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

**Contraindications**

GIAZO is contraindicated in patients with hypersensitivity to salicylates, aminosalicylates, or any of the components of GIAZO tablets. GIAZO is contraindicated in patients with active ulcerative colitis. (5.1)

**Warnings and Precautions**

- Exacerbation of the symptoms of ulcerative colitis was reported. Observe patients closely for worsening of these symptoms while on treatment. (5.1)
- Renal impairment may occur. Assess renal function at the beginning of treatment and periodically during treatment. (5.2)
- Use with caution with pre-existing liver disease. (5.3)

**Adverse Reactions**

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

**Drug Interactions**

Based on in vitro studies, balsalazide and its metabolites (5-aminosalicylic acid (5-ASA), N-acetyl-5-aminosalicylic acid (N-acetyl-5-ASA), 4-aminobenzoic acid (4-ABA), and N-acetyl-4-aminobenzoic acid (N-acetyl-4-ABA) are not expected to inhibit the metabolism of other drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. (7)

**Use in Special Populations**

**Pregnancy**

Pregnancy Category B. Reproduction studies were performed in rats and rabbits at oral doses up to 2 g/kg/day, 2.5 and 4.9 times the recommended human dose based on body surface area for the rat and rabbit, respectively, and revealed no evidence of impaired fertility or harm to the fetus due to balsalazide. (8.1)

**Nursing Mothers**

It is not known whether balsalazide or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GIAZO is administered to a nursing woman. (8.4)

**Pediatric Use**

Safety and effectiveness of GIAZO in pediatric patients have not been established. (8.6)

**Geriatric Use**

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 who were taking mesalamine-containing products. GIAZO is converted into mesalamine in the colon. Caution should be taken to closely monitor blood cell counts during therapy. (8.5)

Clinical trials of GIAZO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing GIAZO. (8.7)

**Overdose**

No cases of overdose has been reported with GIAZO. GIAZO is an aminosalicylate, and symptoms of salicylate toxicity include: hematemesis, tachypnea, hyperpnea, tinnitus, deafness, lethargy, seizures, confusion, or dyspnea. Severe intoxication may lead to electrolyte and blood pH imbalance and potentially to other organ (e.g., renal and liver) involvement. There is no specific antidote for balsalazide overdose. Proper medical care should be sought immediately with appropriate supportive care, including the possible use of emesis, catharsis, and activated charcoal to prevent further absorption. (10)

**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 anti-inflammatory drug. Balsalazide disodium has the chemical name [[-]]-[-]-[[2-(carboxyethyl) aminocarbonyl]phenylazo]-2-hydroxybenzoic acid, disodium salt. Its molecular formula is C_{29}H_{27}N_3Na_2O_7, Molecular Weight: 437.32
Metabolism and Excretion
Following oral administration, balsalazide is cleaved by bacterial azoreductase 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-acetyl-5-ASA and N-acetyl-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 h for balsalazide, while the median T_{max} was 12 h for both 5-ASA and N-acetyl-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
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-acetyl-5-ASA and N-acetyl-4-ABA, respectively.

Following oral administration of repeated doses of 3.3 g GIAZO every 12 h to 250 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-acetyl-5-ASA, 0.40% for 4-ABA, and 1.6% for N-acetyl-4-ABA.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 24-month rat (Sprague Dawley) carcinogenicity study, oral (dietary) balsalazide dosing at doses up to 2 g/kg/day was not tumorigenic. For a 50 kg person of average height this dose represents 64 times the recommended human dose on a body surface area basis. Balsalazide dosing 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 (CHYSKG/HPR) forward mutation test.

The compound 4-aminobenzoyl-ß-alanine, a metabolite of balsalazide dosing, 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 dosing, was not genotoxic in Ames test, the mouse lymphoma cell (L5178Y/Tk+/−) forward mutation test, or the human lymphocyte chromosomal aberration test. Balsalazide dosing 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 TRIALS
14.1 Ulcerative Colitis
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 mainly 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 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 bowel frequency, rectal bleeding, and a combined score of ≤ 2 for bowel frequency and physician's assessment using the MMDAI subscale; the endoscopic subscore was not considered in this definition. Mucosal Healing was defined as an endoscopic/sigmoidoscopic 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GIAZO</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td>55%</td>
<td>40%</td>
<td>0.0237</td>
</tr>
<tr>
<td>Males</td>
<td>57%</td>
<td>40%</td>
<td>0.08</td>
</tr>
<tr>
<td>Females</td>
<td>54%</td>
<td>58%</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* Clinical Improvement: ≥ 3 point 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 subgroup. 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 subgroup in the clinical trial.

15 REFERENCES