

Note to reviewer: This proposed labeling includes a modification of the drug interaction text provided by FDA in the approvable letter to Supplement 115 dated 4/6/01. The FDA text appears in regular type and the modification appears in underline & strikeout (see lines 189 - 199).

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Prescribing Information

**Azulfidine EN-tabs®**  
**sulfasalazine delayed release tablets, USP**

Enteric-coated Tablets

DESCRIPTION

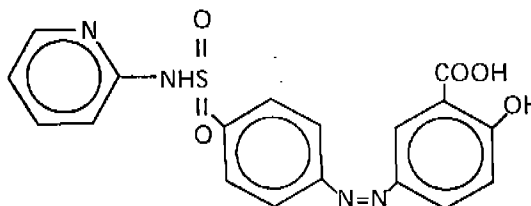
AZULFIDINE EN-tabs Tablets contain sulfasalazine, formulated in a delayed release tablet (enteric-coated), 500 mg, for oral administration.

AZULFIDINE EN-tabs Tablets are film coated with cellulose acetate phthalate to retard disintegration of the tablet in the stomach and reduce potential irritation of the gastric mucosa.

**Therapeutic Classification:** Anti-inflammatory agent and/or immunomodulatory agent.

**Chemical Designation:** 5-([p-(2-pyridylsulfamoyl)phenyl]azo) salicylic acid.

Chemical Structure:



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**Molecular Formula:** C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub>S

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mode of action of sulfasalazine (SSZ) or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), is still under investigation, but may be related to the anti-inflammatory and/or immunomodulatory properties that have been observed in animal and in vitro models, to its affinity for connective tissue, and/or to the relatively high concentration it reaches in serous fluids, the liver and intestinal walls, as demonstrated in autoradiographic studies in animals. In ulcerative colitis, clinical studies utilizing rectal administration of SSZ, SP and 5-ASA have indicated that the major therapeutic action may reside in the 5-ASA moiety. The relative contribution of the parent drug and the major metabolites in rheumatoid arthritis is unknown.

39 **Pharmacokinetics**

40

41 In vivo studies have indicated that the absolute bioavailability of orally administered SSZ is less than  
42 15% for parent drug. In the intestine, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Of  
43 the two species, SP is relatively well absorbed from the intestine and highly metabolized, while 5-  
44 ASA is much less well absorbed.

45

46 **Absorption:** Following oral administration of 1 g of SSZ to 9 healthy males, less than 15% of a dose  
47 of SSZ is absorbed as parent drug. Detectable serum concentrations of SSZ have been found in  
48 healthy subjects within 90 minutes after the ingestion. Maximum concentrations of SSZ occur  
49 between 3 and 12 hours post-ingestion, with the mean peak concentration (6 µg/mL) occurring at 6  
50 hours.

51

52 In comparison, peak plasma levels of both SP and 5-ASA occur approximately 10 hours after dosing.  
53 This longer time to peak is indicative of gastrointestinal transit to the lower intestine, where bacteria-  
54 mediated metabolism occurs. SP apparently is well absorbed from the colon, with an estimated  
55 bioavailability of 60%. In this same study, 5-ASA is much less well absorbed from the  
56 gastrointestinal tract, with an estimated bioavailability of from 10% to 30%.

57

58 **Distribution:** Following intravenous injection, the calculated volume of distribution (V<sub>dss</sub>) for SSZ  
59 was 7.5 ± 1.6 L. SSZ is highly bound to albumin (>99.3%), while SP is only about 70% bound to  
60 albumin. Acetylsulfapyridine (AcSP), the principal metabolite of SP, is approximately 90% bound to  
61 plasma proteins.

62

63 **Metabolism:** As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA.  
64 Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the  
65 liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4  
66 hrs. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism  
67 of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life  
68 of SP is 10.4 hrs, while in slow acetylators it is 14.8 hrs. SP can also be metabolized to 5-hydroxy-  
69 sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in  
70 both the liver and intestine to N-acetyl-5-aminosalicylic acid via a non-acetylation phenotype  
71 dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable  
72 estimates of plasma half-life are not possible.

73

74 **Excretion:** Absorbed SP and 5-ASA and their metabolites are primarily eliminated in the urine  
75 either as free metabolites or as glucuronide conjugates. The majority of 5-ASA stays within the  
76 colonic lumen and is excreted as 5-ASA and acetyl-5-ASA with the feces. The calculated clearance  
77 of SSZ following intravenous administration was 1 L/hr. Renal clearance was estimated to account  
78 for 37% of total clearance.

79

80 **Special Populations**

81

82 **Elderly:** Elderly patients with rheumatoid arthritis showed a prolonged plasma half-life for SSZ, SP,  
83 and their metabolites. The clinical impact of this is unknown.

84

85 **Pediatric:** Small studies have been reported in the literature in children down to the age of 4  
86 years with ulcerative colitis and inflammatory bowel disease. In these populations, relative

87 to adults, the pharmacokinetics of SSZ and SP correlated poorly with either age or dose. To  
88 date, comparative pharmacokinetic trials have not been conducted to determine whether or  
89 not significant pharmacokinetic differences exist between children with juvenile rheumatoid  
90 arthritis and adults with rheumatoid arthritis.

91  
92 **Acetylator Status:** The metabolism of SP to AcSP is mediated by polymorphic enzymes such that  
93 two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian  
94 population can be classified as belonging to the slow acetylator phenotype. These subjects will  
95 display a prolonged plasma half-life for SP (14.8 hrs vs. 10.4 hrs) and an accumulation of higher  
96 plasma levels of SP than fast acetylators. The clinical implication of this is unclear; however, in a  
97 small pharmacokinetic trial where acetylator status was determined, subjects who were slow  
98 acetylators of SP showed a higher incidence of adverse events.

99  
100 **Gender:** Gender appears not to have an effect on either the rate or the pattern of metabolites of SSZ,  
101 SP, or 5-ASA.

## 102 103 INDICATIONS AND USAGE

104  
105 AZULFIDINE EN-tabs Tablets are indicated:

- 106 a) in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe  
107 ulcerative colitis;  
108 b) for the prolongation of the remission period between acute attacks of ulcerative colitis;  
109 c) in the treatment of patients with rheumatoid arthritis who have responded inadequately to  
110 salicylates or other nonsteroidal anti-inflammatory drugs (e.g., an insufficient therapeutic  
111 response to, or intolerance of, an adequate trial of full doses of one or more nonsteroidal anti-  
112 inflammatory drugs); and  
113 d) in the treatment of pediatric patients with polyarticular-course<sup>1</sup> juvenile rheumatoid arthritis who  
114 have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs.  
115

116 AZULFIDINE EN-tabs is particularly indicated in patients with ulcerative colitis who cannot take  
117 uncoated sulfasalazine tablets because of gastrointestinal intolerance, and in whom there is evidence  
118 that this intolerance is not primarily the result of high blood levels of sulfapyridine and its  
119 metabolites, e.g., patients experiencing nausea and vomiting with the first few doses of the drug, or  
120 patients in whom a reduction in dosage does not alleviate the adverse gastrointestinal effects.

121  
122 In patients with rheumatoid arthritis or juvenile rheumatoid arthritis, rest and physiotherapy as  
123 indicated should be continued. Unlike anti-inflammatory drugs, AZULFIDINE EN-tabs does not  
124 produce an immediate response. Concurrent treatment with analgesics and/or nonsteroidal anti-  
125 inflammatory drugs is recommended at least until the effect of AZULFIDINE EN-tabs is apparent.

## 126 127 CONTRAINDICATIONS

128  
129 AZULFIDINE EN-tabs Tablets are contraindicated in:

- 130 Hypersensitivity to sulfasalazine, its metabolites, sulfonamides or salicylates,  
131 Patients with intestinal or urinary obstruction,  
132 Patients with porphyria, as the sulfonamides have been reported to precipitate an acute attack.  
133

134 **WARNINGS**

135

136 Only after critical appraisal should AZULFIDINE EN-tabs Tablets be given to patients with hepatic  
137 or renal damage or blood dyscrasias. Deaths associated with the administration of sulfasalazine have  
138 been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood  
139 dyscrasias, renal and liver damage, irreversible neuromuscular and central nervous system changes,  
140 and fibrosing alveolitis. The presence of clinical signs such as sore throat, fever, pallor, purpura or  
141 jaundice may be indications of serious blood disorders. Complete blood counts, as well as urinalysis  
142 with careful microscopic examination, should be done frequently in patients receiving  
143 AZULFIDINE EN-tabs (see PRECAUTIONS, Laboratory Tests). Oligospermia and infertility have  
144 been observed in men treated with sulfasalazine; however, withdrawal of the drug appears to reverse  
145 these effects.

146

147 **PRECAUTIONS**

148

149 **General:** AZULFIDINE EN-tabs Tablets should be given with caution to patients with severe  
150 allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria  
151 and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be  
152 observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or  
153 hypersensitivity reactions occur, AZULFIDINE EN-tabs should be discontinued immediately.

154

155 Isolated instances have been reported when AZULFIDINE EN-tabs Tablets have passed  
156 undisintegrated. If this is observed, the administration of AZULFIDINE EN-tabs should be  
157 discontinued immediately.

158

159 **Information For Patients:** Patients should be informed of the possibility of adverse effects and of  
160 the need for careful medical supervision. The occurrence of sore throat, fever, pallor, purpura or  
161 jaundice may indicate a serious blood disorder. Should any of these occur, the patient should seek  
162 medical advice.

163

164 Patients should be instructed to take AZULFIDINE EN-tabs in evenly divided doses, preferably after  
165 meals, and to swallow the tablets whole. Additionally, patients should be advised that sulfasalazine  
166 may produce an orange-yellow discoloration of the urine or skin.

167

168 **Ulcerative Colitis:** Patients with ulcerative colitis should be made aware that ulcerative colitis rarely  
169 remits completely, and that the risk of relapse can be substantially reduced by continued  
170 administration of AZULFIDINE EN-tabs at a maintenance dosage.

171

172 **Rheumatoid Arthritis:** Rheumatoid arthritis rarely remits. Therefore, continued administration of  
173 AZULFIDINE EN-tabs is indicated. Patients requiring sulfasalazine should follow up with their  
174 physicians to determine the need for continued administration.

175

176 **Laboratory Tests:** Complete blood counts, including differential white cell count and liver function  
177 tests, should be performed before starting AZULFIDINE EN-tabs and every second week during the  
178 first three months of therapy. During the second three months, the same tests should be done once  
179 monthly and thereafter once every three months, and as clinically indicated. Urinalysis and an  
180 assessment of renal function should also be done periodically during treatment with AZULFIDINE  
181 EN-tabs.

182

183 The determination of serum sulfapyridine levels may be useful since concentrations greater than 50  
184 µg/mL appear to be associated with an increased incidence of adverse reactions.

185  
186 **Drug Interactions:** Reduced absorption of folic acid and digoxin have been reported when those  
187 agents were administered concomitantly with sulfasalazine.

188  
189 When daily doses of sulfasalazine 2g and weekly doses of methotrexate 7.5mg were coadministered  
190 to 15 rheumatoid arthritis patients in a drug-drug interaction study, the pharmacokinetic  
191 disposition of the drugs was not altered.

192  
193 ~~The overall toxicity profile associated with the concomitant administration of sulfasalazine~~  
194 ~~and methotrexate in controlled clinical studies~~Daily doses of sulfasalazine 2g (maximum 3g)  
195 and weekly doses of methotrexate 7.5mg (maximum 15mg) were administered alone or in  
196 combination to 310 rheumatoid arthritis patients in two controlled 52-week clinical studies.  
197 The overall toxicity profile of the combination revealed an increased incidence, of  
198 gastrointestinal adverse events, especially nausea, when compared to the incidence  
199 associated with either drug administered alone.

200  
201 **Drug/Laboratory Test Interactions:** The presence of sulfasalazine or its metabolites in body fluids  
202 has not been reported to interfere with laboratory test procedures.

203  
204 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two year oral carcinogenicity studies were  
205 conducted in male and female F344/N rats and B6C3F1 mice. Sulfasalazine was tested at 84 (496  
206 mg/m<sup>2</sup>), 168 (991 mg/m<sup>2</sup>) and 337.5 (1991 mg/m<sup>2</sup>) mg/kg/day doses in rats. A statistically  
207 significant increase in the incidence of urinary bladder transitional cell papillomas was observed in  
208 male rats. In female rats, two (4%) of the 337.5 mg/kg rats had transitional cell papilloma of the  
209 kidney. The increased incidence of neoplasms in the urinary bladder and kidney of rats was also  
210 associated with an increase in the renal calculi formation and hyperplasia of transitional cell  
211 epithelium. For the mouse study, sulfasalazine was tested at 675 (2025 mg/m<sup>2</sup>), 1350 (4050 mg/m<sup>2</sup>)  
212 and 2700 (8100 mg/m<sup>2</sup>) mg/kg/day. The incidence of hepatocellular adenoma or carcinoma in male  
213 and female mice was significantly greater than the control at all doses tested.

214  
215 Sulfasalazine did not show mutagenicity in the bacterial reverse mutation assay (Ames test) or in the  
216 L51784 mouse lymphoma cell assay at the HGPRT gene. However, sulfasalazine showed equivocal  
217 mutagenic response in the micronucleus assay of mouse and rat bone marrow and mouse peripheral  
218 RBC and in the sister chromatid exchange, chromosomal aberration, and micronucleus assays in  
219 lymphocytes obtained from humans.

220  
221 Impairment of male fertility was observed in reproductive studies performed in rats at a dose of 800  
222 mg/kg/day (4800 mg/m<sup>2</sup>). Oligospermia and infertility have been described in men treated with  
223 sulfasalazine. Withdrawal of the drug appears to reverse these effects.

224

225 **Pregnancy:**

226

227 **Teratogenic Effects: Pregnancy Category B.** Reproduction studies have been performed in rats and  
228 rabbits at doses up to 6 times the human dose and have revealed no evidence of impaired female  
229 fertility or harm to the fetus due to sulfasalazine. There are, however, no adequate and well-  
230 controlled studies in pregnant women. Because animal reproduction studies are not always predictive  
231 of human response, this drug should be used during pregnancy only if clearly needed.

232

233 A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease  
234 (IBD). In 186 pregnancies in women treated with sulfasalazine alone or sulfasalazine and  
235 concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable both to  
236 that of 245 untreated IBD pregnancies, and to pregnancies in the general population.<sup>2</sup>

237

238 A study of 1455 pregnancies associated with exposure to sulfonamides including sulfasalazine,  
239 indicated that this group of drugs did not appear to be associated with fetal malformation.<sup>3</sup> A review  
240 of the medical literature covering 1155 pregnancies in women with ulcerative colitis suggested that  
241 the outcome was similar to that expected in the general population.<sup>4</sup>

242

243 No clinical studies have been performed to evaluate the effect of sulfasalazine on the growth  
244 development and functional maturation of children whose mothers received the drug during  
245 pregnancy.

246

247 **Nonteratogenic Effects:** Sulfasalazine and sulfapyridine pass the placental barrier. Although  
248 sulfapyridine has been shown to have poor bilirubin-displacing capacity, the potential for kernicterus  
249 in newborns should be kept in mind.

250

251 A case of agranulocytosis has been reported in an infant whose mother was taking both sulfasalazine  
252 and prednisone throughout pregnancy.

253

254 **Nursing Mothers:** Caution should be exercised when AZULFIDINE EN-tabs is administered to a  
255 nursing mother. Sulfonamides are excreted in the milk. In the newborn, they compete with bilirubin  
256 for binding sites on the plasma proteins and may cause kernicterus. Insignificant amounts of  
257 uncleaved sulfasalazine have been found in milk, whereas the sulfapyridine levels in milk are about  
258 30% to 60% of those in the maternal serum. Sulfapyridine has been shown to have a poor bilirubin-  
259 displacing capacity.

260

261 **Pediatric Use:** The safety and effectiveness of AZULFIDINE EN-tabs in pediatric patients below  
262 the age of two years with ulcerative colitis have not been established.

263

264 The safety and effectiveness of AZULFIDINE EN-tabs for the treatment of the signs and symptoms  
265 of polyarticular-course juvenile rheumatoid arthritis in pediatric patients aged 6-16 years is  
266 supported by evidence from adequate and well-controlled studies in adult rheumatoid arthritis  
267 patients. The extrapolation from adults with rheumatoid arthritis to children with polyarticular-  
268 course juvenile rheumatoid arthritis is based on similarities in disease and response to therapy  
269 between these two patient populations. Published studies support the extrapolation of safety and  
270 effectiveness for sulfasalazine to polyarticular-course juvenile rheumatoid arthritis<sup>1,5</sup> (see ADVERSE  
271 REACTIONS).

272

273 It has been reported that the frequency of adverse events in patients with systemic-course of juvenile  
274 arthritis is high.<sup>6</sup> Use in children with systemic-course juvenile rheumatoid arthritis has frequently  
275 resulted in a serum sickness-like reaction.<sup>5</sup> This reaction is often severe and presents as fever, nausea,  
276 vomiting, headache, rash, and abnormal liver function tests. Treatment of systemic-course juvenile  
277 rheumatoid arthritis with sulfasalazine is not recommended.

278

## 279 ADVERSE REACTIONS

280

281 The most common adverse reactions associated with sulfasalazine in ulcerative colitis are anorexia,  
282 headache, nausea, vomiting, gastric distress, and apparently reversible oligospermia. These occur in  
283 about one-third of the patients. Less frequent adverse reactions are pruritus, urticaria, fever, Heinz  
284 body anemia, hemolytic anemia and cyanosis, which may occur at a frequency of 1 in 30 patients or  
285 less. Experience suggests that with a daily dose of 4 g or more, or total serum sulfapyridine levels  
286 above 50 µg/mL, the incidence of adverse reactions tends to increase.

287

288 Similar adverse reactions are associated with sulfasalazine use in adult rheumatoid arthritis,  
289 although there was a greater incidence of some reactions. In rheumatoid arthritis studies, the  
290 following common adverse reactions were noted: nausea (19%), dyspepsia (13%), rash  
291 (13%), headache (9%), abdominal pain (8%), vomiting (8%), fever (5%), dizziness (4%),  
292 stomatitis (4%), pruritis (4%), abnormal liver function tests (4%), leukopenia (3%), and  
293 thrombocytopenia (1%). One report<sup>7</sup> showed a 10% rate of immunoglobulin suppression,  
294 which was slowly reversible and rarely accompanied by clinical findings.

295

296 In general, the adverse reactions in juvenile rheumatoid arthritis patients are similar to those  
297 seen in patients with adult rheumatoid arthritis except for a high frequency of serum  
298 sickness-like syndrome in systemic-course juvenile rheumatoid arthritis (see  
299 PRECAUTIONS, Pediatric Use). One clinical trial showed an approximate 10% rate of  
300 immunoglobulin suppression.<sup>1</sup>

301

302 Although the listing which follows includes a few adverse reactions which have not been reported  
303 with this specific drug, the pharmacological similarities among the sulfonamides require that each of  
304 these reactions be considered when AZULFIDINE EN-tabs is administered.

305

306 Less common or rare adverse reactions include:

307

308 **Blood dyscrasias:** aplastic anemia, agranulocytosis, megaloblastic (macrocytic) anemia, purpura,  
309 hypoprothrombinemia, methemoglobinemia, congenital neutropenia, and myelodysplastic syndrome.

310

311 **Hypersensitivity reactions:** erythema multiforme (Stevens-Johnson syndrome), exfoliative  
312 dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, anaphylaxis, serum  
313 sickness syndrome, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis,  
314 pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus  
315 erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes,  
316 fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta  
317 (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema,  
318 conjunctival and scleral injection and alopecia.

319

320 **Gastrointestinal reactions:** hepatitis, pancreatitis, bloody diarrhea, impaired folic acid absorption,  
321 impaired digoxin absorption, diarrhea, and neutropenic enterocolitis.

322

323 **Central Nervous System reactions:** transverse myelitis, convulsions, meningitis, transient lesions  
324 of the posterior spinal column, cauda equina syndrome, Guillain-Barre syndrome, peripheral  
325 neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations; tinnitus and  
326 drowsiness.

327

328 **Renal reactions:** toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, urinary  
329 tract infection, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome.

330

331 **Other reactions:** urine discoloration and skin discoloration.

332

333 The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and  
334 the thiazides), and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have  
335 occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.  
336 Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides and long-term  
337 administration has produced thyroid malignancies in this species.

338

#### 339 **Postmarketing Reports**

340

341 The following events have been identified during post-approval use of products which contain (or are  
342 metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a  
343 population of unknown size, estimates of frequency cannot be made. These events have been chosen  
344 for inclusion due to a combination of seriousness, frequency of reporting, or potential causal  
345 connection to mesalamine:

346

347 **Gastrointestinal:** Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST,  
348 SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis,  
349 and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases  
350 were fatal. One case of Kawasaki-like syndrome, which included hepatic function changes, was also  
351 reported.

352

#### 353 **DRUG ABUSE AND DEPENDENCE**

354

355 None reported.

356

#### 357 **OVERDOSAGE**

358

359 There is evidence that the incidence and severity of toxicity following overdosage is directly related  
360 to the total serum sulfapyridine concentration. Symptoms of overdosage may include nausea,  
361 vomiting, gastric distress and abdominal pains. In more advanced cases, central nervous system  
362 symptoms such as drowsiness, convulsions, etc., may be observed. Serum sulfapyridine  
363 concentrations may be used to monitor the progress of recovery from overdosage.

364

365 There are no documented reports of deaths due to ingestion of large single doses of sulfasalazine.  
366 It has not been possible to determine the LD<sub>50</sub> in laboratory animals such as mice, since the highest  
367 oral daily dose of sulfasalazine which can be given (12 g/kg) is not lethal. Doses of regular  
368 sulfasalazine tablets of 16 g per day have been given to patients without mortality.



369

370 **Instructions for Overdosage:** Gastric lavage or emesis plus catharsis as indicated. Alkalinize urine.  
371 If kidney function is normal, force fluids. If anuria is present, restrict fluids and salt, and treat  
372 appropriately. Catheterization of the ureters may be indicated for complete renal blockage by  
373 crystals. The low molecular weight of sulfasalazine and its metabolites may facilitate their removal  
374 by dialysis

375

## 376 **DOSAGE AND ADMINISTRATION**

377

378 The dosage of AZULFIDINE EN-tabs Tablets should be adjusted to each individual's response and  
379 tolerance

380

381 Patients should be instructed to take AZULFIDINE EN-tabs in evenly divided doses, preferably after  
382 meals, and to swallow the tablets whole.

383

### 384 **Ulcerative Colitis**

385

#### 386 **Initial Therapy:**

387

388 **Adults:** 3 to 4 g daily in evenly divided doses with dosage intervals not exceeding eight hours. It  
389 may be advisable to initiate therapy with a lower dosage, e.g., 1 to 2 g daily, to reduce possible  
390 gastrointestinal intolerance. If daily doses exceeding 4 g are required to achieve the desired  
391 therapeutic effect, the increased risk of toxicity should be kept in mind.

392 **Children, six years of age and older:** 40 to 60 mg/kg of body weight in each 24-hour period,  
393 divided into 3 to 6 doses.

394

#### 395 **Maintenance Therapy:**

396

397 **Adults:** 2 g daily.

398 **Children, six years of age and older:** 30 mg/kg of body weight in each 24-hour period, divided into  
399 4 doses. The response of acute ulcerative colitis to AZULFIDINE EN-tabs can be evaluated by  
400 clinical criteria, including the presence of fever, weight changes, and degree and frequency of  
401 diarrhea and bleeding, as well as by sigmoidoscopy and the evaluation of biopsy samples. It is often  
402 necessary to continue medication even when clinical symptoms, including diarrhea, have been  
403 controlled. When endoscopic examination confirms satisfactory improvement, dosage of  
404 AZULFIDINE EN-tabs should be reduced to a maintenance level. If diarrhea recurs, dosage should  
405 be increased to previously effective levels.

406

407 AZULFIDINE EN-tabs is particularly indicated in patients who cannot take uncoated sulfasalazine  
408 tablets because of gastrointestinal intolerance (e.g., anorexia, nausea). If symptoms of gastric  
409 intolerance (anorexia, nausea, vomiting, etc.) occur after the first few doses of AZULFIDINE EN-  
410 tabs, they are probably due to increased serum levels of total sulfapyridine, and may be alleviated by  
411 halving the daily dose of AZULFIDINE EN-tabs and subsequently increasing it gradually over  
412 several days. If gastric intolerance continues, the drug should be stopped for 5 to 7 days, then  
413 reintroduced at a lower daily dose.

414 **Adult Rheumatoid Arthritis:**

415

416 2 g daily in two evenly divided doses. It is advisable to initiate therapy with a lower dosage of  
417 AZULFIDINE EN-tabs, e.g., 0.5 to 1.0 g daily, to reduce possible gastrointestinal intolerance. A  
418 suggested dosing schedule is given below.  
419

420 In rheumatoid arthritis, the effect of AZULFIDINE EN-tabs can be assessed by the degree of  
421 improvement in the number and extent of actively inflamed joints. A therapeutic response has been  
422 observed as early as 4 weeks after starting treatment with AZULFIDINE EN-tabs, but treatment for  
423 12 weeks may be required in some patients before clinical benefit is noted. Consideration can be  
424 given to increasing the daily dose of AZULFIDINE EN-tabs to 3 g if the clinical response after 12  
425 weeks is inadequate. Careful monitoring is recommended for doses over 2 g per day.  
426

427 **Suggested Dosing Schedule for Adult Rheumatoid Arthritis:**

428

429 430	Week of Treatment	Number of AZULFIDINE EN-tabs Tablets	
		Morning	Evening
431	1	-	One
432	2	One	One
433	3	One	Two
434	4	Two	Two

435

436 **Juvenile Rheumatoid Arthritis - polyarticular course**

437

438 **Children, six years of age and older:** 30 to 50 mg/kg of body weight daily in two evenly divided  
439 doses. Typically, the maximum dose is 2 g per day. To reduce possible gastrointestinal intolerance,  
440 begin with a quarter to a third of the planned maintenance dose and increase weekly until reaching  
441 the maintenance dose at one month.  
442

443 Some patients may be sensitive to treatment with sulfasalazine. Various desensitization-like  
444 regimens have been reported to be effective in 34 of 53 patients,<sup>8</sup> 7 of 8 patients,<sup>9</sup> and 19 of  
445 20 patients.<sup>10</sup> These regimens suggest starting with a total daily dose of 50 to 250 mg  
446 sulfasalazine initially, and doubling it every 4 to 7 days until the desired therapeutic level is  
447 achieved. If the symptoms of sensitivity recur, AZULFIDINE EN-tabs should be  
448 discontinued. Desensitization should not be attempted in patients who have a history of  
449 agranulocytosis, or who have experienced an anaphylactoid reaction while previously  
450 receiving sulfasalazine.  
451

452 **HOW SUPPLIED**

453

454 AZULFIDINE EN-tabs Tablets, 500 mg, are elliptical, gold-colored, film enteric-coated tablets,  
455 monogrammed "102" on one side and "KPh" on the other. They are available in the following  
456 package sizes:

457

Bottles of 100 NDC 0013-0102-01

458

Bottles of 300 NDC 0013-0102-20

459

460 **Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
461 Room Temperature]

462

463

Rx only

464

465

REFERENCES

466

467

1. van Rossum MAJ, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. *Arth Rheum* 1998;41:808-816.

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[Text based on copy code 818 425 001 (100 count), Revised: October 2000]