For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

COOLGUT

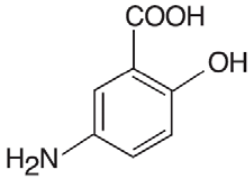
(Mesalazine Prolonged Release Tablets I.P.)

COMPOSITION:

Each enteric coated prolonged release tablet contains:
Mesalazine I.P. 1.2 g
Color: Red oxide of Iron

DESCRIPTION:

Each mesalazine prolonged release tablet for oral administration contains 1200 mg 5 aminosalicylic acid (5-ASA; mesalazine), an anti-inflammatory agent. Mesalazine also has the chemical name 5-amino-2-hydroxybenzoic acid and its structural formula is:



Molecular formula: $C_7H_7NO_3$
Molecular weight: 153.14

CLINICAL PHARMACOLOGY:

Mechanism of Action:

The mechanism of action of mesalazine is not fully understood, but appears to be topical. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxy eicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon. Recent data also suggest that mesalazine can inhibit the activation of NFKB, a nuclear transcription factor that regulates the transcription of many genes for pro inflammatory proteins.

PHARMACOKINETICS:

Absorption:

The total absorption of mesalazine 2.4 g or 4.8 g given once daily was found to be approximately 21-22% of the administered dose. Single dose of mesalazine 1.2g (one tablet) passed intact through the upper gastrointestinal tract. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalazine had distributed throughout this region of the gastrointestinal tract.

In a single dose study, Mesalazine 1.2g, 2.4g and 4.8g were administered in the fasted state to healthy subjects. Plasma concentrations of Mesalazine 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). Mesalazine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was slightly more than dose proportional between 1.2g and 4.8g Mesalazine. Maximum plasma concentrations (Cmax) of Mesalazine increased approximately dose proportionately between 1.2g and 2.4g and subproportionately between 2.4g and 4.8g.

Table 1: Mean (SD) PK Parameters for Mesalazine Following Single Dose Administration of Mesalazine under Fasting Conditions

Parameter [1] of Mesalamine	Mesalamine 1.2g (N=47)	Mesalamine 2.4g (N=48)	Mesalamine 4.8g (N=48)
AUC0-t (ng.h/mL)	9039+ (5054)	20538 (12980)	41434 (26640)
AUC0-∞ (ng.h/mL)	9578 • (5214)	21084 (13185)	44775# (30302)
Cmax (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
Tmax* (h)	9.0** (4.0-32.1)	12.0 (4.0-34.1)	12.0 (4.0-34.0)
Tlag* (h)	2.0** (0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)
T1/2 (h) (Terminal Phase)	8.56 (6.38)	7.05§ (5.54)	7.25# (8.32)

[1]Arithmetic mean of parameter values are presented except for Tmax and Tlag.
* Median (min, max); +N=43, •N=27, §N=33, #N=36, **N=46

Administration of a single dose of Mesalazine 4.8g with a high fat meal resulted in further delay in absorption and plasma concentrations of mesalazine were detectable 4 hours following dosing. However, high fat meal increased systemic exposure of mesalazine (mean Cmax: 91%; mean AUC: 16%) compared to results in the fasted state.

In a single and multiple dose pharmacokinetic study of Mesalazine 2.4g or 4.8g was administered once daily with standard meals to healthy volunteers. Plasma concentrations of mesalazine 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 single dose pharmacokinetics

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

Metabolism:
The major metabolite of mesalazine (5-aminosalicylic acid) is N-acetyl-5-aminosalicylic acid. Its formation is brought about by N-acetyl transferase activity in the liver and intestinal mucosa.

Elimination:
Elimination of mesalazine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid. However, there is also limited excretion of the parent drug in 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.

INDICATIONS AND USAGE:
Mesalazine tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

CONTRAINDICATIONS:
Contraindicated in patients with hypersensitivity to salicylates (including mesalazine) or to any of the components of mesalazine tablet.

WARNINGS AND PRECAUTIONS:
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 mesalazine or are converted to mesalazine.

It is recommended that patients have an evaluation of renal function prior to initiation of Mesalazine therapy and periodically while on therapy. Exercise caution when using mesalazine in patients with known renal dysfunction or a history of renal disease.

In animal studies, the kidney was the principal organ for toxicity.

Mesalazine-Induced Acute Intolerance Syndrome
Mesalazine 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 mesalazine 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 mesalazine.

Hypersensitivity Reactions
Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to mesalazine tablets or to other compounds that contain or are converted to mesalazine.

Mesalazine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with mesalazine and other mesalazine medications. Caution should be taken in prescribing this medicine to patients with conditions predisposing them to the development of myocarditis or pericarditis.

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

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

Interference with Laboratory Tests
Use of mesalazine 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 mesalazine's main metabolite, N-acetylaminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

Special Populations:
Pediatric Use:
Safety and effectiveness of mesalazine tablets in pediatric patients have not been established.

Geriatric Use:
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 mesalazine. Reports from uncontrolled clinical studies and post-marketing reporting

systems suggest a higher incidence of blood dyscrasias, i.e., agranulocytosis, neutropenia, pancytopenia, in subjects receiving mesalazine who are 65 years or older. Caution should be taken to closely monitor blood cell counts during drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. It is recommended that all patients have an evaluation of renal function prior to initiation of mesalazine tablets and periodically while on mesalazine therapy.

Renal Insufficiency:
Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure has been reported in patients taking mesalazine tablets as well as other compounds which contain or are converted to mesalazine. In animal studies (rats, dogs), the kidney is the principal target organ for toxicity. At doses of approximately 750 mg/kg to 1000 mg/kg [15 to 20 times the administered recommended human dose (based on a 50 kg person) on a mg/kg basis and 3 to 4 times on a mg/m2 basis], mesalazine causes renal papillary necrosis. Therefore, caution should be exercised when using mesalazine (or other compounds which contain or are converted to mesalazine or its metabolites) in patients with known renal dysfunction or history of renal disease. It is recommended that all patients have an evaluation of renal function prior to initiation of mesalazine tablets and periodically while on mesalazine therapy.

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

Information for Patients:
Patients should be instructed to swallow mesalazine tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact to protect the active ingredient, mesalazine, and ensure its availability throughout the colon.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In a 104-week dietary carcinogenicity study in CD-1 mice, mesalazine at doses up to 2500 mg/kg/day was not tumorigenic. This dose is 2.2 times the maximum recommended human dose (based on a body surface area comparison) of mesalazine. Furthermore, in a 104-week dietary carcinogenicity study in Wistar rats, mesalazine up to a dose of 800 mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose of mesalazine. No evidence of mutagenicity was observed in an in vitro Ames test or an in vivo mouse micronucleus test. In

dogs, 6 grams of mesalazine (Approximately 12.5 times the recommended human dose) resulted in renal papillary necrosis but was not fatal.

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalazine up to 400 mg/kg/day (0.7 times the maximum recommended human dose based on a body surface area comparison). Semen abnormalities and infertility in men, which have been reported in association with sulfasalazine, have not been seen with other mesalazine products during controlled clinical trials

DRUG INTERACTION:

The concurrent use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of renal reactions. In patients receiving azathioprine or 6-mercaptopurine, concurrent use of mesalazine can increase the potential for blood disorders.

PREGNANCY:

Pregnancy Category C

Risk summary

There are no adequate well controlled studies of mesalazine use in pregnant women. Limited published human data on mesalazine show no increase in the overall rate of congenital malformations. Some data show an increased rate of preterm birth, stillbirth, and low birth weight; however, these adverse pregnancy outcomes are also associated with active inflammatory bowel disease. Furthermore, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4 percent for major malformations, and 15 to 20 percent for pregnancy loss. No evidence of fetal harm was observed in animal reproduction studies of mesalazine in rats and rabbits at oral doses approximately 1.6 times (rat) and 3.2 times (rabbit) the recommended human dose. Mesalazine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human data

Mesalazine crosses the placenta. In prospective and retrospective studies of over 600 women exposed to mesalazine during pregnancy, the observed rate of congenital malformations was not increased above the background rate in the general population. Some data show an increased rate of preterm birth, stillbirth, and low birth weight, but it is unclear whether this was due to underlying maternal disease, drug exposure, or both, as active inflammatory bowel disease is also associated with adverse pregnancy outcomes.

Animal data:

Reproduction studies have been performed in rats at oral doses up to 480 mg/kg/day (about 1.6 times the recommended human treatment dose on a body surface area basis) and rabbits at oral

doses up to 480 mg/kg/day (about 3.2 times the recommended human treatment dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalazine.

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.

Nursing Mothers:
Mesalazine and its N-acetyl metabolite are present in human milk. In published lactation studies, maternal mesalazine doses from various oral and rectal formulations and products ranged from 500 mg to 3 g daily. The concentration of mesalazine in milk ranged from non-detectable to 0.11 mg/L. The concentration of the N-acetyl-5-aminosalicylic acid metabolite ranged from 5 to 18.1 mg/L. Based on these concentrations, estimated infant daily doses for an exclusively breastfed infant are 0 to 0.017 mg/kg/day of mesalazine and 0.75 to 2.72 mg/kg/day of N-acetyl-5-aminosalicylic acid.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mesalazine and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Exercise caution when mesalazine is administered to a nursing mother.

ADVERSE REACTIONS:
Most common adverse reactions observed with mesalazine were colitis flare; dizziness, nausea, joint pain, rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild indigestion and cramping; headache, aching, vomiting, muscle cramps, a stuffy head, plugged ears, fever, pharyngitis, rhinitis, dyspepsia, hypertonia, flatulence, dysmenorrhea, chest pain, chills, flu syndrome, peripheral edema, myalgia, colitis exacerbation, increased cough, arthritis, insomnia, decreased libido, rheumatoid arthritis, stomatitis, gastrointestinal hemorrhage, infection, joint disorder, migraine, nervousness, rectal disorder, rectal hemorrhage, tenesmus, urinary frequency, flatulence.

Other adverse reactions like abdominal enlargement, anxiety, bronchitis, ear disorder, ear pain, gastroenteritis, nervousness, paresthesia, Eructation, sinusitis, stool abnormalities, vasodilatation and vision abnormalities were also sometime reported. In addition to the adverse events listed above, the following events have been reported in clinical studies, literature reports, and postmarketing use of products which contain (or have been metabolized to) mesalazine. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness or potential causal connection to mesalazine.

Body as a Whole: Neck pain, facial edema, edema, lupus-like syndrome, drug fever (rare) and asthenia.

Cardiovascular: tachycardia, hypertension, hypotension, Pericarditis (rare), myocarditis (rare), pericardial effusion and vasodilation.

Gastrointestinal: Anorexia, pancreatitis, gastritis, increased appetite, cholecystitis, dry mouth, oral ulcers, perforated peptic ulcer (rare), rectal polyp, bloody diarrhea. There have been rare reports of hepatotoxicity including, jaundice, cholestatic jaundice, hepatitis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. Asymptomatic elevations of liver enzymes which usually resolve during continued use or with discontinuation of the drug have also been reported. One case of Kawasaki-like syndrome which included changes in liver enzymes was also reported.

Hematologic: Agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Musculoskeletal: Gout and arthralgia.

Nervous: Depression, somnolence, emotional lability, hyperesthesia, vertigo, confusion, tremor, peripheral neuropathy (rare), transverse myelitis (rare), Guillain-Barré syndrome (rare).

Respiratory/Pulmonary: Eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis and pharyngolaryngeal pain.

Skin: Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, urticaria, acne, pruritus, and face edema.

Immune System Disorders: anaphylactic reaction, angioedema, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS)

Special Senses: Eye pain, taste perversion, blurred vision, tinnitus and conjunctivitis.

Urogenital: Renal Failure (rare), interstitial nephritis, minimal change nephropathy, dysuria, urinary urgency, hematuria, epididymitis, menorrhagia.
Laboratory Abnormalities: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated GGT, elevated LDH, elevated bilirubin, elevated serum creatinine and BUN.

DRUG ABUSE AND DEPENDENCY:
Abuse: None reported.
Dependency: Drug dependence has not been reported with chronic administration of mesalazine.

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 1.2g tablets to be taken once daily with meal for a total daily dose of 2.4g or 4.8g. Treatment duration in controlled clinical trials was up to 8 weeks.

OVERDOSAGE:
Mesalazine is an aminosalicylate, and symptoms of salicylate toxicity may include tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting, and diarrhea. Severe intoxication may lead to disruption of electrolyte balance and blood-pH, hyperthermia, and dehydration. Conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. This includes prevention of further gastrointestinal tract absorption by emesis and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate intravenous therapy. Adequate renal function should be maintained.

INSTRUCTIONS FOR USE:
Tablets to be swallowed whole, not to be crushed or chewed.

EXPIRY DATE:
Do not use later than the date of expiry.

STORAGE:
Store at a temperature not exceeding 30^{o}C, protected from light and moisture.
Keep out of reach of children

PRESENTATION:
Coolgut tablet is available as strip of 10 tablets.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

COOL/NOV 2014/Ver 04