HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GIAZO safely and effectively. See full prescribing information for GIAZO.

GIAZO® (balsalazide disodium) tablets, for oral use
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

• Dosage and Administration (2)	10/2020
• Warnings and Precautions,	
Hypersensitivity Reactions (5.3)	10/2020
Photosensitivity (5.5)	10/2020
Nephrolithiasis (5.6)	10/2020
Sodium Content of GIAZO (5.7)	10/2020
Interference with Laboratory Tests (5.8)	10/2020

INDICATIONS AND USAGE

GIAZO is an aminosalicylate indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older. (1)

Limitations of Use

- Effectiveness in female patients was not demonstrated in clinical trials. (1)
- Safety and effectiveness of GIAZO beyond 8 weeks have not been established. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 3.3 g (three 1.1 g tablets) twice daily with or without food for up to 8 weeks. (2)
- Drink an adequate amount of fluids. (2, 5.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 1.1 g balsalazide disodium (3)

CONTRAINDICATIONS

Known or suspected hypersensitivity to salicylates, aminosalicylates, or to any of the components of GIAZO tablets or balsalazide metabolites. (4)

WARNINGS AND PRECAUTIONS

- Renal Impairment: Assess renal function at the beginning of treatment and periodically during treatment. Evaluate the risks and benefits in patients with known renal impairment or taking nephrotoxic drugs; monitor renal function. (5.1, 7.2, 8.6)
- Mesalamine-Induced Acute Intolerance Syndrome: Symptoms may be difficult to distinguish from an exacerbation of ulcerative colitis; monitor for worsening symptoms; discontinue treatment if acute intolerance syndrome is suspected. (5.2)
- Hypersensitivity Reactions, including Myocarditis and Pericarditis: Evaluate patients immediately and discontinue if a hypersensitivity reaction is suspected. (5.3)
- Hepatic Failure: Evaluate the risks and benefits in patients with known liver impairment. (5.4)
- Photosensitivity: Advise patients with pre-existing skin conditions to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors. (5.5)
- Nephrolithiasis: Stones containing mesalamine, the active moiety of GIAZO, are undetectable by standard radiography or computed tomography (CT). Ensure adequate fluid intake during treatment. (5.6)
- Sodium Content of GIAZO: Take sodium content of GIAZO tablets into consideration in patients on a sodium-restricted diet. (5.7)
- Interference with Laboratory Tests: Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. (5.8)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) in male UC patients are anemia, diarrhea, pharyngolaryngeal pain, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older.

Limitations of Use:

- Effectiveness of GIAZO in the treatment of female patients was not demonstrated in clinical trials *[see Clinical Trials (14)]*.
- Safety and effectiveness of GIAZO therapy beyond 8 weeks have not been established.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is 3.3 g (three 1.1 g tablets) orally twice daily with or without food *[see Clinical Pharmacology (12.3)]* for up to 8 weeks.

Drink an adequate amount of fluids *[see Warnings and Precautions (5.6)]*.

3 DOSAGE FORMS AND STRENGTHS

GIAZO is available as yellow, oval, film-coated tablets containing 1.1 g balsalazide disodium, with “BZT” debossed on one side of the tablet.

4 CONTRAINDICATIONS

GIAZO is contraindicated in patients with known or suspected hypersensitivity to salicylates, aminosalicylates or their metabolites, or to any of the components of GIAZO tablets *[see Warnings and Precautions (5.3), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Impairment

Renal impairment, including minimal change disease, acute and chronic interstitial nephritis and renal failure, has been reported in patients given products that release mesalamine in the gastrointestinal tract. Evaluate renal function prior to initiation of GIAZO and periodically while on therapy. Evaluate the risks and benefits of using GIAZO in patients with known renal impairment, a history of renal disease or taking nephrotoxic drugs *[see Drug Interactions (7.2), Use in Specific Populations (8.6)]*.

5.2 Mesalamine-Induced Acute Intolerance Syndrome

Balsalazide is converted to mesalamine, which has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. In controlled clinical trials with GIAZO in adults with ulcerative colitis, 7% of male patients reported exacerbation of the symptoms of ulcerative colitis. Symptoms include cramping, acute abdominal pain and bloody diarrhea, sometimes fever, headache, and rash. Monitor patients for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with GIAZO.

5.3 Hypersensitivity Reactions

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to GIAZO or to other compounds that contain or are converted to mesalamine.

Mesalamine-induced hypersensitivity reactions may present as internal organ involvement, including myocarditis, pericarditis, nephritis, hepatitis, pneumonitis, and hematologic abnormalities. Evaluate patients immediately if signs or symptoms of a hypersensitivity reaction are present. Discontinue GIAZO if an alternative etiology for the signs and symptoms cannot be established.

5.4 Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Because balsalazide is converted to mesalamine, evaluate the risks and benefits of GIAZO in patients with known liver impairment.

5.5 Photosensitivity

Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported more severe photosensitivity reactions. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors.

5.6 Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalamine, the active moiety of GIAZO, including stones with 100% mesalamine content. Mesalamine-containing stones are radiotransparent and undetectable by standard radiography or computed tomography (CT). Ensure adequate fluid intake during treatment with GIAZO.

5.7 Sodium Content of GIAZO

Each 1.1 g tablet of GIAZO contains 126 mg of sodium. The recommended dosage of GIAZO (6.6 g/day) provides about 756 mg of sodium per day. Take the sodium content of GIAZO into consideration when administering to patients on a sodium-restricted diet or those at risk for developing congestive heart failure.

5.8 Interference with Laboratory Tests

Use of GIAZO, which is converted to mesalamine, may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection because of the similarity in the chromatograms of normetanephrine and mesalamine's main metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). Consider an alternative, selective assay for normetanephrine.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Renal Impairment *[see Warnings and Precautions (5.1)]*
- Mesalamine-Induced Acute Intolerance Syndrome *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Hepatic Failure *[see Warnings and Precautions (5.4)]*
- Photosensitivity *[see Warnings and Precautions (5.5)]*
- Nephrolithiasis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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

The data described below reflect exposure of GIAZO in 565 ulcerative colitis patients with mildly to moderately active disease. GIAZO was evaluated in one placebo-controlled trial (168 treated with GIAZO), one active-controlled trial (210

treated with GIAZO); and a subset of these patients also participated in an uncontrolled, open-label, extension study (additional 187 treated with GIAZO). The population studied had a mean age of 43.1 (range: 18-80) years; approximately 94% of patients were < 65 years old, 49% were male, and 84% were white.

In the placebo-controlled trial, the most common adverse reactions with GIAZO in male patients were headache, nasopharyngitis, anemia, diarrhea, fatigue, pharyngolaryngeal pain, and urinary tract infection. 10% of patients in the GIAZO group and 13% of patients in the placebo group discontinued treatment due to an adverse reaction. The majority of adverse reactions were mild to moderate in severity. The most common serious adverse reactions in both the placebo and GIAZO groups were gastrointestinal disorders, which were mainly associated with symptoms of ulcerative colitis.

Adverse reactions occurring in at least 2% of male patients and at a rate numerically higher than placebo in the placebo-controlled trial are listed in Table 1.

Table 1: Adverse Reactions Experienced by at Least 2% of GIAZO–Treated Male Patients and at a Rate Numerically Greater than Placebo in a Placebo-Controlled Trial

Adverse Reaction	GIAZO 6.6 g/day N=82	PLACEBO N=37
Anemia	3.7%	0%
Diarrhea	3.7%	0%
Pharyngolaryngeal Pain	3.7%	0%
Urinary Tract Infection	3.7%	0%
Arthralgia	2.4%	0%
Insomnia	2.4%	0%
Musculoskeletal Pain	2.4%	0%

Data collected from all three trials (placebo-controlled, active-controlled, and open-label) showed that female patients reported adverse reactions more frequently than did male patients (76% and 66%, respectively).

The following adverse reactions, presented by body system, were reported by less than 1% of GIAZO-treated ulcerative colitis patients in controlled trials.

Cardiovascular and Vascular: increased blood pressure, increased heart rate

Dermatological: erythema nodosum, rash

Respiratory, Thoracic and Mediastinal Disorders: dyspnea

Gastrointestinal Disorders: abdominal pain, constipation, defecation urgency, diarrhea, dry mouth, hard feces, flatulence, gastroesophageal reflux disease, vomiting

Hepatobiliary Disorders: increased aspartate aminotransferase

Infections and Infestations: gastroenteritis, upper respiratory infection

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, myalgia

Nervous System Disorders: dizziness, lethargy

General Disorders and Administrative Site Disorders: face edema, fatigue, malaise, pain, pyrexia, swelling

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of balsalazide, or other products which contain or are metabolized to mesalamine. Because these reactions are reported voluntarily from a population of

uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular and Vascular: myocarditis, pericarditis, vasculitis *[see Warnings and Precautions (5.3)]*

Respiratory: alveolitis, pleural effusion, pneumonia (with and without eosinophilia)

Gastrointestinal: pancreatitis

Renal: interstitial nephritis, renal failure, nephrolithiasis *[see Warnings and Precautions (5.1, 5.6)]*.

Hepatobiliary Disorders: elevated liver enzymes (AST, ALT, GGT, LDH, alkaline phosphatase), elevated bilirubin, jaundice, cholestatic jaundice, cirrhosis, hepatocellular damage including liver necrosis and liver failure, Kawasaki-like syndrome including hepatic dysfunction. Some of these cases were fatal *[see Warnings and Precautions (5.4)]*.

Dermatological: alopecia, pruritus

7 DRUG INTERACTIONS

7.1 Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs), may increase the risk of renal reactions. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions *[see Warnings and Precautions (5.1)]*.

7.2 Azathioprine or 6-Mercaptopurine

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine and/or any other drugs known to cause myelotoxicity may increase the risk for blood disorders, bone marrow failure, and associated complications. If concomitant use of GIAZO and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

7.3 Interference With Urinary Normetanephrine Measurements

Use of GIAZO, which is converted to mesalamine, may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection *[see Warnings and Precautions (5.8)]*. Consider an alternative, selective assay for normetanephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published data from meta-analyses, cohort studies and case series on the use of mesalamine, the active moiety of GIAZO, during pregnancy have not reliably informed an association with mesalamine and major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are adverse effects on maternal and fetal outcomes associated with ulcerative colitis in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of balsalazide disodium in pregnant rats and rabbits during organogenesis at doses up to 2.4 and 4.7 times, respectively, the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Human Data

Published data from meta-analyses, cohort studies and case series on the use of mesalamine, the active moiety of GIAZO, during early pregnancy (first trimester) and throughout pregnancy have not reliably informed an association of mesalamine and major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is no clear evidence that mesalamine exposure in early pregnancy is associated with an increase risk in major congenital malformations, including cardiac malformations. Published epidemiologic studies have important methodological limitations which hinder interpretation of the data, including inability to control for confounders, such as underlying maternal disease, and maternal use of concomitant medications, and missing information on the dose and duration of use for mesalamine products.

Animal Data

Reproduction studies in rats and rabbits following administration of balsalazide disodium during organogenesis at oral doses up to 2 g/kg/day, equivalent to 2.5 and 4.9 times the recommended human dose, respectively, based on body surface area, revealed no evidence of no adverse embryofetal developmental effects due to balsalazide disodium.

8.2 Lactation

Risk Summary

Data from published literature report the presence of mesalamine and its metabolite, N acetyl-5 aminosalicylic acid, in human milk in small amounts with relative infant doses (RID) of 0.1% or less for mesalamine *(see Data).* There are case reports of diarrhea in breastfed infants exposed to mesalamine (*see Clinical Considerations*). There is no information on the effects of the drug on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of GIAZO to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GIAZO and any potential adverse effects on the breastfed child from GIAZO or from the underlying maternal condition.

Clinical Considerations

Advise the caregiver to monitor breastfed infants for diarrhea.

Data

In published lactation studies, maternal mesalamine doses from various oral and rectal mesalamine formulations and products ranged from 500 mg to 4.8 g daily. The average concentration of mesalamine in milk ranged from non-detectable to 0.5 mg/L. The average concentration of N-acetyl-5-aminosalicylic acid in milk ranged from 0.2 to 9.3 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 to 0.075 mg/kg/day (RID 0 to 0.1%) of mesalamine and 0.03 to 1.4 mg/kg/day of N-acetyl-5-aminosalicylic acid.

8.4 Pediatric Use

Safety and effectiveness of GIAZO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of GIAZO did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently than younger subjects. Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias, i.e., neutropenia and pancytopenia, in patients who were 65 years or older compare to younger patients taking mesalamine-containing products. GIAZO is converted into mesalamine in the colon. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with GIAZO. In general, consider the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients when prescribing GIAZO *[see Use in Specific Populations (8.6)]*.

8.6 Renal Impairment

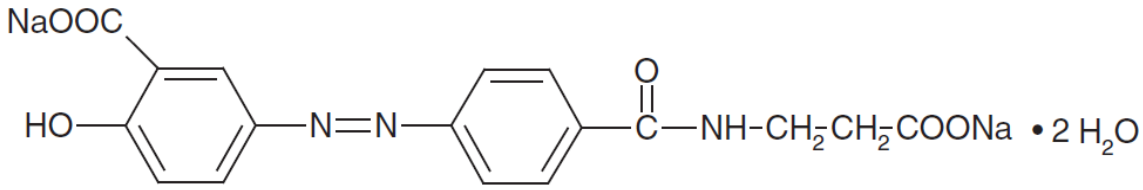
Mesalamine is known to be substantially excreted by the kidney, and the risk of adverse reactions to GIAZO, which is converted to mesalamine, may be greater in patients with impaired renal function. Evaluate renal function in all patients prior to initiation and periodically while on GIAZO therapy. Monitor patients with known renal impairment or history of renal disease or taking nephrotoxic drugs for decreased renal function and mesalamine-related adverse reactions *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), Drug Interactions (7.1)]*.

10 OVERDOSAGE

GIAZO is an aminosalicylate, and symptoms of salicylate toxicity include: nausea, vomiting and abdominal pain, tachypnea, hyperpnea, tinnitus, and neurologic symptoms (headache, dizziness, confusion, seizures). Severe intoxication with salicylates may lead to electrolyte and blood pH imbalance and potentially to other organ (e.g., renal and liver) damage. There is no specific antidote for balsalazide overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage and may include gastrointestinal tract decontamination to prevent of further absorption. Proper medical care should be sought immediately with appropriate supportive care, including the possible use of emesis, cathartics, and activated charcoal to prevent further absorption. Correct fluid and electrolyte imbalance by the administration of appropriate intravenous therapy and maintain adequate renal function.

11 DESCRIPTION

Each GIAZO tablet contains 1.1 g of balsalazide disodium, an orally available prodrug that is enzymatically cleaved to produce mesalamine (5-aminosalicylic acid, 5-ASA), an aminosalicylate. Balsalazide disodium has the chemical name (E)-5-[[-4-[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate. Its structural formula is:



Molecular Weight: 437.32

Molecular Formula: $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$

Balsalazide disodium is a stable, odorless, orange to yellow, microcrystalline powder. It is insoluble in acid, but soluble at a pH of at least 4.5. It is freely soluble in water and isotonic saline, sparingly soluble in methanol and ethanol, and practically insoluble in all other organic solvents.

Inactive Ingredients: Each tablet contains hypromellose, magnesium stearate, and Opadry II Yellow. The sodium content of each tablet is approximately 126 mg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Balsalazide is a prodrug of mesalamine (5-aminosalicylic acid, 5-ASA). The mechanism of action of 5-ASA is not fully understood, but appears to be a local anti-inflammatory effect on colonic epithelial cells. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with ulcerative colitis, and it is possible that 5-ASA diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

12.3 Pharmacokinetics

Following oral administration, balsalazide is cleaved by azoreductases produced by anaerobic bacteria found in the gut, to release equimolar quantities of 5-ASA, the active moiety, and 4-aminobenzoyl-ß-alanine (4-ABA), a carrier moiety. Both of these moieties are N-acetylated to form N-Ac-5-ASA and N-Ac-4-ABA, respectively.

Absorption

After single-dose administration of 3.3 g GIAZO in 18 healthy subjects, the median time of peak plasma concentration (T_{max}) was 0.5 hr for balsalazide, while the median T_{max} was 12 hr for both 5-ASA and N-Ac-5-ASA (Table 2). Pharmacokinetic parameters exhibited high variability, with %CV ranging from 31% to 67% for AUC and from 27% to 68% for C_{max}.

Pharmacokinetics were also estimated in healthy subjects after repeated doses of 3.3 g GIAZO tablets every 12 hours for 7 days. After multiple doses, steady-state was achieved after about 3 days for balsalazide and all metabolites. The AUC and C_{max} were the highest for N-Ac-5-ASA, followed by 5-ASA and balsalazide. There was minimal accumulation of balsalazide, as suggested by a 1.2-fold increase in AUC; however, a relatively larger increase in the systemic exposure to metabolites was observed at steady-state. The accumulation ratios based on AUC for the metabolites were 6.1 for 5-ASA, 3.6 for N-Ac-5-ASA, 4.8 for 4-ABA, and 3.6 for N-Ac-4-ABA.

Table 2: Pharmacokinetic Parameters for Balsalazide and Metabolites (5-ASA and N-Ac-5-ASA) Following Single- and Repeated-Doses (every 12 hours) of 3.3 g Balsalazide Disodium as GIAZO (N=18)

	Single Dose		Repeated Dose	
Parameter	**Mean**	**SD**	**Mean**	**SD**
C_{max} (mcg/mL)				
Balsalazide	0.3	0.2	0.3	0.2
5-ASA	0.5	0.3	1.5	0.6
N-Ac-5-ASA	1.2	0.4	2.2	0.6
T_{max}[a] (hr)				
Balsalazide	0.5	(0.5-2)	0.5	(0.5-2)
5-ASA	12	(8-16)	12	(1.5-16)
N-Ac-5-ASA	12	(8-16)	10	(1-16)
AUC_{tau} (mcg•hr/mL)				
Balsalazide	1.3	0.7	1.6	0.9
5-ASA	2.2	1.6	13.4	6.3
N-Ac-5-ASA	5.9	2.9	21	6.4
$AUC_{0-\infty}$ (mcg•hr/mL)				
Balsalazide	1.4	0.8	NA	NA
5-ASA	8.5	3.9	NA	NA
N-Ac-5-ASA	33.5	14.1	NA	NA
$T_{½}$[b] (hr)				
Balsalazide	1.9	0.7	8.4	12.4
5-ASA	9.5[b]	10.1	9.0	8.6
N-Ac-5-ASA	10.4[b]	17.6	7.2	6.8

a Expressed as median and range.
b N=17

Effect of Food

After administration of single dose of 3.3 g (3 × 1.1 g tablets) of GIAZO with a high-fat meal in healthy subjects, the AUC of balsalazide was unaffected compared to fasted administration, but the presence of food reduced both peak concentrations and AUC of the metabolites 5-ASA and N-Ac-5-ASA. A high fat meal increased the median T_{max} for balsalazide from 0.5 to 2 hours; for 5-ASA from 12 to 24 hours; and for N-Ac-5-ASA from 12 to 24 hours. Under fed conditions, the mean C_{max} was reduced by 44% for balsalazide, 65% for 5-ASA, and 48% for N-Ac-5-ASA. No significant changes were observed for $AUC_{0-\infty}$ for balsalazide; however, $AUC_{0-\infty}$ was reduced for 5-ASA by 46% and for N-Ac-5-ASA by 17% *[see Dosage and Administration (2)]*.

Distribution

The binding of balsalazide to human plasma proteins was ≥ 99%; 5-ASA and N-Ac-5-ASA were 43% and 78% bound, respectively, to plasma proteins.

Elimination

Metabolism

Following oral administration, balsalazide is cleaved by bacterial azoreduction to release equimolar quantities of 5-ASA, the active moiety, and 4-ABA, a carrier moiety. Mesalamine (5-ASA) and 4-ABA are further acetylated to N-Ac-5-ASA and N-Ac-4-ABA, respectively in the intestinal mucosa and liver. The terminal half-life was 1.9 hr for balsalazide, 9.5 h for 5-ASA, and 10.5 h for N-Ac-5-ASA.

Excretion

At steady-state following administration of repeated doses of 3.3 g GIAZO every 12 hours in healthy volunteers, the combined % of dose excreted in urine for balsalazide and its metabolites over 12 hours was 23%. The mean % of dose excreted in urine over 12 hours was 0.16% for balsalazide, 4.6% for 5-ASA, 15.6% for N-Ac-5-ASA, 0.40% for 4-ABA, and 1.8% for N-Ac-4-ABA.

Drug Interaction Studies

Based on *in vitro* studies, balsalazide and its metabolites [5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), 4-aminobenzoyl-ß-alanine (4-ABA), and N-acetyl-4-aminobenzoyl-ß-alanine (N-Ac-4-ABA)] are not expected to inhibit the metabolism of other drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month rat (Sprague Dawley) carcinogenicity study, oral (dietary) balsalazide disodium at doses up to 2 g/kg/day was not tumorigenic. For a 50 kg person of average height this dose represents 2.5 times the recommended human dose on a body surface area basis. Balsalazide disodium was not genotoxic in the following *in vitro* or *in vivo* tests: Ames test, human lymphocyte chromosomal aberration test, and mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, or mouse micronucleus test. However, it was genotoxic in the *in vitro* Chinese hamster lung cell (CH V79/HGPRT) forward mutation test.

The compound 4-aminobenzoyl-ß-alanine, a metabolite of balsalazide disodium, was not genotoxic in the Ames test and the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test but was positive in the human lymphocyte chromosomal

aberration test. N-acetyl-4-aminobenzoyl-ß-alanine, a conjugated metabolite of balsalazide disodium, was not genotoxic in Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, or the human lymphocyte chromosomal aberration test. Balsalazide disodium at oral doses up to 2 g/kg/day, 2.5 times the recommended human dose based on body surface area, was found to have no effect on fertility and reproductive performance in rats.

14 CLINICAL STUDIES

A double-blind, placebo-controlled, multi-center trial was conducted in 250 adult patients with mildly to moderately active ulcerative colitis. The trial population was primarily white (84%), had a mean age of 44 years (7% age 65 years or older), and 49% were men. Disease activity was assessed using a modified Mayo Disease Activity Index (MMDAI), which was a sum of four subscores (bowel frequency, rectal bleeding, endoscopic appearance, and physician's global assessment), each ranging from 0 to 3, with higher scores indicating worse disease. The median baseline MMDAI score was 8 and the median baseline rectal bleeding subscore was 2. Patients were randomized 2:1 to receive 8 weeks of treatment with either GIAZO 3.3 g twice daily or placebo.

The primary efficacy endpoint was the proportion of patients that achieved clinical improvement and improvement in the rectal bleeding subscale of the MMDAI at the end of 8 weeks of treatment. Clinical Improvement was defined as having both a ≥ 3 point improvement from baseline in the MMDAI score and a ≥ 1 point improvement from baseline in the rectal bleeding subscore. Two key secondary efficacy endpoints were the proportion of patients with Clinical Remission and Mucosal Healing at the end of 8 weeks of treatment. Clinical Remission was defined as a score of 0 for rectal bleeding and a combined score of ≤ 2 for bowel frequency and physician's assessment using the MMDAI subscale; the endoscopic sub-score was not considered in this definition. Mucosal Healing was defined as an endoscopy/sigmoidoscopy score of 0 or 1, where a score of 1 could include signs of erythema or decreased vascular pattern; by definition, the presence of friability indicated a score of 2 or 3.

After 8 weeks of treatment, the proportion of patients who met the definition of Clinical Improvement was greater for the GIAZO-treated group compared to the placebo group (Table 3).

Table 3: Proportion of Patients with Clinical Improvement* at Week 8 for the Total Population and by Gender Subgroups

	GIAZO	**Placebo**	p-value
Total Population	55%	40%	0.0237
Males	57%	20%	
Females	54%	58%	

* Clinical Improvement: ≥ 3 improvement in MMDAI score and ≥ 1 point improvement in rectal bleeding.

These differences were statistically significant in the overall population; however, these effects were entirely driven by the results in the male subpopulation. With adjustment for multiplicity, statistically significant differences were also seen in the male patients for Clinical Remission (35% with GIAZO vs. 13% for placebo) and for Mucosal Healing (52% with GIAZO vs. 20% for placebo). Effectiveness of GIAZO was not demonstrated in the female subpopulation in the clinical trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

GIAZO is available as oval, yellow, film-coated tablets containing 1.1 g balsalazide disodium, with "BZT" debossed on one side of the tablet.

Bottles of 180 tablets NDC 65649-102-02

Storage

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

17 PATIENT COUNSELING INFORMATION

Renal Impairment

Inform patients that GIAZO may decrease their renal function, especially if they have known renal impairment or are taking nephrotoxic drugs, including NSAIDs, and periodic monitoring of renal function will be performed while they are on therapy. Advise patients to complete all blood tests ordered by their healthcare provider *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Mesalamine-Induced Acute Intolerance Syndrome and Other Hypersensitivity Reactions

Inform patients of the signs and symptoms of hypersensitivity reactions. Instruct patients to stop taking GIAZO and report to their healthcare provider if they experience new or worsening symptoms of Acute Intolerance Syndrome (cramping, abdominal pain, bloody diarrhea, fever, headache, and rash) or other symptoms suggestive of mesalamine-induced hypersensitivity *[see Warnings and Precautions (5.2, 5.3)]*.

Hepatic Failure

Inform patients with known liver disease of the signs and symptoms of worsening liver function and advise them to report to their healthcare provider if they experience such signs or symptoms *[see Warnings and Precautions (5.4)]*.

Photosensitivity

Advise patients with pre-existing skin conditions to avoid sun exposure, wear protective clothing, and use a broad-spectrum sunscreen when outdoors *[see Warnings and Precautions (5.5)]*.

Nephrolithiasis

Instruct patients to drink an adequate amount of fluids during treatment in order to minimize the risk of kidney stone formation and to contact their healthcare provider if they experience signs or symptoms of a kidney stone (e.g., severe side or back pain, blood in the urine) *[see Warnings and Precautions (5.6)]*.

Sodium Content of GIAZO

Inform patients on a sodium-restricted diet or patients at risk of developing congestive heart failure of the sodium content of GIAZO tablets (126 mg per tablet) *[see Warnings and Precautions (5.7)]*.

Blood Disorders

Inform elderly patients and those taking azathioprine or 6-mercaptopurine of the risk for blood disorders and the need for periodic monitoring of complete blood cell counts and platelet counts while on therapy. Advise patients to complete all blood tests ordered by their healthcare provider *[see Drug Interactions (7.2), Use in Specific Populations (8.5)]*.

Administration

Instruct patients:

- GIAZO tablets can be taken with or without food *[see Dosage and Administration (2)]*.
- Drink an adequate amount of fluids.

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