

NDA 7-073/S-110

Pharmacia & Upjohn Company  
Attention: Gregory A. Brier  
0637-298-113  
7000 Portage Road  
Kalamazoo, MI 49001

**AUG 13 1999**

Dear Mr. Brier:

Please refer to your supplemental new drug application dated February 12, 1999, received February 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azulfidine (sulfasalazine) Tablets and EN-tabs.

We acknowledge receipt of your submission dated February 26, 1999.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for revision of the ADVERSE REACTIONS section of the package insert for the EN-tabs to create a Postmarketing Reports subsection re:hepatotoxicity, in response to our September 1, 1998 letter. Your submissions stated February 16, 1999 (100 count bottle) and February 3, 1999 (300 count bottle) as the implementation date for the change.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert and immediate container and carton labels submitted February 12, 1999 [100 count] and February 26, 1999 [300 count]). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 7-073/S-110

Page 2

If you have any questions, contact Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.  
Director  
Division of Gastrointestinal and Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

# Azulfidine EN-tabs7

sulfasalazine delayed release tablets, USP



## DESCRIPTION

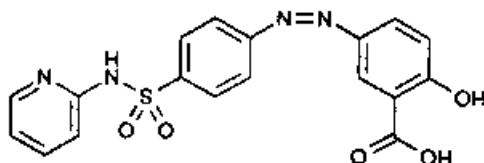
AZULFIDINE EN-tabs Tablets contain sulfasalazine, formulated in a delayed release tablet (enteric-coated), 500 mg, for oral administration.

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:**



**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 remains under investigation.

### Pharmacokinetics

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

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

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

**Distribution:** Following intravenous injection, the calculated volume of distribution (V<sub>dss</sub>) for SSZ was 7.5-11.6 L. SSZ is highly bound to albumin (>99.3%) while SP is only about 70% bound to albumin. Acetylsulfapyridine (AcSP), the principal metabolite of SP, is approximately 90% bound to plasma proteins.

**Metabolism:** As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6-13.4 hours. The primary route of metabolism of SP is via acetylation to form ACSP. The rate of metabolism of SP to ACSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours, while in slow acetylators it is 14.8 hours. SP can also be metabolized to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a non-acetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible.

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

### Special Populations

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

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

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

### INDICATIONS AND USAGE

AZULFIDINE EN-tabs Tablets are indicated:

- a) in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis;
- b) for the prolongation of the remission period between acute attacks of ulcerative colitis; and
- c) in the treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other non-steroidal anti-inflammatory drugs.

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

AZULFIDINE EN-tabs is recommended in the management of adults with active, classic and definitive rheumatoid arthritis who have had an insufficient therapeutic response to or are intolerant of an adequate trial of full doses of one or more non-steroidal anti-inflammatory drugs. In rheumatoid arthritis, concurrent treatment with analgesics and/or non-steroidal anti-inflammatory drugs is recommended at least until the effect of AZULFIDINE EN-tabs is apparent. Rest and physiotherapy as indicated should be continued. Unlike anti-inflammatory drugs, AZULFIDINE EN-tabs does not produce an immediate response.

### CONTRAINDICATIONS

AZULFIDINE EN-tabs Tablets are contraindicated in:

Hypersensitive to sulfasalazine its metabolites, sulfonamides or salicylates

Pediatric patients under two years of age,  
Patients with intestinal or urinary obstruction,  
Patients with porphyria, as the sulfonamides have been reported to precipitate an acute attack.

## WARNINGS

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

## PRECAUTIONS

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

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

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

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

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

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

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

The determination of serum sulfapyridine levels may be useful since concentrations greater than 50  $\mu\text{g/mL}$  appear to be associated with an increased incidence of adverse reactions.

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

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

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two year oral carcinogenicity studies were conducted in male and female F344/N rats and B6C3F1 mice. Sulfasalazine was tested at 84 (496  $\text{mg/m}^2$ ), 168 (991  $\text{mg/m}^2$ ) and 337.5 (1991  $\text{mg/m}^2$ )  $\text{mg/kg/day}$  doses in rats. A statistically significant increase in the incidence of urinary bladder

transitional cell papillomas was observed in male rats. In female rats, two (4%) of the 337.5 mg/kg rats had transitional cell papilloma of the kidney. The increased incidence of neoplasms in the urinary bladder and kidney of rats was also associated with an increase in the renal calculi formation and hyperplasia of transitional cell epithelium. For the mouse study, sulfasalazine was tested at 675 (2025 mg/m<sup>2</sup>), 1350 (4050 mg/m<sup>2</sup>) and 2700 (8100 mg/m<sup>2</sup>) mg/kg/day. The incidence of hepatocellular adenoma or carcinoma in male and female mice was significantly greater than the control at all doses tested.

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

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

### **Pregnancy:**

**Teratogenic effects: Pregnancy Category B.** Reproduction studies have been performed in rats and rabbits at doses up to 6 times the human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to sulfasalazine. 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.

A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease (IBD). In 186 pregnancies in women treated with sulfasalazine alone or sulfasalazine and concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable both to that of 245 untreated IBD pregnancies as well as to pregnancies in the general population.<sup>1</sup>

A study of 1,455 pregnancies associated with exposure to sulfonamides including sulfasalazine, indicated that this group of drugs did not appear to be associated with fetal malformation.<sup>2</sup> A review of the medical literature covering 1,155 pregnancies in women with ulcerative colitis suggested that the outcome was similar to that expected in the general population.<sup>3</sup>

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

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

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

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

**Pediatric Use:** The safety and effectiveness of AZULFIDINE EN-tabs in pediatric patients below the age of two years with ulcerative colitis have not been established. The safety and effectiveness in juvenile rheumatoid arthritis have not been established. It has been reported that the frequency of adverse events in patients with systemic onset of juvenile arthritis is high.<sup>4</sup>

### **ADVERSE REACTIONS**

Clinical experience to date has indicated that patients with rheumatoid arthritis treated with AZULFIDINE EN-tabs Tablets appear to have a similar profile and incidence of adverse effects to patients with ulcerative colitis. There are no known adverse effects that are specific to patients with rheumatoid arthritis treated with sulfasalazine with the possible exception of skin rash, which was seen in 13%, of patients in rheumatoid arthritis clinical trials but in about

1 in 30 patients or less in ulcerative colitis studies. The estimated incidence of adverse effects other than skin rash in patients treated with sulfasalazine is as follows for both ulcerative colitis and rheumatoid arthritis.

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

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

Other adverse reactions which occur rarely, in approximately 1 in 1000 patients or less are:

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

**Hypersensitivity reactions:** erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, anaphylaxis, serum sickness syndrome, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, parapsoriasis varioliformis acuta (MUCHA-HABERMAN syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia.

**Gastrointestinal reactions:** hepatitis, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea, abdominal pains, and neutropenic enterocolitis.

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

**Renal reactions:** toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, hematuria, crystalluria, proteinuria, and hemolytic uremic syndrome.

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

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

### **Postmarketing Reports**

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

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

### **DRUG ABUSE AND DEPENDENCE**

None reported

### **OVERDOSAGE**

There is evidence that the incidence and severity of toxicity following overdosage is directly related to the total serum sulfapyridine concentration. Symptoms of overdosage may include nausea, vomiting, gastric distress and

abdominal pains. In more advanced cases, central nervous system symptoms such as drowsiness, convulsions, etc. may be observed. Serum sulfapyridine concentrations may be used to monitor the progress of recovery from overdose.

There are no documented reports of deaths due to ingestion of large single doses of sulfasalazine.

It has not been possible to determine the LD<sub>50</sub> in laboratory animals such as mice, since the highest oral daily dose of sulfasalazine which can be given (12 g/kg) is not lethal. Doses of regular sulfasalazine tablets of 16 g per day have been given to patients without mortality.

**Instructions for Overdosage:** Gastric lavage or emesis plus catharsis as indicated. Alkalinize urine. If kidney function is normal, force fluids. If anuria is present, restrict fluids and salt, and treat appropriately. Catheterization of the ureters may be indicated for complete renal blockage by crystals. The low molecular weight of sulfasalazine and its metabolites may facilitate their removal by dialysis. For agranulocytosis, discontinue the drug immediately, hospitalize the patient, and institute appropriate therapy. For hypersensitivity reactions, discontinue treatment immediately. Such reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. When, in the physician's opinion, reinstitution of AZULFIDINE EN-tabs Tablets is warranted, regimens modeled upon recommended desensitization procedures may be attempted approximately two weeks after treatment has been discontinued and symptoms have disappeared (see DOSAGE AND ADMINISTRATION).

### **DOSAGE AND ADMINISTRATION**

The dosage of AZULFIDINE EN-tabs Tablets should be adjusted to each individual's response and tolerance. The drug should be given in evenly divided doses over each 24-hour period, intervals between nighttime doses should not exceed 8 hours, with administration after meals recommended when feasible. Experience suggests that with daily dosages of 4 g or more, the incidence of adverse effects tends to increase, hence, patients receiving these dosages should be instructed about, and carefully observed for, the appearance of adverse effects.

Some patients may be sensitive to treatment with sulfasalazine. Various desensitization-like regimens have been reported to be effective in 34 of 53 patients,<sup>5</sup> 7 of 8 patients,<sup>6</sup> and 19 of 20 patients.<sup>7</sup> These regimens suggest starting with a total daily dose of 50 to 250 mg sulfasalazine initially, and doubling it every 4 to 7 days until the desired therapeutic level is achieved. If the symptoms of sensitivity recur, AZULFIDINE EN-tabs should be discontinued. Desensitization should not be attempted in patients who have a history of agranulocytosis, or who have experienced an anaphylactoid reaction while previously receiving sulfasalazine.

### **Usual Dosage**

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

### **Ulcerative Colitis**

#### ***Initial Therapy***

**Adults:** 3 to 4 g daily in evenly divided doses. It may be advisable to initiate therapy with a lower dosage, eg, 1 to 2 g daily, to reduce possible gastrointestinal intolerance. If daily doses exceeding 4 g are required to achieve the desired therapeutic effect, the increased risk of toxicity should be kept in mind.

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

#### ***Maintenance Therapy***

**Adults:** 2 g daily.

**Children, two years of age and older:** 30 mg per kg of body weight in each 24-hour period, divided into 4 doses.

The response of acute ulcerative colitis to AZULFIDINE EN-tabs can be evaluated by clinical criteria, including the presence of fever, weight changes, and degree and frequency of diarrhea and bleeding, as well as by sigmoidoscopy and the evaluation of biopsy samples. It is often necessary to continue medication even when clinical symptoms, including diarrhea, have been controlled. When endoscopic examination confirms satisfactory



improvement, dosage of AZULFIDINE EN-tabs is reduced to a maintenance level. If diarrhea recurs, dosage should be increased to previously effective levels.

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

### Rheumatoid arthritis

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

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

### Suggested Dosing Schedule:

Week of Treatment	Number of AZULFIDINE EN- tabs Tablets	
	Morning	Evening
1	-	One
2	One	One
3	One	Two
4	Two	Two

### HOW SUPPLIED

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

Bottles of 100	NDC 0013-0102-01
Bottles of 300	NDC 0013-0102-20

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

L only

### REFERENCES

1. Mogadam M, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. *Gastroenterology* 1981;80:72-6.
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5. Korelitz B. et al, Desensitization to sulfasalazine in allergic patients with IBD: an important therapeutic modality. *Gastroenterology* 1982;82:1104.
6. Holdworth CG. Sulphasalazine desensitization. *Br Med J* 1981;282:110.

7. Taffet SL, Das KM. Desensitization of patients with Inflammatory bowel disease to sulfasalazine. Am J Med 1982;73:520-4.

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Revised: October 1998  
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By: Pharmacia & Upjohn AB  
Stockholm, Sweden