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

COOLGUT

1. Generic Name

Mesalazine Prolonged Release Tablets I.P.

2. Qualitative and quantitative Composition:

Each enteric coated prolonged release tablet contains:

Mesalazine I.P……. 1.2 g

Color: Red oxide of Iron

3. Dosage form and strength

Dosage form: Prolonged Release Tablets

Strength: 1200mg

4. Clinical particulars

4.1 Therapeutic indication

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

4.2 Posology and method of administration

Posology

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.

Method of administration

Tablets to be swallowed whole, not to be crushed or chewed.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Renal Impairment

Renal impairment, including minimal change disease, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products that contain mesalamine or are converted to mesalamine. In animal studies, the kidney was the principal organ of mesalamine toxicity.

Evaluate renal function prior to initiation of mesalamine therapy and periodically while on therapy. Evaluate the risks and benefits of using mesalamine in patients with known renal impairment, history of renal disease, or taking concomitant nephrotoxic drugs. Discontinue mesalamine if renal function deteriorates while on therapy.

Mesalazine-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. Monitor patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some of these patients may have a similar reaction to mesalamine delayed-release tablets or to other compounds that contain or are converted to mesalamine.

As with sulfasalazine, 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 mesalamine tablets if an alternative etiology for the signs or symptoms cannot be established.

Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Evaluate the risks and benefits of using mesalamine in patients with known liver impairment.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with the use of mesalamine. Discontinue mesalamine delayed-release tablets at the first appearance of signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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. Avoid mesalamine in patients at risk of upper gastrointestinal tract obstruction.

Photosensitivity

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

Nephrolithiasis

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

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.

4.5 Drugs interactions

Nephrotoxic Agents, Including Non-Steroidal Anti-Inflammatory Drugs

The concurrent use of mesalamine with known nephrotoxic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), may increase the risk of nephrotoxicity. Monitor patients taking nephrotoxic drugs for changes in renal function and mesalamine-related adverse reactions.

Azathioprine and 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 mesalamine and azathioprine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

Interference with Urinary Normetanephrine Measurements

Use of mesalamine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection. Consider an alternative, selective assay for normetanephrine.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk summary

mesalamine during pregnancy have not reliably informed an association with mesalamine and major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are adverse effects on maternal and fetal outcomes associated with ulcerative colitis in pregnancy.

In animal reproduction studies, there were no adverse developmental outcomes with administration of oral mesalamine during organogenesis to pregnant rats and rabbits at doses 1.8 and 2.9 times, respectively, the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated populations 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 miscarriages 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 2,500 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 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 increased risk of 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, maternal use of concomitant medications, and missing information on the dose and duration of use for mesalamine products.

Animal data:

Reproduction studies with mesalamine during organogenesis have been performed in rats at doses up to 1,000 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 harm to the fetus due to mesalamine.

Lactation

Risk Summary

Data from published literature report the presence of mesalamine and its metabolite, Nacetyl-5-aminosalicylic acid in human milk in small amounts with relative infant doses (RID) of 0.1% or less for mesalamine. There are case reports of diarrhea in breastfed infants exposed to mesalamine. 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 mesalamine to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mesalamine and any potential adverse effects on the breastfed child from mesalamine or from the underlying maternal condition.

Clinical Considerations

Advise the caregiver to monitor the breastfed infant for diarrhea.

Data

In published lactation studies, maternal mesalamine doses from various oral and rectal 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 mg/L to 9.3 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 mg/kg/day to 0.075 mg/kg/day (RID 0% to 0.1%) of mesalamine and 0.03 mg/kg/day to 1.4 mg/kg/day of N-acetyl-5-aminosalicylic acid.

Pediatric Use:

The safety and effectiveness of mesalamine have been established for the treatment of mildly to moderately active ulcerative colitis in pediatric patients weighing at least 24 kg. Use of mesalamine in this population is supported by evidence from adequate and wellcontrolled trials in adults, a multicenter, randomized, double-blind, parallel group trial in 105 pediatric patients 5 to 17 years of age, and additional pharmacokinetic analyses. The safety profile in pediatric patients was similar to that observed in adults.

The safety and effectiveness of mesalamine have not been established in patients weighing less than 24 kg.

Geriatric Use:

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. Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias (i.e., agranulocytosis, neutropenia, and pancytopenia) in patients who were 65 years or older who were taking mesalaminecontaining products such as mesalamine delayed-release tablets compared to younger patients. Monitor complete blood cell counts and platelet counts in elderly patients during treatment with mesalamine.

Systemic exposures are increased in elderly subjects.

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 mesalamine. Consider starting at the low end of the dosing range for induction in elderly patients.

Renal Insufficiency:

Mesalamine is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Evaluate renal function in all patients prior to initiation and periodically while on mesalamine 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. Discontinue mesalamine if renal function deteriorates while on 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.

4.7 Effects on ability to drive and use machines

Not Available

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated list of adverse reactions

Adults

The most common adverse reactions occurring in at least 1% of mesalamine- or placebo-treated adult patients with mildly to moderately active ulcerative colitis in two eight-week, randomized, double-blind, placebo-controlled trials.

Table 1: Adverse Reactions* in Two Eight-Week, Placebo-Controlled Trials of Induction Therapy (Study 1 and Study 2) in Adults with Mildly to Moderately Active Ulcerative Colitis

Adverse Reaction	Mesalamine 2.4 g once daily (n=177)	Mesalamine 4.8 g once daily (n=179)	Placebo (n=179)
Headache	6%	3%	<1%
Flatulence	4%	3%	3%
Liver Function Test Abnormal	<1%	2%	1%
Alopecia	0	1%	0
Pruritus	<1%	1%	1%
*Reported in at least 1% of patients in at least one mesalamine group and greater than placebo			

Pancreatitis occurred in less than 1% of patients during induction in clinical trials and resulted in discontinuation of therapy with mesalamine in patients experiencing this event.

Maintenance of Remission

A mesalamine dosage of 2.4 g/day, administered as either 1.2 g twice daily or 2.4 g once daily, was evaluated for safety in three maintenance trials in patients with mildly to moderately active ulcerative colitis: a 6-month double-blind, active-controlled study and two 12- to 14-month open-label studies. The most common adverse reactions with mesalamine in these maintenance trials are listed in Table 2.

Table 2: Adverse Reactions* in Three Trials of Maintenance of Remission in Adults with Ulcerative Colitis

	Mesalamine 2.4 g/day# (n=1082)
Adverse Reaction	**%**

Headache	3%
Liver function test abnormal	2%
Abdominal pain	2%
Diarrhea	2%
Abdominal distension	1%
Abdominal pain upper	1%
Dyspepsia	1%
Back pain	1%
Rash	1%
Arthralgia	1%
Fatigue	1%
Hypertension	1%
*Reported in at least 1% of patients	
[#]Administered either as 1.2 g twice daily or 2.4 g once daily	

The following adverse reactions, presented by body system, were reported in less than 1% of mesalamine-treated patients with ulcerative colitis in either induction or maintenance trials:

Cardiac Disorder: tachycardia

Ear and Labyrinth Disorders: ear pain

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

General Disorders and Administrative Site Disorders: asthenia, face edema, fatigue, pyrexia

Investigations: decreased platelet count

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain

Nervous System Disorders: dizziness, somnolence, tremor

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain

Skin and Subcutaneous Tissue Disorders: acne, prurigo, rash, alopecia, pruritus, urticaria

Vascular Disorders: hypertension, hypotension

Pediatrics

Mesalamine was evaluated in 105 pediatric patients 5 through 17 years of age with mildly to moderately active ulcerative colitis. The adverse reaction profile was similar to that of adults. The most common adverse reactions reported in at least 5% of pediatric patients treated with

mesalamine were: abdominal pain, upper respiratory tract infection, vomiting, anemia, headache, and viral infection.

Description of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Mesalamine is an aminosalicylate, and symptoms of salicylate toxicity may include nausea, vomiting, 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 end organ (e.g., renal and liver) 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 and may include gastrointestinal tract decontamination to prevent further absorption. Correct fluid and electrolyte imbalance by the administration of appropriate intravenous therapy and maintain adequate renal function.

Mesalamine is a pH-dependent, product and this factor should be considered when treating a suspected overdose.

5 Pharmacological properties

5.1 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.

5.2 Pharmacodynamic properties

Not Available

5.3 Pharmacokinetic properties

Absorption:

The total absorption of mesalamine from mesalamine delayed-release tablets 2.4 g or 4.8 g given once daily for 14 days to healthy subjects was found to be approximately 21% to 22% of the administered dose.

Gamma-scintigraphy studies have shown that a single dose of mesalamine delayedrelease tablets 1.2 g (one tablet) passed intact through the upper gastrointestinal tract of fasted healthy subjects. Scintigraphic images showed a trail of radio-labeled tracer in the colon, suggesting that mesalamine had distributed through this region of the gastrointestinal tract.

In a single-dose study, mesalamine delayed-release tablets 1.2 g, 2.4 g, and 4.8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalamine

were detectable after 2 hours and reached a maximum by 9 to 12 hours on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects (Table 3). 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 mesalamine delayed-release tablets. Maximum plasma concentrations (C_{max}) 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 of mesalamine delayed-release tablets, with the dose normalized value at 4.8 g representing, on average, 74% of that at 2.4 g based on geometric means.

Table 3: Mean (SD) PK Parameters for Mesalazine Following Single Dose Administration of Mesalazine under Fasting Conditions

Parameter* of Mesalamine	**Mesalamine 1.2 g (N=47)**	**Mesalamine 2.4 g (N=48)**	**Mesalamine 4.8 g (N=48)**
AUC_{0-t} (ng·h/mL)	9039[†] (5054)	20538 (12980)	41434 (26640)
$AUC_{0-\infty}$ (ng·h/mL)	9578[‡] (5214)	21084 (13185)	44775[§] (30302)
C_{max} (ng/mL)	857 (638)	1595 (1484)	2154 (1140)
T_{max}[¶] (h)	9.0[#] (4.0 to 32.1)	12.0 (4.0 to 34.1)	12.0 (4.0 to 34.0)
T_{lag}[¶] (h)	2.0[#] (0 to 8.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)
T1/2 (h) (Terminal Phase)	8.56[‡] (6.38)	7.05[Þ] (5.54)	7.25[§] (8.32)
*Arithmetic mean of parameter values are presented except for Tmax and Tlag.			
[†]N=43, [‡]N=27, [§]N=36, [¶]Median (min, max), [#]N=46, [Þ]N=33			

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

Elimination:

<u>Metabolism</u>

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

Excretion

Excretion of mesalamine is mainly via the renal route following metabolism to N-acetyl-5aminosalicylic acid (acetylation); however, there is also limited excretion of the parent drug in urine. Of the approximately 21% to 22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid. The mean renal clearance (CLR) in adults ranged from 1.8 L/h to 2.9 L/h following single dose administration and ranged from 5.5 L/h to 6.4 L/h after a multiple dosing for 14 days. The apparent terminal half-lives for mesalamine and its major metabolite after administration of mesalamine 2.4 g and 4.8 g were, on average, 7 to 9 hours and 8 to 12 hours, respectively.

Systemic exposures in adult subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Geriatric Patients

In a single-dose pharmacokinetic study of mesalamine, 4.8 g was administered in the fasted state to 71 healthy male and female subjects (28 young (18 to 35 years); 28 elderly (65 to 75 years); 15 elderly (>75 years)). Increased age resulted in increased systemic exposure (approximately 2-fold in Cmax) to mesalamine and its metabolite Nacetyl-5-aminosalicylic acid. Increased age resulted in a slower apparent elimination of mesalamine, though there was high between-subject variability.

Table 4: Mean (SD) Pharmacokinetic Parameters for Mesalamine Following Single-Dose Administration of Mesalamine 4.8 g under Fasting Conditions to Young and Elderly Subjects

Parameter of 5-ASA	**Young Subjects (18 to 35 years) (N=28)**	**Elderly Subjects (65 to 75 years) (N=28)**	**Elderly Subjects (75 years and older) (N=15)**
AUC0-t (ng·h/mL)	51570 (23870)	73001 (42608)	65820 (25283)
AUC0-∞ (ng·h/mL)	58057[*] (22429)	89612[†] (40596)	63067[‡] (22531)
Cmax (ng/mL)	2243 (1410)	4999 (4381)	4832 (4383)
tmax [§] (h)	22.0 (5.98 to 48.0)	12.5 (4.00 to 36.0)	16.0 (4.00 to 26.0)
tlag [§] (h)	2 (1 to 6)	2 (1 to 4)	2 (2 to 4)
t1/2 (h), terminal phase	5.68[*] (2.83)	9.68[†] (7.47)	8.67[‡] (5.84)
Renal clearance (L/h)	2.05 (1.33)	2.04 (1.16)	2.13 (1.20)
Arithmetic mean (SD) data are presented, N = Number of subjects; 5-ASA = 5-aminosalicylic acid			
[*]N=15, [†]N=16, [‡]N=13, [§]Median (min-max)			

Pediatric Patients

In pediatric patients 5 years to 17 years of age diagnosed with ulcerative colitis, systemic exposure of mesalamine, as measured by mean AUC and C , increased in a dose-proportional manner between 30 and 60 mg/kg/day of mesalamine and increased in a sub-proportional between 60 and 100 mg/kg/day doses. Pharmacokinetic parameters had moderate to high inter-subject variability with CV% ranging from 36% to 52% in pediatric patients.

The overall systemic exposure of mesalamine following oral administration of 4.8 g once daily for 7 days in a limited number of pediatric patients 5 years to 17 years of age (AUC range of 30,556 to 50,388 ng·hr/mL, n=3) was in similar range to that was observed in the healthy adults (AUC of 41,434 ± 26,640 ng·hr/mL, n=48) after single dose administration.

The mean renal clearance (CL) of mesalamine in pediatric patients (range from approximately 5.0 to 6.5 L/h) seems to be similar to that observed with healthy adult subjects after multiple dose administration.

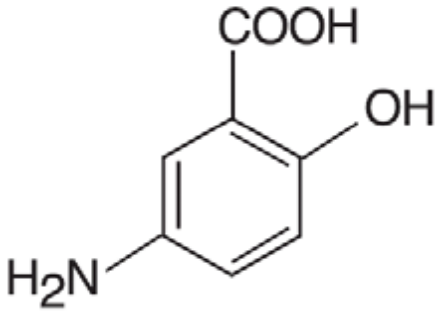
6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

In animal studies with mesalamine, a 13-week oral toxicity study in mice and 13-week and 52-week oral toxicity studies in rats and cynomolgus monkeys have shown the kidney to be the major target organ of mesalamine toxicity. Oral daily doses of 2,400 mg/kg in mice and 1,150 mg/kg in rats produced renal lesions including granular and hyaline casts, tubular degeneration, tubular dilation, renal infarct, papillary necrosis, tubular necrosis, and interstitial nephritis. In cynomolgus monkeys, oral daily doses of 250 mg/kg or higher produced nephrosis, papillary edema, and interstitial fibrosis.

7 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: C7H7NO3

Molecular weight: 153.14

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

COOLGUT tablet is available as strip of 10 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30ºC, protected from light and moisture.

Keep out of reach of children

9 Patient Counselling Information

Package leaflet: Information for the user

COOLGUT

(Mesalazine Prolonged Release Tablets I.P.)

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What COOLGUT is and what it is used for

COOLGUT is a Mesalazine Prolonged Release Tablet.

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

9.2 What you need to know before you take COOLGUT

Do not take COOLGUT

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 disease, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported in patients given products that contain mesalamine or are converted to mesalamine. In animal studies, the kidney was the principal organ of mesalamine toxicity.

Evaluate renal function prior to initiation of mesalamine therapy and periodically while on therapy. Evaluate the risks and benefits of using mesalamine in patients with known renal impairment, history of renal disease, or taking concomitant nephrotoxic drugs. Discontinue mesalamine if renal function deteriorates while on therapy.

Mesalazine-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. Monitor patients closely for worsening of these symptoms while on treatment. If acute intolerance syndrome is suspected, promptly discontinue treatment with mesalamine.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported in patients taking sulfasalazine. Some of these patients may have a similar reaction to mesalamine delayed-release tablets or to other compounds that contain or are converted to mesalamine.

As with sulfasalazine, 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 mesalamine tablets if an alternative etiology for the signs or symptoms cannot be established.

Hepatic Failure

There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Evaluate the risks and benefits of using mesalamine in patients with known liver impairment.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with the use of mesalamine. Discontinue mesalamine delayed-release tablets at the first appearance of signs or symptoms of severe cutaneous adverse reactions or other signs of hypersensitivity and consider further evaluation.

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. Avoid mesalamine in patients at risk of upper gastrointestinal tract obstruction.

Photosensitivity

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

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalamine, including stones with a 100% mesalamine content. Mesalamine-containing stones are radiotransparent and

undetectable by standard radiography or computed tomography (CT). Ensure adequate hydration during treatment with mesalamine.

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.

Pregnancy, breast-feeding and fertility

Pregnancy

Risk summary

mesalamine during pregnancy have not reliably informed an association with mesalamine and major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are adverse effects on maternal and fetal outcomes associated with ulcerative colitis in pregnancy.

In animal reproduction studies, there were no adverse developmental outcomes with administration of oral mesalamine during organogenesis to pregnant rats and rabbits at doses 1.8 and 2.9 times, respectively, the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated populations 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 miscarriages 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 2,500 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 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 increased risk of 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, maternal use of concomitant medications, and missing information on the dose and duration of use for mesalamine products.

Animal data:

Reproduction studies with mesalamine during organogenesis have been performed in rats at doses up to 1,000 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 harm to the fetus due to mesalamine.

Lactation

Risk Summary

Data from published literature report the presence of mesalamine and its metabolite, Nacetyl-5-aminosalicylic acid in human milk in small amounts with relative infant doses (RID) of 0.1% or less for mesalamine. There are case reports of diarrhea in breastfed infants exposed to mesalamine. 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 mesalamine to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for mesalamine and any potential adverse effects on the breastfed child from mesalamine or from the underlying maternal condition.

Clinical Considerations

Advise the caregiver to monitor the breastfed infant for diarrhea.

Data

In published lactation studies, maternal mesalamine doses from various oral and rectal 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 mg/L to 9.3 mg/L. Based on these concentrations, estimated infant daily dosages for an exclusively breastfed infant are 0 mg/kg/day to 0.075 mg/kg/day (RID 0% to 0.1%) of mesalamine and 0.03 mg/kg/day to 1.4 mg/kg/day of N-acetyl-5-aminosalicylic acid.

Driving and using machines

Not Available

9.3 How to take COOLGUT

Tablets to be swallowed whole, not to be crushed or chewed.

9.4 Possible side effects

The following clinically significant adverse reactions are described

Renal impairment, including renal failure

Mesalamine-induced acute intolerance syndrome

Hypersensitivity reactions

Hepatic failure

Severe cutaneous adverse reactions

Upper gastrointestinal tract obstruction

Photosensitivity

Nephrolithiasis

9.5 How to store COOLGUT

Store at a temperature not exceeding 30oC, protected from light and moisture.

Keep out of reach of children.

9.6 Contents of the pack and other information

Coolgut tablet is available as strip of 10 tablets.

10 Details of manufacturer

Manufactured by

TORRENT PHARMACEUTICALS LTD.

32 No.Middle.camp.NH-10

East District, Gangtok, Sikkim-737.135

11. Date of revision

SEP 2022

MARKETED BY

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IN/COOLGUT/SEP-22/05/PI