MESALO OD Delayed-Release Tablets (Mesalamine)

Composition

MESALO OD Tablets
Mesalamine .................................. 1.2 g

Dosage Form

Delayed-release tablet for oral use.

Pharmacology

Pharmacodynamics

The pharmacodynamic actions of mesalamine occur in the colonic/rectal mucosae local to the delivery of drug into the lumen. There is information suggesting that severity of colonic inflammation in ulcerative colitis patients treated with mesalamine is inversely correlated with mucosal concentrations of mesalamine. However, plasma concentrations representing systemically absorbed mesalamine are not believed to contribute extensively to efficacy.

Mechanism of Action

The mechanism of action of mesalamine is not fully understood, but appears to be topical. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

Mesalamine has the potential to inhibit the activation of nuclear factor kappa B (NFkB) and consequently the production of key pro-inflammatory cytokines. It has been proposed that reduced expression of PPARγ nuclear receptors (γ-form of peroxisome proliferator-activated receptors) may be implicated in ulcerative colitis. There is substantial evidence that mesalamine produces pharmacodynamic effects through direct activation of PPARγ receptors in the colonic/rectal epithelium.

Pharmacokinetics

Absorption:
The total absorption of mesalamine 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21–22% of the administered dose. Gamma-scintigraphy studies have shown that a single dose of mesalamine 1.2 g (one tablet) passed intact through the upper gastrointestinal tract of healthy volunteers in the fasted state. Scintigraphic images showed a trail of radiolabeled tracer in the colon, suggesting that mesalamine had distributed throughout this region of the gastrointestinal tract.

In a single-dose study, mesalamine in doses of 1.2 g, 2.4 g and 4.8 g was administered in the fasted state to healthy subjects. Plasma concentrations of mesalamine were detectable after 2 hours and reached a maximum by 9–12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (Table 1).
Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose-proportional between 1.2 g and 4.8 g of mesalamine. Maximum plasma concentrations (C<sub>max</sub>) of mesalamine increased approximately dose-proportionately between 1.2 g and 2.4 g and sub-proportionately between 2.4 g and 4.8 g mesalamine, with the dose-normalized value at 4.8 g representing, on average, 74% of that at 2.4 g based on geometric means.

Table 1: Mean (SD) pharmacokinetic parameters for mesalamine following single-dose administration of mesalamine 1.2 g tablets under fasting conditions

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Mesalamine 1.2 g (N = 47)</th>
<th>Mesalamine 2.4 g (N = 48)</th>
<th>Mesalamine 4.8 g (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0–t&lt;/sub&gt; (ng·h/mL)</td>
<td>9039 (5054)</td>
<td>20538 (12980)</td>
<td>41434 (26640)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–∞&lt;/sub&gt; (ng·h/mL)</td>
<td>9578 (5214)</td>
<td>21084 (13185)</td>
<td>44775 (30302)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>857 (638)</td>
<td>1595 (1484)</td>
<td>2154 (1140)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>9.0**(4.0–32.1)</td>
<td>12.0 (4.0–34.1)</td>
<td>12.0 (4.0–34.0)</td>
</tr>
<tr>
<td>T&lt;sub&gt;lag&lt;/sub&gt; (h)</td>
<td>2.0** (0–8.0)</td>
<td>2.0 (1.0–4.0)</td>
<td>2.0 (1.0–4.0)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h) (Terminal Phase)</td>
<td>8.56 (6.38)</td>
<td>7.05* (5.54)</td>
<td>7.25* (8.32)</td>
</tr>
</tbody>
</table>

Arithmetic mean of parameter values are presented except for T<sub>max</sub> and T<sub>lag</sub>.

* Median (min, max); *N = 43, N = 27, †N = 33, ‡N = 36, ★N = 46

Administration of a single dose of mesalamine 4.8 g with a high-fat meal resulted in further delay in the absorption and plasma concentrations of mesalamine were detectable 4 hours following dosing. However, a high-fat meal increased the systemic exposure of mesalamine (mean C<sub>max</sub>: ↑91%; mean AUC: ↑16%) compared to results in the fasted state.

Mesalamine 1.2 g tablets were administered with food in the controlled clinical trials that supported its approval. In a single and multiple-dose pharmacokinetic study of mesalamine 1.2 g tablets, dose of 2.4 g or 4.8 g was administered once daily with standard meals to 28 healthy volunteers per dose group.

Plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. Steady state was achieved generally by 2 days after dosing. Mean AUC at steady state was only modestly greater (1.1- to 1.4-fold) than predictable from the single-dose pharmacokinetics.

In a single dose pharmacokinetic study of mesalamine 1.2 g tablets, a dose of 4.8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young (18-35yrs); 28 elderly (65-75yrs); 15 elderly (>75yrs)). Increased age resulted in increased systemic exposure (approximately 2-fold in C<sub>max</sub>), to mesalamine and its metabolite N-acetyl-5-aminosalicylic acid. Increased age resulted in a slower apparent elimination of mesalamine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Table 2: Mean (SD) PK parameters for mesalamine following single dose administration of mesalamine 1.2 g tablets in a dose of 4.8 g under fasting conditions to young and elderly subjects
### Parameter of 5-ASA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Young Subjects (18-35 yrs) (N=28)</th>
<th>Elderly Subjects (65-75 yrs) (N=28)</th>
<th>Elderly Subjects (&gt;75 yrs) (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (ng.h/mL)</td>
<td>51570 (23870)</td>
<td>73001 (42608)</td>
<td>65820 (25283)</td>
</tr>
<tr>
<td>AUC0-∞ (ng.h/mL)</td>
<td>58057a (22429)</td>
<td>89612c (40596)</td>
<td>63067e (22531)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2243 (1410)</td>
<td>4999 (4381)</td>
<td>4832 (4383)</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>22.0 (5.98 - 48.0)</td>
<td>12.5 (4.00 - 36.0)</td>
<td>16.0 (4.00 - 26.0)</td>
</tr>
<tr>
<td>tlag (h)</td>
<td>2.00 (1.00 - 6.00)</td>
<td>2.00 (1.00 - 4.00)</td>
<td>2.00 (2.00 - 4.00)</td>
</tr>
<tr>
<td>t½ (h), terminal phase</td>
<td>5.68b (2.83)</td>
<td>9.68c (7.47)</td>
<td>8.67c (5.84)</td>
</tr>
<tr>
<td>Renal clearance (L/h)</td>
<td>2.05 (1.33)</td>
<td>2.04 (1.16)</td>
<td>2.13 (1.20)</td>
</tr>
</tbody>
</table>

Arithmetic mean (SD) data are presented, N = Number of subjects  

*Median (min - max), †N=15, ‡N=16, ³N=13

### Distribution:
Mesalamine is approximately 43% bound to plasma proteins at the concentration of 2.5 μg/mL.

### Metabolism:
The only major metabolite of mesalamine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyltransferase (NAT) activity in the liver and intestinal mucosa cells, principally by NAT-1.

### Elimination:
Elimination of mesalamine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in the urine. Of the approximately 21–22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The apparent terminal half-lives for mesalamine and its major metabolite after administration of mesalamine 1.2 g tablets in doses of 2.4 g and 4.8 g were, on average, 7–9 hours and 8–12 hours, respectively.

### Indications
MESALO OD tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis and for the maintenance of remission of ulcerative colitis.

### Dosage And Administration

The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is two to four 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g or 4.8 g.

The recommended dosage for the maintenance of remission is two 1.2 g tablets taken once daily with a meal for a total daily dose of 2.4 g.

### Contraindications

MESALO OD tablets are contraindicated in patients with a hypersensitivity to salicylates or aminosalicylates or to any of the components of this product.
**Warnings And Precautions**

**General**

*Mesalamine-Induced Acute Intolerance Syndrome*

Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from an exacerbation of ulcerative colitis. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalamine or sulfasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash. Observe patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine.

*Hypersensitivity Reactions*

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to mesalamine tablets or to other compounds that contain or are converted to mesalamine. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with mesalamine containing medications. Caution should be taken in prescribing this medicine to patients with conditions predisposing them to the development of myocarditis or pericarditis.

*Interference with Laboratory Tests*

Use of 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 aminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

*Upper GI Tract Obstruction*

Pyloric stenosis or other organic or functional obstruction in the upper gastrointestinal tract may cause prolonged gastric retention of mesalamine which would delay mesalamine release in the colon.

**Drug Interactions**

The potential effect of mesalamine (4.8 g given once daily) on the pharmacokinetics of four commonly used antibiotics were evaluated in healthy subjects. The four antibiotics studied and their dosing regimens were as follows: amoxicillin (single 500 mg dose), ciprofloxacin XR (single 500 mg dose), metronidazole (750 mg twice daily for 3.5 days), and sulfamethoxazole/trimethoprim (800 mg/160 mg twice daily for 3.5 days). Coadministration of mesalamine did not result in clinically significant changes in the pharmacokinetics of any of the four antibiotics. The change in $C_{max}$ and AUC of amoxicillin, ciprofloxacin and metronidazole when they were co-administered with mesalamine were all ≤3%. There was an increase of 12% in $C_{max}$ and an increase of 15% in AUC of sulfamethoxazole when sulfamethoxazole/trimethoprim was coadministered with mesalamine.

No investigations have been performed between mesalamine tablets and other drugs. However, there have been reports of interactions between mesalamine medications and other drugs as follows:

*Nephrotoxic agents, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*

The concurrent use of mesalamine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions.

*Azathioprine or 6-mercaptopurine*

The concurrent use of mesalamine with azathioprine or 6-mercaptopurine can increase the potential for blood disorders.

**Renal Impairment**

Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal
failure, has been reported in patients given products that contain mesalamine or are converted to mesalamine. It is recommended that patients have an evaluation of renal function prior to initiation of mesalamine therapy and periodically while on therapy. Exercise caution when using mesalamine in patients with known renal dysfunction or a history of renal disease. In animal studies, the kidney was the principal organ for toxicity.

Hepatic Impairment

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Caution should be exercised when administering mesalamine to patients with liver disease.

Pregnancy

Pregnancy Category B. Reproduction studies with mesalamine have been performed in rats at doses up to 1000 mg/kg/day (1.8 times the maximum recommended human dose based on a body surface area comparison) and rabbits at doses up to 800 mg/kg/day (2.9 times the maximum recommended human dose based on a body surface area comparison) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. 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. Mesalamine is known to cross the placental barrier.

Lactation

Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. The clinical significance of this has not been determined and there is limited experience of nursing women using mesalamine. Caution should be exercised if mesalamine is administered to a nursing woman.

Pediatric Use

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

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. Caution should be taken to closely monitor blood cell counts during mesalamine therapy. Clinical trials of mesalamine did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Systemic exposures are increased in elderly subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concurrent disease or other drug therapy in elderly patients.

Undesirable Effects

The most serious adverse reactions seen with mesalamine 1.2 g tablets in clinical trials or with other products that contain or are metabolized to mesalamine are:

- Renal impairment, including renal failure
- Mesalamine-induced acute intolerance syndrome
- Hypersensitivity reactions
- Hepatic impairment, including hepatic failure
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.

Mesalamine 1.2 g tablets have been evaluated in 1368 ulcerative colitis patients in controlled and open-label trials.

**Induction of Remission**

In two 8-week placebo-controlled clinical trials involving 535 ulcerative colitis patients, 356 received mesalamine 1.2 g tablets in doses of 2.4 g/day or 4.8 g/day and 179 received placebo. The most frequent adverse reaction leading to discontinuation from mesalamine therapy was exacerbation of ulcerative colitis (0.8%). Pancreatitis occurred in less than 1% of patients during clinical trials and resulted in discontinuation of therapy with mesalamine in patients experiencing this event.

Adverse reactions occurring in mesalamine 1.2 g tablets or placebo groups at a frequency of at least 1% in two 8-week, double blind, placebo-controlled trials are listed in Table 3. The most common adverse reactions with mesalamine 1.2 g tablets in doses of 2.4 g/day and 4.8 g/day were headache (5.6% and 3.4%, respectively) and flatulence (4% and 2.8%, respectively).

**Table 3: Adverse reactions in two eight-week placebo-controlled trials experienced by at least 1% of the mesalamine group and at a rate greater than placebo**

<table>
<thead>
<tr>
<th>Event</th>
<th>Mesalamine 2.4 g/day (n = 177)</th>
<th>Mesalamine 4.8 g/day (n = 179)</th>
<th>Placebo (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10 (5.6%)</td>
<td>6 (3.4%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>7 (4%)</td>
<td>5 (2.8%)</td>
<td>5 (2.8%)</td>
</tr>
<tr>
<td>Liver Function Test Abnormal</td>
<td>1 (0.6%)</td>
<td>4 (2.2%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>2 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.6%)</td>
<td>2 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
</tbody>
</table>

* Adverse reactions for which the placebo rate equalled or exceeded the rate for at least one of the mesalamine treatment groups were abdominal pain, dizziness, dyspepsia, and nausea.

The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by mesalamine (1.2 g tablets) -treated ulcerative colitis patients in the two controlled trials.

**Cardiac Disorder:** tachycardia

**Vascular Disorders:** hypertension, hypotension

**Skin and Subcutaneous Tissue Disorders:** acne, prurigo, rash, urticaria

**Gastrointestinal Disorders:** abdominal distention, colitis, diarrhea, pancreatitis, rectal polyp, vomiting

**Investigations:** decreased platelet count

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

**Nervous System Disorders:** somnolence, tremor

**Respiratory, Thoracic and Mediastinal Disorders:** pharyngolaryngeal pain

**General Disorders and Administrative Site Disorders:** asthenia, face edema, fatigue, pyrexia
Ear and Labyrinth Disorders: ear pain

Maintenance of Remission of Ulcerative Colitis

The dose evaluated in three studies of mesalamine 1.2 g tablets given for the maintenance of remission in patients with ulcerative colitis was 1.2 g twice daily or 2.4 g/once daily. One of these studies was a 6-month double-blind comparator study while two were 12- to 14-month open-label studies.

The most common adverse reactions with mesalamine 1.2 g tablets in the maintenance arms of long-term trials were colitis ulcerative (5.8%), headache (2.9%), liver function test abnormal (2.3%), and abdominal pain (2.2%). Of the 1082 subjects in the all maintenance studies pooled, 1.9% had severe adverse reactions. The most common severe adverse reactions were gastrointestinal disorders; these were mainly symptoms associated with ulcerative colitis.

Table 4: Adverse reactions in three maintenance trials experienced by at least 1% of the mesalamine 1.2 g tablets group (maintenance phases of trials)

<table>
<thead>
<tr>
<th>All mesalamine 1.2 g tablets (n=1082)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>Colitis ulcerative</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Liver function test abnormal</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

The following adverse reactions, presented by body system, were reported infrequently (less than 1%) by mesalamine (1.2 g tablets)-treated ulcerative colitis patients in the three long-term maintenance trials (maintenance phases of these trials):

Cardiac Disorder: tachycardia

Skin and Subcutaneous Tissue Disorders: acne, alopecia, pruritis, urticaria Gastrointestinal Disorders: colitis, flatulence, nausea, pancreatitis, rectal polyp, vomiting

Nervous System Disorders: dizziness

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain
General Disorders and Administrative Site Disorders: asthenia, pyrexia
Ear and Labyrinth Disorders: ear pain

Postmarketing Experience

In addition to the adverse reactions reported above in clinical trials involving mesalamine 1.2 g tablets, the adverse events listed below have been identified during post-approval use of mesalamine 1.2 g tablets and other mesalamine-containing products. Because many of these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: lupus-like syndrome, drug fever
Cardiac Disorders: pericarditis, pericardial effusion, myocarditis
Gastrointestinal: pancreatitis, cholecystitis, gastritis, gastroenteritis, gastrointestinal bleeding, perforated peptic ulcer
Hepatic: jaundice, cholestatic jaundice, hepatitis, liver necrosis, liver failure, Kawasaki-like syndrome including changes in liver enzymes
Hematologic: agranulocytosis, aplastic anemia
Neurological/Psychiatric: peripheral neuropathy, Guillain-Barre syndrome, transverse myelitis
Renal Disorders: interstitial nephritis
Respiratory, Thoracic and Mediastinal Disorders: hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis)
Skin: psoriasis, pyoderma gangrenosum, erythema nodosum
Urogenital: reversible oligospermia

Overdosage

Mesalamine is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, seizures, hyperventilation, dyspnea, vomiting, and diarrhea. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, dehydration, and end organ damage. There is no specific known antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

Incompatibility

Not applicable.

Shelf-Life

2 years from the date of manufacture.

Storage And Handling Instructions

Keep out of reach of children. Store below 30ºC. Protect from light and moisture.

Packaging Information

Strip pack of 10 tablets.

Last updated: April 2016