CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-243

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

NDA # 21-243
M.O. REVIEW #1.
SUBMISSION DATE: October 18, 1999
REVIEW COMPLETED: July 20, 2000
NAME: Azulfidine (sulfasalazine) EN-tabs
SPONSOR: Pharmacia & Upjohn Co.
DOSAGE FORM / ROUTE OF ADMINISTRATION: Tablets, po
REVIEWER: Kent Johnson, M.D.
SUBMISSION TYPE: Type 6, NDA
CSO: Sandra Cook

CONTENTS

I. CLINICAL BACKGROUND

NDA 7-073, approved June 20, 1950, provides for both Azulfidine (sulfasalazine) Tablets and Azulfidine EN-tabs Tablets for the treatment and maintenance of remission of ulcerative colitis. Azulfidine EN-tabs Tablets are also indicated in the treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDS). The rheumatoid arthritis indication was the subject of a

Type 6 NDA (20-465) submitted to the Pilot Drug Evaluation Staff (HFD-007) and subsequently transferred to and approved by the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) on October 17, 1996. In the August 2, 1995 approvable letter for the rheumatoid arthritis indication, the sponsor was requested to assess the safety and efficacy of sulfasalazine (SSZ) in patients with juvenile rheumatoid arthritis (JRA) as a Phase 4 commitment.

In the current submission, the sponsor provides an assessment of efficacy and safety of SSZ in JRA based on published literature reports, and proposes the following indication: "for the treatment of pediatric patients with pauciarticular, polyarticular, and spondylitic courses of juvenile rheumatoid arthritis who have responded inadequately to salicylates or other onosteroidal anti-inflammatory drugs." It should be noted that the Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (issued February, 1999) addresses JRA in the section entitled "Special Considerations for JRA." This section of the Guidance is attached to the review, and includes a brief explanation of the JRA subtypes (pauciarticular, polyarticular, and systemic) and the distinction between the subtype at outset (onset subtype) versus that at a later point (course subtype). It also provides a rationale for the extrapolation of adult rheumatoid arthritis efficacy data to poly-articular course JRA. With regard to SSZ, the Guidance (p. 37) specifically states that "...adequate efficacy information exists for a labeled indication for JRA patients with a polyarticular course. For such agents, a labeling claim could be supported using only PK, PD, and safety data in JRA patients, although submission of additional JRA efficacy data is encouraged." The clinical aspects of the current submission are reviewed in this context.

II. LITERATURE EVIDENCE

The submission consists of 19 published studies but only one adequately designed randomized clinical trial (RCT), the placebo-controlled trial of van Rossum, et al (attached, ref 2). The total number of JRA patients in these 19 studies was 598, of which there was qualititative information provided for 499. The only interpretable efficacy evidence comes from the van Rossum study (reviewed below), and even here the trial was not specifically designed to assess polyarticular course JRA. The sponsor was asked to systematically tabulate, as best possible from a literature of widely divergent quality, the adverse drug reaction (ADR) experience. In particular, we requested quantitative assessments of the ADR profiles for the following:

mild versus serious/severe ADRs
dose-toxicity effects
time-to-onset of ADR
ADRs leading to drug discontinuation
subtype associations: pauci, poly, systemic; by onset and course

Some of these goals, for example ADRs by subtypes, as were only possible in a very limited way, given the limitations of the literature reports. These results were submitted to the NDA

on March 30, 2000. Pertinent tables regarding the ADR experience are described in section IV.

III. REVIEW OF RANDOMIZED CLINICAL TRIAL (REF 2)

PROTOCOL

DESIGN: This was a 6 month trial of 69 patients, stratified by onset type (poly- vs pauci-articular), randomized to SSZ 50mg/kg/d or placebo (PLC). Systemic onset JRA patients were excluded by protocol.

PRIMARY ENDPOINT: The primary endpoint was by-patient clinical efficacy, defined as improvement of joint score (swelling or tenderness, on 0-3 scale) by 2 grades or to 0 in at least 30% of responsive joints, with no new activity in initially inactive joints, OR improvement of joint score by 2 grades or to 0 in at least 50% of responsive joints, with new activity in at most 10% of initially inactive joints. Thus, the primary endpoint was a composite of two clinical observations, tenderness and swelling, assessed at all joints.

SECONDARY ENDPOINTS: The secondary clinical endpoints were numerous, and included the total tender joint score and total swollen joint scores (the individual ratings of which are used to construct the primary endpoint noted above), the total tender and total swollen joint counts (without any scoring of each joint), a loss of motion (LOM) joint score, plus physician, patient, and parent global assessment, and a pain assessment. A radiographic endpoint, defined as the x-ray change in two affected joints designated for each patient at outset, standard laboratory measures, and safety questions were also collected. The full protocol is attached (ref 3).

PRIMARY ANALYSIS PLAN: The two protocol-specified primary analyses (see p22, protocol) both employ intention-to-treat. The first is an all timepoint (weeks 0,4,8,12,18,24) analysis (called the "On Treatment ITT-analysis", using a regression model) with values for dropped out patients carried forward to all the subsequent timepoints. This is a strict last-observation-carried-forward (LOCF) procedure. The second analysis is a 6-month timepoint analysis only (called the "6-Months ITT-analysis", using a Pearson chi-square test). This analysis imputes with LOCF only if no data are available. In most cases patients continued to have formal assessments even though their assigned treatment may have been discontinued, and new therapy may have been initiated.

> Note: The protocol as written was not easily interpretable as to the particulars of the primary analysis. It did not specify the statistical method/test to be used. What is stated above is consistent with this ambiguous protocol language, but other interpretations are also possible (for instance, a different interpretation was used in the Statistical Review). Although, in general, this post hoc latitude in protocol interpretation is highly undesirable because of issues of multiplicity and alpha spending, and for this reason should be avoided by forethought, in this instance no primary inferential use is being made of the efficacy results.

POWERING: With no priors, the response rate for the primary endpoint was estimated to be 25% for PLC patients, and it was set at 60% for SSZ patients to encompass a perceived "clinically important effect." Alpha was set at 5% and power at 80%. With these assumptions the sample size was calculated to be 70, assuming a 10% patient dropout.

ENTRY CRITERIA:

Inclusion Criteria

1. Diagnosis of juvenile chronic arthritis (JCA, the term preferred by Europeans) by the EULAR (European League Against Rheumatism) criteria (detailed in Appendix 7 of the attached protocol), which includes the requirement of symptoms for at least 3 months.
2. Disease activity of at least one swollen and/or effused joint, or at least one joint with two of the following: limitation of motion, heat, or pain/tenderness.
3. Prior therapy failure as evidenced by an insufficient response to an optimally dosed non-steroidal anti-inflammatory drug (NSAID) for at least three months, and (if applicable) to intra-articular corticosteroid injections.
4. Age 2-18 years with onset prior to the 16th birthday.
5. JCA onset type of polyarticular or pauciarticular only.

Exclusion criteria

1. JCA EULAR exclusion criteria (see protocol, appendix 7)
2. Systemic-onset JRA
3. Prior treatment with SSZ
4. Use of corticosteroids
5. Hypersensitivity to sulfa or salicylates
6. Numerous laboratory parameters
7. Known G-6-PD deficiency or porphyria
8. Pregnancy or possibility of conception

TREATMENT PLAN: SSZ was given at 50mg/kg/d in 2 doses, with a maximum of 2000mg/d. A forced dose escalation design was used, with the initial dose being 12.5mg/kg/d,. and a stepwise, weekly, 25% increase, reaching maintenance dose in 4 weeks. Concomitant medications included any NSAID, but without change of drug or dose except for intolerance during the trial. Acetaminophen was permitted, but not oral or intra-articular corticosteroids or other disease-modifying anti-rheumatic drugs. Any prior second-line agent or oral corticosteroids needed a 4-week pretrial washout, 8 weeks for intra-articular corticosteroids.

MONITORING: ADR, CBC/platelet, creatinine, liver enzymes (AST, ALT, GGT, alkaline phosphatase), ESR, and CRP were collected on every visit, occurring every other week for the first three months, then every 6 weeks for the last three months.

COMMENT ON DESIGN: As has been noted, this trial was not designed with an explicit hypothesis of poly-course efficacy, the primary issue of this review. More specifically, if this were the intent of the trial, it would need to be powered with treatment response estimates from poly-course patients similar to patients to be enrolled. This would also mean

that if other subtypes were enrolled, they would likely need to be stratified, and there would need to be agreement on how to analyze patients whose subtype changed during the trial (which turned out to be the case in five patients, see below).

RESULTS

DEMOGRAPHICS

	SSZ	PLC
Age (yrs., SD)	8.4 (4.4)	9.7 (3.6)
Gender (M/F)	12/23	11/23
Disease duration (mo:med(range))	26.8 (4.7-176.1)	16.7 (5.5-142.1)
Subset type at onset (poly/pauci)	16/19	16/18
Systemic steroids, ever	0	2
DMARDs, ever	4	1
Uveitis / Iridocyclitis	4	1

BASELINE VALUES

Anti-nuclear antibody present	18 (53%)	15 (50%)
HLA-B27 present	7 (20%)	4 (12%)
IgG (gm/L)	13.42	16.05
IgA (gm/L)	1.62	2.04
IgM (gm/L)	1.57	1.55
X-ray joint space narrowing	9	10
X-ray erosions	6	8

JRA SUBTYPE DISTRIBUTION: The 69 patients randomized showed the following distribution of JRA subtypes. Subtype at onset is that at time of diagnosis. Subtype at the start of the trial reflected the conversion of some patient to a different subtype, the most frequent being a pauci to poly switch. There were five patient (all in placebo) who made this clinical conversion during the trial itself.

	SSZ	PLC
Total	35	34
Poly-onset	16	16
Pauci-onset	19	18
Poly-course at start of trial	21	17
Pauci-course at start of trial	14	17
Poly-course at end of trial	21	22
Pauci-course at end of trial	14	12

PATIENT ACCOUNTABILITY: Of the 69 patients enrolled, 68 (35 SSZ, 33 PLC) were included in the intention-to-treat analysis. One PLC patient was excluded "for ineligibility" (not otherwise specified) from the sponsor's analyses, but not the FDA analyses (see below). Fifty-two patients (24 SSZ, 28 PLC) completed the trial, 20 poly-onset and 32 pauci-onset. The reasons for dropouts were as follows:

	SSZ	PLC
Randomized	35	34
Total analyzed	35	34
Completed trial	24	28
Dropped out prematurely	11	6
Reasons for dropout		
Inefficacy	0	3
Toxicity	10	0
Withdrawal of consent	0	2
Non-compliance	1	0
Ineligible	0	1

EFFICACY

SPONSOR ANALYSES

Protocol Specified Primary Analysis #1

Title	On Treatment ITT-analysis
Statistical test	Logistic regression model with a random patient effect, to take account of the association between the repeated measurement in the same patient, using the Egret-package. This was a global comparison of all five timepoints (weeks 4, 8, 12, 18, 24) simultaneously of SSZ to PLC. Since every score, at all timepoints, was a change score comparing that timepoint to baseline, the analysis needed to adjust for the overrepresentation of baseline data.
Result	$p<0.01$. This result is shown graphically in the figure below.

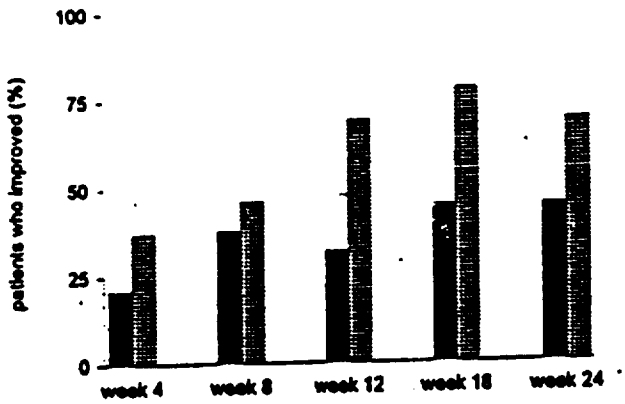


Figure 3. Patients' response to sulfasalazine therapy (□) as compared with placebo (■). Response was defined as improvement in the severity score of joint swelling by 2 grades or a score of 0 in 50% or more of the joints involved at baseline, and, if applicable, development of disease activity in ≤10% of the other joints, with the restriction that the number of deteriorated joints had to be ≤50% of the number of improved joints.

Subtypes There was no statistically significant difference between response rates by this analysis in the poly-onset compared to the pauci-onset subtype (p=0.34). (Data not shown.)

Protocol Specified Primary Analysis #2

Title 6-Months ITT-analysis
Statistical test Pearson chi-square
Proportions 22/32 SSZ vs 13/29 PLC
Result p=0.059

Note: Three SSZ and two PLC patients could not be included due to missing data.

FDA ANALYSES:

I obtained patient data listings of "responder success" by both the protocol and the JRA coreset (see below) for all timepoints for all 69 patients and did the following analyses.

FDA analysis #1a

Title Responders at 6-months

Rationale This analysis is that used for other RA trial analyses recently. It uses the protocol specified responder criteria (see primary endpoint discussion, above), but it also required the patient to have completed the full six months of the trial. Thus, anyone not completing six months, for any reason, is a non-responder, and contributes only to the denominator.

Statistical test Fisher's exact
Proportions 19/35 SSZ vs 12/34 PLC
Result p=0.179

FDA analysis #1b

This is the same as #1a except dropped out patients have their last value carried forward, rather than all dropouts automatically being considered non-responders.

Proportions 22/35 SSZ vs 15/34 PLC
Result p=0.187

FDA Analysis #2a

Title JRA Coreset Responder Index
Rationale This data-driven responder index, published in 1997 (see JRA section of the RA Guidance Document), defined a responder as one showing at least a 30% improvement in 3 of 6 variables (physician and patient/parent globals, number of active joints, number of joints with limited range of motion, functional ability, and ESR), with no more than one variable showing a 30% or more worsening. The definition was modified to 3 of 5, as no functional measure was collected. Thus, this analysis is the same as the FDA analysis #1 above, except the (modified) JRA Coreset is used instead of the protocols definitions to determine responder / non-responder status.

Statistical Test Fisher's exact
Proportion 15/35 SSZ vs 9/34 PLC
Result p=0.239

FDA analysis #2b

This is the same as #2a except dropped out patients have their last value carried forward, rather than all dropouts automatically being considered non-responders.

Proportions 16/35 SSZ vs 10/34 PLC
Result p=0.250

SUBTYPE ANALYSES

Given the number of patients whose subtype changed prior to trial entry (see Demographics, above), it is unlikely that the strength of the evidence would differ substantially if the patients were classified by course rather than onset subtype. The sponsor did the primary

analysis #1 for the two subtypes, poly-onset and pauci-onset, and found no difference in their response rates, p=0.34 (data not shown).

I also analyzed these results by subtype, but because the numbers were so small, no statistical tests were performed.

	Proportion responding	
	Protocol definition	JRA coreset definition
SSZ arm		
Poly-onset		
Completers	7/9	6/9
Dropouts	2/7	0/7
Pauci-onset		
Completers	12/15	9/15
Dropouts	1/4	1/4
PLC arm		
Poly-onset		
Completers	5/11	2/11
Dropouts	2/5	1/5
Pauci-onset		
Completers	7/17	7/17
Dropouts	1/1	0/1

SECONDARY ENDPOINTS:

Comparison of mean changes, SSZ versus PLC, (by intention-to-treat) for secondary endpoints are given below:

Clinical Endpoints	SSZ	PLC	p value*
Number of swollen joints	-5.10**	-1.43	0.025
Number of tender joints	-4.11	-1.81	0.120
Number of joints with LOM	-2.49	-1.97	0.640
Patient global (1-5 scale)	-0.92	-0.24	0.008
Parent global (1-5)	-0.98	-0.44	0.010
Physician global (0-5)	-1.95	-0.99	0.0002
ESR (mm/hr)	-0.74	-0.04	<0.0001
CRP (mg/liter)	-0.45	-0.01	0.030

* by Student's t-test
**minus values indicate improvement

The relative contribution of the poly- and pauci-subtypes was determined for the three joint score secondary endpoints.

Endpoint	SSZ vs PLC p value*	
	poly-onset	pauci-onset
swollen joint score	0.47	0.035
tender joint score	0.13	0.29
LOM joint score	0.32	0.21

* by Student's t-test

RADIOGRAPHIC ENDPOINT: The radiographic analysis was conducted on 65 patients with evaluable films. The mean number of joints rated as improved, unchanged, or worsened for each arm are shown below. None of these comparisons reached statistical significance.

	SSZ	PLC
Improved	0.71	0.53
Unchanged	5.1	4.3
Worsened	0.71	1.23

SAFETY

DROPOUTS FOR TOXICITY: Ten patients dropped out for toxicity, all on SSZ. These are listed below by time of dropout. Most reactions were described as resolving after discontinuation of SSZ. The low IgA levels were described as "appearing to recover, albeit very slowly." (See discussion, below.)

Month 1
N=2 Toxic reaction with malaise, rash, and increased LFT > x3 over baseline in both cases. One patient also had fever, headache, lymphadenopathy, nausea, abdominal pain, and was deemed "serious".

Month 2
N=1 anorexia and malaise
N=1 leukopenia*

Month 3
N=1 easy bruising, elevated bleeding time (> 8 min.)**
N=1 leukopenia*

Months 4-6
N=1 Ongoing malaise and diarrhea
N=3 Very low IgA levels***

* Nadirs: 2500, 2300
**Resolved after discontinuation of the SSZ and concomitant naproxen.

*** Three cases of decreased IgA showed the following baseline and nadirs (gm/L):

2.45 →0.11, 1.53 →0.09, and 0.8 →0.21.

OVERALL TOXICITY PROFILE

	SSZ (n=35)	PLC(n=34)
	(no. of patients)	
DERM		
rash	9	3
pruritis	8	8
urticaria		1
purpura	1	
hematoma	2	
eczema	1	1
oral ulcers		1
GI		
anorexia	17	7
nausea	10	4
abdominal discomfort	17	11
vomiting	3	3
diarrhea	5	5
CONSTITUTIONAL		
headache	9	5
dizziness		1
general unwell feeling	13	7
change of behavior	8	8
fever	9	5
"flu-like" illness	4	3
RESPIRATORY		
respiratory tract infection	13	16
LABORATORY		
elevated liver transaminases*	2	
leukopenia	2	
hypoimmunoglobulinemia	4	
proteinuria		1

* >3x baseline

FURTHER EVALUATION OF IMMUNOGLOBULIN LEVELS: Below are mean baseline and change from baseline values for immunoglobulins.

Variable	Baseline		Change		p value*
(g/L)	SSZ	PLC	SSZ	PLC	
IgG	13.42	16.05	-2.85	-0.10	<0.001
IgA	1.62	2.04	-0.70	0.16	<0.001
IgM	1.57	1.55	-0.50	0.09	<0.001

*by mixed-model analysis of variance, adjusted for baseline values

Comment: In general, the ADR profile in this study resembles that for SSZ seen in the literature and in practice for adult RA. (In this regard some aspects of the adult RA SSZ labeling need to be readdressed, see below). The van Rossum article is the first study to systematically document an association of immunoglobulin suppression with SSZ in JRA. Three cases of significant IgA depression are notable. None was described as having clinical manifestations, and all were described as subsequently recovering, but only after 10-14 months. More detail would be helpful, but three cases of an otherwise rare event in 35 patients is clearly supportive of attribution, so this needs to be noted in the label.

OVERALL DISCUSSION OF CLINICAL TRIAL

This trial supports the extrapolation of SSZ efficacy in adult RA to poly-course JRA, per the RA Guidance Document (see I. Clinical Background). The small trial size and small apparent effect size do not, given the absence of priors, provide evidence for efficacy for pauci-course JRA. The various primary analyses are concordant, and secondary analyses are supportive. No radiographic effect was seen, not surprising, given the large potential for type 2 error. The trial data contribute importantly to safety generally (see IV. Overall Safety Review), and they also show the immunoglobulin lowering association in children that has been observed in adult RA patients (see below).

IV. OVERALL SAFETY REVIEW

The 19 literature reports which catalogued 499 JRA patients treated with SSZ were intensively reviewed to ascertain the best overall ADR information. There are six tables following which supply ADR information. The tables were constructed by the sponsor at our request, to try to characterize the frequency, severity, dose-response, and temporal pattern of ADRs with the use of SSZ in JRA and its subtypes.

Table 1. Title: Adverse Reactions, Total and Serious/Severe, Cumulative Numbers.

Description: These are the entirety of the ADRs reported in the 19 articles, arranged by body system. Severe/serious connotes a reaction which lead to discontinuation of SSZ.

System	Adverse Reaction	Number Patients Reporting	
		Total	Serious/Severe
Hematologic/Immunologic	Leukopenia/Neutropenia	17 *	7 *
	Thrombocytopenia	2	1
	Leukopenia And Thrombocytopenia	1	1
	Eosinophilia	1	0
	Serum-Sickness-Like Reaction	4	4
	Nausea/Vomiting/Headache/Abnormal Liver Function Test (In Systemic Onset JRA))	1	1
	Immediate Allergic Reaction	1	1
	Hypoimmunoglobulinemia	4	3
	Hemolytic Anemia	1	1
Gastrointestinal	Abdominal Pain/Discomfort	26	2
	Anorexia	21	1
	Nausea And/Or Vomiting	18 *	1 *
	GI Intolerance, Upset; Dyspepsia	13	5
	Diarrhea, Bloody Diarrhea	11	4
	Liver Function Abnormality	9	7
	Mouth Ulcer	1	0
CNS/Special Senses	Headache	16 *	2 *
	Migraine	1	1
	Dizziness	1	1
	Agitation	1	1
	Loss Of Taste	1	1
	Convulsion	*	*
Skin	Rash	48 *	21 *
	Skin Hematomas	2	1
Other	Fever	3	1
	Hematuria	*	*

* adverse reaction listed in HOZA, et al paper[7]; no report of number of occurrences

Table 2. Title: Total Occurrences of Adverse Reactions from Table 2
Description: The 19 articles entailed 499 patients, and this table reflects percentage calculation for ADRs by body system as in Table 2.

% of SSZ-treated patients in studies which appeared to report counts of adverse reactions (denominator of 499) and % of adverse reactions rated serious/severe

System	Adverse Reaction	% Exposed To SSZ With Reaction	% Reactions Rated Serious/Severe
Hematologic/Immunologic	Leukopenia/Neutropenia	3.4	41
	Thrombocytopenia	0.4	50
	Leukopenia And Thrombocytopenia	0.2	100
	Eosinophilia	0.2	0
	Serum-Sickness-Like Reaction	0.8	100
	Nausea/Vomiting/Headache/Abnormal Liver Function Test (In Systemic Onset JRA)	0.2	100
	Immediate Allergic Reaction	0.2	100
	Hypoimmunoglobulinemia	0.8	75
	Hemolytic Anemia	0.2	100
Gastrointestinal	Abdominal Pain/Discomfort	5.2	7.7
	Anorexia	4.2	4.8
	Nausea And/Or Vomiting	3.6	5.6
	Gi Intolerance,Upset; Dyspepsia	2.6	38.5
	Diarrhea, Bloody Diarrhea	2.2	36.4
	Liver Function Abnormality	1.8	77.8
	Mouth Ulcer	0.2	0
CNS/Special Senses	Headache	3.2	12.5
	Migraine	0.2	100
	Dizziness	0.2	100
	Agitation	0.2	100
	Loss Of Taste	0.2	100
Skin	Rash	9.6	43.8
	Skin Hematomas	0.4	50
Other	Fever	0.6	33

Table 3. Title: Number of Adverse Reactions By Study
Description: This table shows each of the 19 articles separately, with number of enrollees, number of ADRs by percentage, and number of ADRs leading to withdrawal of SSZ by percentage.

Some patients report multiple reactions and numbers of patients withdrawn for adverse reactions

Study Ref. #	Number Patients Enrolled	Number Adverse Reactions (As % Of Total # Enrolled)	Number (%) Withdrawn For Adverse Reaction
1	51	13 (25.5)	8 (15.7)
2	17	- -	3 * (-)
3	13	- -	None mentioned
4	48	7 (14.6)	3 (6.3)
5	10	2 (20)	1 (10)
6	12	8 (66.7)	2 (16.7)
7	21	- -	4 (19.0)
8	36	4 (11.1)	1 (2.8)
9	139	44 (31.7)	27 (19.4)
10	23	4 (17.4)	2 (8.7)
11	41	5 (12.2)	4 (9.8)
12	18	6 (33.3)	1 (5.6)
13	14	1 (7.1)	1 (7.1)
14	28	5 (17.9)	5 (17.9)
15	18	17 (94.4)	0 (0)
16	15	2 (13.3)	2 (13.3)
17	11	2 (18.2)	1 (9.1)
18	35	77 (220)	10 (28.6)
19	48	11 (22.9)	1 (2.1)
Aggregate %		38.0	12.9

* paper states 3 patients withdrawn but does not specify reason. This number not included in totals.

Table 4. Title: Interval Until Adverse Reaction Occurrence
Description: This table notes the time of treatment onset to the occurrence of the ADR. Again, very limited data on this proved available from the 19 articles.

Adverse Reaction	Interval on SSZ Until Onset Of Adverse Reaction			
	≤ 1 Week	1-2 Weeks	2-4 Weeks	> 4 Weeks
Nausea, Vomiting		5		
Gastric, Abdominal Pain		4	1	
Anorexia		4		
Bloody Diarrhea		1		
Abnormal Liver Function			1	
"Immediate Allergic Reaction"	1			
Serum Sickness Reaction		3		
Leukopenia				1
Thrombocytopenia		1		1
Leukopenia & Thrombocytopenia			1	
Rash (skin), Hives			16*	
Headache			2	
Headache, Dizziness			1	

*13 of these events from one study reporting mean interval 20 days (range 1-60 days)

Table 5 Title: Fraction of Patients Withdrawing For Drug Intolerance At Lower & Higher Dose Ranges

Description: This table supplies a modicum of dose-toxicity information, comparing rates in patients on <50mg/kg/d with those on ≥ 50mg/kg/d.

Study Reference #	Number Withdrawn for Adverse Reaction/Number in Study		
	Dose < 50 mg/kg/day	Dose Includes 50 mg/kg/day	Indeterminate
1	8/51		
2			-/17
3			-/13
4		3/48	
5		1/10	
6		2/12	
7	4/21		
8	1/36		
9	27/139		
10		2/23	
11		4/41	
12		1/18	
13	1/14		
14	5/28		
15		0/18	
16			2/15
17		1/11	
18		10/35	
19		1/48	
TOTALS	**46/289**	**25/264**	

Table 6. Title: Total Number of Adverse Reactions By Diagnostic Subgroup*
Description: Only one study (n=139) supplied subtype information for ADRs.

JRA Type	Total #-Patients	Adverse Reactions	
		# Patients	%
Systemic	5	2	40
Polyarticular, seropositive	9	1	11
Polyarticular, seronegative	48	5	10
Pauciarticular, all types	69	12	17
Pauciarticular, girls < 8 years ANA +	16	3	19
Pauciarticular, HLA-B27 + Spondyloarthropathy	15	2	13
SEA	6	2	33
Gluten sensitive IBD	2	1	50

* data derived only from Imundo et al (study #9)

APPEARS THIS WAY
ON ORIGINAL

DISCUSSION OF SAFETY:

The above information and the six tables are the extent of the literature experience. It does appear to comport well with clinical experience with the use of SSZ in JRA. Except for the unusual predilection of systemic-JRA for significant, multi-system, allergic/constitutional reactions on SSZ – which merits mentioning in the label, the ADR profile generally parallels that observed in the adult RA experience. The immunoglobulin suppression seen in JRA has also been observed in adult RA (see below). Some aspects of the adult RA SSZ label need revision (see VI. Labeling Recommendations). The clinical significance of the major suppression of immunoglobulins seen in about 10% of the patients in the van Rossum study can only be ascertained with formal prospective hypothesis-testing designs. Meanwhile, it deserves mentioning in the label.

V. OBSERVATIONS ON IMMUNOGLOBULIN LEVELS IN SULFASALAZINE TREATED ADULT RA PATIENTS.

There have been a number of reports on immunoglobulin declines with SSZ in adult RA patients. The only large series is a 1991 report (ref 4) from Birmingham, U.K., of 350 patients on SSZ followed from 1 to 10 years. 306 of these patients had RA, 29 psoriatic arthritis, and the remaining 15 various other inflammatory arthritides. All patients attended a single clinic and were treated with SSZ, beginning at a dose of 0.5 gm/d, and increasing to a dose of 2.0gm/d over a one-month period in the majority. 25 patients had a maximum dose of 1.5gm/d, and 30 patients had a maximum of 2.5-3.0gm/d. Clinical assessments and IgG/A/M levels (by laser nephelometry) were done periodically, monthly for the first 3 months, then 3-monthly for a year, then 6-monthly thereafter.

Normal immunoglobulin levels and deficiency states were defined as follows.

Normal IgG	8.0-18.0g/L
Normal IgA	0.9-4.5g/L
Normal IgM	0.6-3.0g/L
Low IgG	<6.0g/L (on at least Selective IgA deficiency<0.5g/L two consecutive occasions)
Low IgM	<0.4g/L

OBSERVATIONS: The following immunoglobulin deficiency states and time of onset observed in this cohort are given below. None of the patients had an immunodeficiency state at the outset of SSZ treatment.

Low IgG levels	(4-52 wks)	6 patient	(1.7%)
Selective IgA deficiency	(8-20 wks)	10 patients	(2.9%)
Low IgM levels	(12-28 wks)	17 patients	(4.9%)
Panhypogammaglobulinemia	(12-72 wks)	3 patients	(0.9%)
Total		36 patients	(10.3%)

The course of these patients varied. All IgG and IgA deficient patients showed a persistent deficit throughout treatment; 30% of the IgM deficient had transient deficits. Two of the three panhypogammaglobulinemia patients had a preceding selective IgA deficiency. Only one patient had SSZ discontinued – a patient with panhypogammaglobulinemia who then developed rash, edema and thrombocytopenia, all of which resolved within the subsequent three months.

In summary, the overall rate of decreases in Ig levels, roughly 10%, is approximately the same as seen in the JRA study, and few clinical sequalae were seen.

VI. LABELING RECOMMENDATIONS:

The following are the labeling changes recommended for describing the use of SSZ in polyarticular course JRA. Sections are shown as added, or deleted, compared to the label supplied by the sponsor.

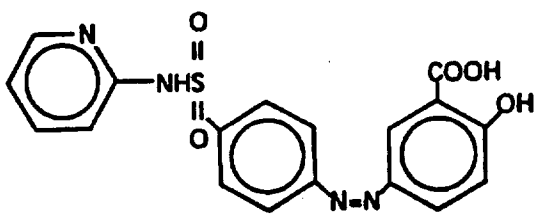
DESCRIPTION

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: $C_{18}H_{14}N_4O_5S$

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 [redacted] is unknown.

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 μg/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 gastrointestinal tract, with an estimated bioavailability of from 10% to 30%.

Distribution: Following intravenous injection, the calculated volume of distribution (Vdss) for SSZ was 7.5 ± 1.6 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 ± 3.4 hrs. 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 hrs, while in slow acetylators it is 14.8 hrs. 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.

Pediatric: Small studies have been reported in the literature in children down to the age of 4 years with ulcerative colitis and inflammatory bowel disease. In these populations, relative to adults, the pharmacokinetics of SSZ and SP correlated poorly with either age or dose. To date comparative pharmacokinetic trials have not been conducted to determine whether or not significant pharmacokinetic differences exist between children with juvenile rheumatoid arthritis and adults with rheumatoid arthritis.

Reviewer's Comments: Although there are no comparative PK data between adults with RA and children with JRA, given prior experience with SSZ, the available data support the indication in polyarticular course JRA. The sponsor will be requested to study PK in children with JRA phase 4.

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 hrs vs. 10.4 hrs) 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 who 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 nonsteroidal anti-inflammatory drugs (e.g., [redacted]);

d) in the treatment of pediatric patients with [redacted] polyarticular [1]course [redacted] juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal ant-inflammatory drugs.

Reviewer's Comment: This language is standard for so-called second-line agents in the treatment of either adult or juvenile rheumatoid arthritis, because there exists a subset of patients with mild disease needing only 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.

In patients with rheumatoid arthritis or juvenile rheumatoid arthritis, rRest and physiotherapy as indicated should be continued. Unlike anti-inflammatory drugs, AZULFIDINE EN-tabs does not produce an immediate response.

Reviewer's Comment: The large part of the above paragraph has been deleted because the information is incorporated into the indication c) for RA.

Reviewer's Comment: The above paragraph is deleted, and the information is incorporated into the indication d) for poly-articular course JRA.

CONTRAINDICATIONS

AZULFIDINE EN-tabs Tablets are contraindicated in:

Hypersensitivity to sulfasalazine, its metabolites, sulfonamides or salicylates,

Patients with intestinal or urinary obstruction,

Patients with porphyria, as the sulfonamides have been reported to precipitate an acute attack.

Reviewer's comment: The contraindication for pediatric patients under two years of age is deleted. Unless there is some absolute contraindication related to age per se, lack of information regarding safety and effectiveness for a particular age is usually reflected by a statement in the Pediatric Use section.

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 [redacted]. 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; however, ~~W~~withdrawal of the drug appears to reverse these effects.

Reviewer's comment: The sentence starting [redacted] was struck and the reference to PRECAUTIONS – Laboratory Tests was added, because that section recommends that laboratory tests in addition to the CBC and urinalysis be performed.

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 patient 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 μg/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 mg/m^2), 168 (991 mg/m^2) and 337.5 (1991 mg/m^2) 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^2), 1350 (4050 mg/m^2) and 2700 (8100 mg/m^2) 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) or in the 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^2). 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, and to pregnancies in the general population.[33]

A study of 1455 pregnancies associated with exposure to sulfonamides including sulfasalazine, indicated that this group of drugs did not appear to be associated with fetal malformation.[34] A review

of the medical literature covering 1155 pregnancies in women with ulcerative colitis suggested that the outcome was similar to that expected in the general population.[45]

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 of AZULFIDINE EN-tabs for the treatment of the signs and symptoms of polyarticular course juvenile rheumatoid arthritis in pediatric patients aged 6-16 years is supported by evidence from adequate and well controlled studies in adult rheumatoid arthritis patients. The extrapolation from adults with rheumatoid arthritis to children with polyarticular course is based on similarities in disease and response to therapy between these two patient populations. Published studies safety for sulfasalazine in polyarticular course (see Adverse Reactions).

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

Reviewer's Comment: Many practitioners have suspected that patients with systemic-type JRA are more predisposed to drug intolerance, although good data to support this are hard to find, and the separation of disease from drug effect is inherently more difficult here because of the constitutional symptoms common with this subtype. However, the evidence does clearly show this phenomena in the instance of serum-sickness like reactions, and it merits mentioning in labeling.

ADVERSE REACTIONS

The most common adverse reactions associated with sulfasalazine in ulcerative colitis 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, rash, fever, Heinz body anemia, hemolytic anemia and cyanosis, which may occur at a frequency of 1 in 30 patients or less. Experience suggests that with a daily dose of 4 g or more, or total serum sulfapyridine levels above 50 μg/mL, the incidence of adverse reactions tends to increase.

Reviewer's Comment: The first paragraph in the ADVERSE REACTIONS section was struck and replaced with the paragraph below to give a clearer representation of the experience in RA. As a result, the second paragraph was modified to indicate that it reflects the experience in ulcerative colitis. "Rash" was added to the second paragraph, because it had been noted in the first paragraph as occurring at a rate of approximately 1 in 30 patients with ulcerative colitis.

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

In general, the adverse reactions in juvenile rheumatoid arthritis patients are similar to those seen in patients with adult rheumatoid arthritis except for a high frequency of serum sickness-like syndrome in systemic-course juvenile rheumatoid arthtis (see PRECAUTIONS, Pediatric Use).

One clinical trial showed an approximate 10% rate of immunoglobulin suppression.

Reviewer's comment: The adverse reaction paragraph for pediatric patients added here is straightforward and has been previously explained. The one additional comment regarding the JRA safety profile compared to that in adult RA is mention of a higher rate of leukopenia and thrombocytopenia. I have also added some clarity to the information regarding SSZ use in adult RA, as in some cases there appear to be differences in the nature of the safety profile here versus SSZ use in ulcerative colitis. In particular,

percentage rates for common events in use in RA are supplied, obtained in the Medical Officer Review for Azulfidine in RA (L.. L. Katz, June 20, 1995, Section 4: Safety). I have also included reference to the immunoglobulin suppression seen in a small fraction of adult (and juvenile) RA patients.

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.

[redacted]

Less common or rare adverse reactions include:

Reviewer's Comment: Certain adverse events, such as leukopenia and thrombocytopenia were seen at a rate exceeding 1 in 1000 in the RA and JRA experience. For that reason, the heading [redacted] was struck, and the heading "Less common or rare adverse reactions include" is suggested instead.

Blood dyscrasias: aplastic anemia, agranulocytosis, [redacted] megaloblastic (macrocytic) anemia, purpura, [redacted] 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, fulminant hepatitis, sometimes leading to liver transplantation, 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, [redacted] diarrhea, [redacted] and neutropenic enterocolitis.

Reviewer's Comment: [redacted] were seen at a rate exceeding 1 % in the adult RA experience. Therefore, they are struck from this section, and noted in the paragraph describing the adult RA experience.

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, urinary tract infections, [redacted] 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.

Reviewer's comment: This paragraph is replaced by the paragraph inserted immediately after the paragraph describing the common AEs in adult RA.

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 overdosage.

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_{50} 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

Reviewer's comment: The sentences in the paragraph above are struck because they address the treatment of selected adverse reactions, which are not necessarily related to overdose. Likewise, desensitization does not seem pertinent to overdose.

DOSAGE AND ADMINISTRATION

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

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

Reviewer's comment: The section above has been modified so that it applies to both ulcerative colitis and RA. The sentence that notes that the interval between nighttime doses and has been incorporated into the section below that specifically addresses dosing for ulcerative colitis.

Reviewer's comment: This section has been moved to the end of the D & A section. See below.

[redacted]

Reviewer's comment: This statement appears above.

Ulcerative Colitis

Initial Therapy:

Adults: 3 to 4 g daily in evenly divided doses with dosage intervals not exceeding eight hours. It may be advisable to initiate therapy with a lower dosage, e.g., 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.

Reviewer's comment: Because the first paragraph in the D & A section was modified and the statement noting that [redacted] was removed, the phrase "with dosage intervals not exceeding eight hours" is added to the above section.

Children, two years of age and older: 40 to 60 mg/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/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 should be 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 (eg, 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.

Adult Rheumatoid Arthritis:

~~Adults:~~ 2 g daily [redacted] in two evenly divided doses. It is advisable to initiate therapy with a lower dosage of AZULFIDINE EN-tabs, eg, 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 4 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

Juvenile Rheumatoid Arthitis - polyarticular course

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

Some patients may be sensitive to treatment with sulfasalazine. Various desensitization-like regimens have been reported to be effective in 34 of 53 patients,[8] 7 of 8 patients,[9] and 19 of 20 patients.[10] 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.

Reviewer's comment: The above rearrangement of these sections of the label is primarily a matter of formatting. The one substantive aspect regarding use in JRA is the lower age limit of six years, as there are too few data on use in younger ages. Dosing escalation and laboratory monitoring in children is similar to that in adults.

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 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Rx only

REFERENCES

1. van Rossum MAJ, Fiselier TJW, Franssen MJAM, Zwinderman AH, ten Cate R, 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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Mfd for: Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

by: Pharmacia & Upjohn AB
Stockholm, Sweden

VII. OVERALL SUMMARY

There is sufficient safety and PK data describing the use of SSZ in polyarticular course JRA to enable it to be labeled for use, given the sufficient similarity in disease and response to therapies between adult RA and polyarticular course JRA. This similarity scientifically justifies the extrapolation of efficacy from adult to the polyarticular

course subtype of JRA. The labeling above reflect the characteristics of the safety profile that are particular to JRA, and some newer aspects of the adult RA safety profile. It would be prudent to ask for some basic PK data in selected children with JRA as a phase 4 commitment.

VIII. REFERENCE ATTACHMENTS

1. Pediatric Section of the RA Guidance Document
2. Van Rossum M, et al.: Sulfasalazine in the treatment of juvenile chronic artiritis: a randomized, double-blind, placebo-controlled, multicenter study. Arth Rheum 1998; 41:808-816.
3. Full protocol of the van Rossum clinical trial.
4. Farr M, et al.: Immunodeficiencies associated with sulphasalazine therapy in inflammatory arthritis. Br J Rheum 1991; 30:413-417.

/S/ 8/11/00

Kent Johnson, M.D., Medical Reviewer

/S/ 8/11/00

Karen Midthun, M.D., Team Leader

Attachments (4)

CC: Original NDA #21-243; NDA #7-073
HFD-550/Div. File
/K. Midthun
/K. Johnson
/S. Cook
/L. Vacarri
/D. Bashaw
/S. Choi
HFD-160/Div. File
/M. McNeil
/L. Talarico

Addendum to Medical Officer Review

NDA # 21-243
NAME: Azulfidine (sulfasalazine) EN-tabs
SPONSOR: Pharmacia & Upjohn Co.
REVIEWER: Kent Johnson, M.D.
CSO: Sandra Cook
Date: August 10, 2000

In a telecon with the sponsor on August 10, 2000, a number of minor label alterations were made.

1. A sentence (the last in the paragraph) was added regarding concurrent treatment with analgesics and nonsteroidal anti-inflammatory drugs.

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

2. The last sentence was changed to incorporate the concept that the published studies, including the one reviewed in the Medical Review proper, are, in this context, supportive of the extrapolation of safety and efficacy in polyarticular course JRA.

The safety and effectiveness of AZULFIDINE EN-tabs for the treatment of the signs and symptoms of polyarticular course juvenile rheumatoid arthritis in pediatric patients aged 6-16 years is supported by evidence from adequate and well controlled studies in adult rheumatoid arthritis patients. The extrapolation from adults with rheumatoid arthritis to children with polyarticular course juvenile rheumatoid arthritis is based on similarities in disease and response to therapy between these two patient populations. Published studies support the extrapolation of safety and effectiveness for sulfasalazine to polyarticular course juvenile rheumatoid arthritis [1,6] (see Adverse Reactions).

3. Two more datapoints, [redacted] were supplied by the sponsor from the sulfsalazine NDA (ISS/table 7/p08/01593). This meant the sentence mentioning these as higher in JRA compared to adult RA was not necessary. These changes are reflected in the paragraphs below.

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

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

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.

Less common or rare adverse reactions include:

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

/S/ 8/11/00

Kent Johnson, M.D., Medical Reviewer

/S/ 8/11/00

Karen Midthun, M.D., Team Leader

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