Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Colisticol-1200

2. Qualitative and quantitative composition
Each film coated delayed release tablet contains: Mesalamine USP 1200 mg
This product contains lactose
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film coated delayed release tablet Brick red coloured, elongated, biconvex, score on one side, plain on other side film coated delayed release tablet.

4. Clinical particulars

4.1 Therapeutic indications
MESALAMINE DELAYED-RELEASE TABLET are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. Safety and effectiveness of MESALAMINE DELAYEDRELEASE TABLET beyond 8 weeks has not been established.

4.2 Posology and method of 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.

4.3 Contraindications
MESALAMINE DELAYED-RELEASE TABLET is contraindicated in patients with hypersensitivity to salicylates (including mesalamine) or to any of the components of MESALAMINE DELAYED-RELEASE TABLET.

4.4 Special warnings and precautions for use
General:
Patients with pyloric stenosis may have prolonged gastric retention of MESALAMINE DELAYED-RELEASE TABLET, which could delay mesalamine release in the colon. The majority of patients who are intolerant or hypersensitive to sulfasalazine can take mesalamine medications without risk of similar reactions. However, caution should be exercised when treating patients allergic to sulfasalazine. Mesalamine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. 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, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required. Mesalamine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported with MESALAMINE DELAYED-RELEASE TABLET and other mesalamine medications. Caution should

be taken in prescribing this medication to patients with conditions predisposing to the development of myocarditis or pericarditis.

Renal:
Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine medications and prodrugs of mesalamine. For any patient with known renal dysfunction, caution should be exercised and MESALAMINE DELAYED-RELEASE TABLET should be used only if the benefits outweigh the risks. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment. 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 2400 mg/kg in mice and 1150 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. Hepatic Impairment: No information is available on patients with hepatic impairment, and therefore, caution is recommended in these patients.

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

Pediatric Use:
Safety and effectiveness of MESALAMINE DELAYED-RELEASE TABLET in pediatric patients who are less than 18 years of age have not been studied.

Geriatric Use:
Clinical trials of MESALAMINE DELAYED-RELEASE TABLET did not include sufficient numbers of patients aged 65 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. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Mesalamin OD' tablets should not be given with lactulose or similar preparations, which lower stool pH and may prevent release of Mesalamine.

Concurrent use of other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions.
Mesalamine inhibits thiopurine methyltransferase. In patients receiving azathioprine or 6- mercaptopurine and/or any other active substances known to cause myelotoxicity, caution is recommended for concurrent use of mesalamine as this can increase the potential for blood dyscrasias, bone marrow failure, and associated complications.
Administration with coumarin-type anticoagulants e.g., warfarin, could result in decreased anticoagulant activity. Prothrombin time should be closely monitored if this combination is essential.

4.6 Pregnancy and Lactation

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.

Nursing Mothers:

Low concentrations of mesalamine and higher concentrations of its Nacetyl metabolite have been detected in human breast milk. While there is limited experience of lactating women using mesalamine, caution should be exercised if MESALAMINE DELAYED-RELEASE TABLET is administered to a nursing mother, and used only if the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines

Patients should be warned about engaging in activities requiring mental alertness eg, driving a car or operating appliances, machinery and others.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) within the pooled safety analysis of clinical studies with Mesalamine 1200mg, were colitis (including ulcerative colitis) 5.8%, abdominal pain 4.9%, headache 4.5%, liver function test abnormal, 2.1%, diarrhoea 2.0%, and nausea 1.9%.
The safety profile in the paediatric population is consistent with the safety profile in adult studies and in post-marketing experience.
Adverse reactions are listed by System Organ Class (see table below). Within each system organ class, adverse reactions are listed under headings of frequency using the categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

System/Organ Class	Incidence Category	Adverse drug reaction
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
	Rare	Agranulocytosis
	Not known	Aplastic anaemia, Leukopenia, Neutropenia, Pancytopenia
Immune system disorders	Uncommon	Face oedema
	Not known	Hypersensitivity, Anaphylactic shock, Angioedema, Drug rash with eosinophilia and systemic symptoms (DRESS)
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, Somnolence, Tremor
	Not known	Intracranial pressure increased, Neuropathy
Ear and labyrinth disorders	Uncommon	Ear pain
Cardiac disorders	Uncommon	Tachycardia
	Not known	Myocarditis, Pericarditis
Vascular disorders	Common	Hypertension
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Pharyngolaryngeal pain
	Not known	Hypersensitivity pneumonitis (including interstitial Pneumonitis, allergic alveolitis, eosinophilic pneumonitis), Bronchospasm
Gastrointestinal disorders	Common	Abdominal distension, Abdominal pain, Colitis, Diarrhoea, Dyspepsia, Vomiting, Flatulence, Nausea
	Uncommon	Pancreatitis, Rectal polyp
Hepatobiliary disorders	Common	Liver Function Test abnormal (e.g., ALT; AST, Bilirubin)
	Not known	Hepatitis, Hepatotoxicity, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Pruritus, Rash
	Uncommon	Acne, Alopecia, Urticaria
	Rare	Photosensitivity
	Not known	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Back pain
	Uncommon	Myalgia
	Not known	Systemic-lupus erythematosus-like syndrome, Lupus-like syndrome
Renal and urinary disorders	Rare	Renal failure

	Not known	Interstitial nephritis, Nephrotic syndrome, Nephrolithiasis

Description of selected adverse reactions

Increased intracranial pressure

Cases of increased intracranial pressure with papilledema (pseudotumor cerebri or benign intracranial hypertension) have been reported with the use of mesalamines. If undetected, this condition may result in restriction of the visual field and may progress to permanent loss of vision. Mesalamine should be discontinued, if this syndrome occurs.

Photosensitivity

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalamine treatment. **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via https://pv.pharmacyboardkenya.org

4.9 Overdose

MESALAMINE DELAYED-RELEASE TABLET 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The mechanism of action of mesalamine is not fully understood. 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. Recent data also suggest that mesalamine can inhibit the activation of NFκB, a nuclear transcription factor that regulates the transcription of many genes for pro-inflammatory proteins.

5.2 Pharmacokinetic properties

Absorption

Gamma-scintigraphy studies have shown that a single dose of mesalamine 1200 mg passed rapidly and intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labelled tracer through the colon, indicating that mesalamine had spread throughout this region of the gastrointestinal tract. Complete disintegration of mesalamine and complete release of mesalamine occurred after approximately 17.4 hours.

The total absorption of mesalamine from 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.

In a single dose study, mesalamine 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 (median) and reached a maximum by 9-12 hours (median) on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects. Mesalamine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was dose proportional between 1.2 g and 4.8 g mesalamine. Maximum plasma concentrations (Cmax) of mesalamine increased approximately dose proportionately between 1.2 g and 2.4 g and less than dose proportional between 2.4 g and 4.8 g mesalamine, with the dose normalised value at 4.8 g representing, on average, 74% of that at 2.4 g based on geometric means. In a single- and multiple dose pharmacokinetic study of mesalamine 2.4 and 4.8 g administered with standard meals in 56 healthy volunteers, plasma concentrations of mesalamine were detectable after 4 hours and were maximal by 8 hours after the single dose. At steady state (achieved generally by 2 days after dosing), 5-ASA accumulation was 1.1- to 1.4- fold for the 2.4 g and 4.8 g dose, respectively, above that expected on the basis of single dose pharmacokinetics.

Administration of a single dose of mesalamine 4.8 g with a high-fat meal resulted in further delay in absorption and mesalamine plasma levels were detectable after approximately 4 hours following dosing. However, a high-fat meal increased systemic exposure of mesalamine (mean Cmax by 91%; mean AUC 16%) compared to results in the fasted state. Mesalamine was administered with food in the Phase 3 trials.

In a single dose pharmacokinetic study of mesalamine, 4.8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young (18-35 years); 28 elderly (65-75 years); 15 elderly (>75 years)). Increased age resulted in increased systemic exposure (up to approximately 2- fold, based on AUC0-t, AUC0-∞ and Cmax) to mesalamine and its metabolite N-acetyl-5- aminosalicylic acid but did not affect the percentage of mesalamine absorbed. 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.

In a Phase 1, multicentre, open-label study (SPD476-112) in paediatric subjects (aged 5 to 17 years) diagnosed with UC, dosing of mesalamine was stratified by weight. Subjects were randomized to 1 of 3 possible treatments: 30, 60, or 100 mg/kg/day. Subjects received a total dose between 900 and 4,800 mg of mesalamine per day for 7 days. Pharmacokinetic steady-state was attained by Day 5 for all doses. On Day 7, systemic 5-ASA exposure, as measured by mean AUCs and Cmax, increased in a dose-proportional manner between 30 and 60 mg/kg/day of mesalamine. Between 60 and 100 mg/kg/day, systemic exposure of mesalamine increased in a sub-proportional manner. The mean percentage of mesalamine absorbed (based on urinary recovery) was similar at 30 and 60mg/kg/day doses, being 29.4% and 27.0%, respectively. These results are similar to the percentage of mesalamine dose absorbed in adults from a previous study (SPD476-105), with values ranging from 17-22% for adult males and 24-32% for adult females. The percentage of mesalamine absorbed was lower at 100 mg/kg/day 5-ASA (22.1%). There was no discernible difference of 5-ASA (and N-Ac-5-ASA) systemic exposure between children (aged 5 through 12 years) and adolescents (aged 13 through 17 years) with this weight-based (i.e., mg/kg) dosing paradigm.

Distribution

Following dosing of mesalamine the distribution profile of mesalamine is presumed to be the same as that of other mesalamine containing products. Mesalamine has a relatively small volume of distribution of approximately 18 L confirming minimal extravascular penetration of systemically available drug. Mesalamine is 43% bound and N-acetyl-5-aminosalicylic 78-83% bound to plasma proteins when in vitro plasma concentrations are up to 2.5 µg/mL and up to 10 µg/mL, respectively.

Biotransformation

The only major metabolite of mesalamine is N-acetyl-5-aminosalicylic acid, which is pharmacologically inactive. Its formation is brought about by Nacetyltransferase-1 (NAT-1) activity in the liver and in the cytosol of intestinal mucosal cells.

Elimination

Elimination of absorbed 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 urine. Of the approximately 21-22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine at steady state after 24 hours, compared with greater than 13% for Nacetyl-5-aminosalicylic acid. 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, 7-9 hours and 8-12 hours, respectively.

In adults, the mean renal clearances (CLR) were 1.8 L/h and 2.9 L/h for single doses of 2.4 g and 4.8 g, respectively, and slightly higher on Day 14 of multiple dosing: 5.5 L/h and 6.4 L/h for 2.4 g/day and 4.8 g/day. Mean renal clearances for the metabolite were higher, at approximately 12-15 L/h following single and multiple doses of mesalamine 2.4 g/day and 4.8 g/day.

In paediatric patients, the mean renal clearance of 5-ASA at steady state ranged from approximately 5.0-6.5 L/h (83-108 mL/min), which

is similar to that observed with adult volunteers. There was a trend for CLR to decrease with increasing dose, and individual CLR estimates were highly variable. The mean CLR of N-Ac-5-ASA ranged from 10.0-16.2 L/h (166-270 mL/min), with a trend to decrease with increasing dose.

Hepatic Impairment

There are no data in patients with hepatic impairment taking mesalamine.

Systemic exposure to mesalamine increased by up to 2-fold in elderly subjects (>65 years, with a mean creatinine clearance of 68–76 mL/min) compared with younger adult subjects (18-35 years, mean creatinine clearance 124 mL/min) after a 4.8g single dose of mesalamine.

Renal impairment

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

Elderly

Pharmacokinetics data have not been investigated in elderly people. The potential impact on the safe use of mesalamine in the elderly population in clinical practice should be considered. Furthermore, in patients with renal impairment, the resultant decrease in the rate of elimination and increased systemic concentration of mesalamine may constitute an increased risk of nephrotoxic adverse reactions. In different clinical studies with mesalamine, mesalamine plasma AUC in females appeared up to 2-fold higher than in males.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a 104-week dietary carcinogenicity study in CD-1 mice, mesalamine 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 MESALAMINE DELAYED-RELEASE TABLET. Furthermore, in a 104-week dietary carcinogenicity study in Wistar rats, mesalamine up to a dose of 800 mg/kg/day was not tumorigenic. This dose is 1.4 times the recommended human dose (based on a body surface area comparison) of MESALAMINE DELAYED-RELEASE TABLET.

No evidence of mutagenicity was observed in an in vitro Ames test or an in vivo mouse micronucleus test. No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalamine 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 mesalamine products during controlled clinical trials.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose Povidone (As PVP k-30)

Crospovidone Purified Talc Magnesium Stearate Colloidal anhydrous silica Purified Water Acetone Iso Propyl Alcohol Polysorbate-80 Colour Red Oxide of Iron Methyl Methacrylate (RGLAX Coat-ECMSL21)

6.2 Incompatibilities
Not applicable

6.3 Shelf-Life
36 Months

6.4 Special Precautions for storage
Stored at a temperature not exceeding 30ºC, in a cool and dark place, protect from direct sunlight.

6.5 Nature and Content of container
3 x 10 pack: 10 tablets packed in Alu-Alu blister and such 3 blisters are packed in single carton along with pack insert.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
GALAXY PHARMACEUTICAL LTD.
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8. Marketing Authorization Number
CTD10471

9. Date of first authorization/renewal of the authorization
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10. Date of revision of the text
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