free\* through 6 Months**  
316 **in APRISO Maintenance Studies**  
317

	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

318 \* Relapse counted as rectal bleeding score  $\geq 1$  and mucosal appearance score  $\geq 2$ , or premature withdrawal  
319 from study.

320  
321 Examination of gender subgroups did not identify difference in response to APRISO among  
322 these subgroups. There were too few elderly and too few African-American patients to  
323 adequately assess difference in effects in those populations.

324  
325 The use of APRISO for treating ulcerative colitis beyond six months has not been evaluated  
326 in controlled clinical trials.

327

## 328 15 REFERENCES

- 329 1. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, *et al.*  
330 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis,  
331 proctosigmoiditis, and proctitis. *Gastroenterology* 1987;92(6):1894-1898.

332

333 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

337  
338 NDC 65649-103-02 Bottles of 120 capsules  
339 NDC 65649-103-01 Bottles of 4 capsules

340  
341 *Storage:*

342 Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and  
343 86°F). See USP Controlled Room Temperature.

344

345 **17 PATIENT COUNSELING INFORMATION**

346 **17.1 Patients with Phenylketonuria**

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

351 **17.2 General Counseling Information**

- 352 • Instruct patients not to take APRISO capsules with antacids, because it could affect  
353 the way APRISO dissolves.
- 354 • Instruct patients to contact a health care provider if they experience a worsening of  
355 ulcerative colitis symptoms, because it could be due to a reaction to APRISO.

356

357 Manufactured by Catalent Pharma Solutions for Salix Pharmaceuticals, Inc., Morrisville, NC  
358 27560

359 \* APRISO™ is a trademark of Salix Pharmaceuticals, Inc.

360 © 2008 Salix Pharmaceuticals, Inc.

361

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

363

364 VENART-113-0

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