**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. Name of the medicinal product
MESAMIN OD

## 2. Qualitative and quantitative composition
Each tablet contains 1200mg of Mesalamine.
For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form
A brick red color, elongated shape, biconvex, enteric coated prolonged released tablet.

## 4. Clinical particulars
### 4.1 Therapeutic indications
Mesalamine prolonged release tablets 1200mg is indicated for:
Ulcerative colitis: For the treatment of mild to moderate acute exacerbations. For the maintenance of remission.
Crohn's ileo-colitis: For the maintenance of remission.

### 4.2 Posology and method of administration
Swallow whole with water. Do not break, crush or chew the tablets before swallowing.
ADULTS:
Oral:
Acute disease: Two tablets (2400mg) a day in divided doses, with concomitant corticosteroid therapy where clinically indicated.
Maintenance therapy: One to two tablets once daily or in divided doses.
ELDERLY: The normal adult dosage may be used unless renal function is impaired (see section 4.4).
CHILDREN: There is no dosage recommendation.

### 4.3 Contraindications
A history of sensitivity to salicylates or renal sensitivity to sulfasalazine. Confirmed severe renal impairment (GFR less than 20 ml/min). Hypersensitivity to any of the ingredients. Severe hepatic impairment. Gastric or duodenal ulcer, haemorrhagic tendency. Children under 2 years of age.

### 4.4 Special warnings and precautions for use
Geriatric Use
Use in the elderly should be cautious and subject to patients having normal renal function

Intolerance
Discontinue treatment immediately if acute symptoms of intolerance occur including vomiting, abdominal pain or rash. This medicine contains lactose.

Patients with the rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because of the presence of lactose monohydrate.
Mesalamine inhibits the thiopurine methyl-transferase (TPMT) activity in vitro and may therefore impair the metabolism of azathioprine and 6-mercaptopurine. Standard haematological indices (including the white cell count) should be monitored repeatedly in patients taking azathioprine, especially at the beginning of such combination therapy, whether or not Mesalamine is prescribed.

Renal Disorder
Mesalamine is excreted rapidly by the kidney, mainly as its metabolite, N-acetyl-5-aminosalicylic acid. In rats, large doses of Mesalamine injected intravenously produce tubular and glomerular toxicity. Mesalamin OD should be used with extreme caution in patients with confirmed mild to moderate renal impairment. Patients on Mesalamine should have renal function monitored, (with serum creatinine levels measured) prior to treatment start. Renal function should then be monitored periodically during treatment, for example every 3 months for the first year, then every 6 months for the next 4 years and annually thereafter, based on individual patient history. Physicians should take into account risk factors such as prior and concomitant medications, duration and severity of disease and concurrent illnesses. Treatment with Mesalamine should be discontinued if renal function deteriorates. If dehydration develops, normal electrolyte and fluid balance should be restored as soon as possible.

Blood Dyscrasias
Serious blood dyscrasias (some with fatal outcome) have been reported very rarely with Mesalamine. Hematological investigations including a complete blood count may be performed prior to initiation and whilst on therapy according to the physician's judgement. Such tests should be done immediately if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Treatment should be stopped if there is suspicion or evidence of blood dyscrasia.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with Mesalamine treatment.

Mesalamine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity

**4.5 Interaction with other medicinal products and other forms of interaction**
Mesalamine 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. Mesalamine is recommended to be administered with food.

**4.6 Fertility, pregnancy and lactation**

Pregnancy: Mesalamine is known to cross the placental barrier, but the limited data available on its use in pregnant women do not allow accurate assessment of possible adverse effects. Mesalamine should therefore be used with caution during pregnancy and lactation when the potential benefit outweighs the possible hazards in the opinion of the physician. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Lactation: Low concentrations of Mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human milk. While the clinical significance of this has not been determined, caution should be exercised when Mesalamine is administered to a nursing woman. Hypersensitivity reactions like diarrhoea cannot be excluded. Therefore, if the suckling neonate develops suspected adverse reactions consideration should be given to discontinuation of breast-feeding or discontinuation of treatment of the mother.

Fertility: No effects on fertility have been observed.

**4.7 Effects on ability to drive and use machines**

Not Applicable.

**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 |

| | | |
|---|---|---|
| Reproductive system and breast disorders | Not known | Oligospermia (reversible) |
| General disorders and administration site conditions | Common | Asthenia, Fatigue, Pyrexia |

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 is an amino salicylate, and signs of salicylate toxicity include tinnitus, vertigo, headache, confusion, drowsiness, pulmonary oedema, dehydration as a result of sweating, diarrhea and vomiting, hypoglycaemia, hyperventilation, disruption of electrolyte balance and blood-pH and hyperthermia.

Conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Hypoglycaemia, fluid and electrolyte imbalance should be corrected by the administration of appropriate therapy. Adequate renal function should be maintained.

# 5. Pharmacological properties

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** anti-inflammatory ATC code: A07EC02

**Pharmacodynamic effects**

Mechanism of action: Mesalamine contains Mesalamine, also known as 5-aminosalicylic acid, which has an anti- inflammatory effect through a mechanism that has not yet been fully clarified. Mesalamine has been shown to inhibit LTB4-stimulated migration of intestinal macrophages and thus may reduce intestinal inflammation by restricting migration of macrophages to inflamed areas. The production of pro-inflammatory leukotrienes (LTB4 and 5-HETE) in macrophages of the intestinal wall is inhibited. Mesalamine has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses.

Pharmacodynamic effects: Under trial conditions Mesalamine inhibited the cyclooxygenase and thus, the release of thromboxane B2 and prostaglandin E2, but the clinical meaning of this effect is still unclear. Mesalamine inhibits the formation of platelet activating factor (PAF). Mesalamine is also an antioxidant; it has been shown to decrease formation of reactive oxygen products and to capture free radicals.

## 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 N-

acetyltransferase-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 N-acetyl-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

Effects in nonclinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

## 6. Pharmaceutical particulars

**6.1 List of excipients**
Hydroxy propyl methyl cellulose k-100 BP
Calcium sulfate dihydrate BP
Carmelose sodium BP
Purified water BP
Microcrystalline cellulose BP
Sodium starch glycolate (Type A) BP
Magnesium Stearate BP
Colloidal anhydrous silica BP
Insta coat moist shield HIS
Isopropyl alcohol BP
Dichloromethane BP
Enteric coat material HIS
Red oxide of Iron HIS
Purified Talc BP

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
24 Months.

**6.4 Special precautions for storage**
Do not store above 30˚C. Protect from light.

**6.5 Nature and contents of container**
A brick red color, elongated shape, biconvex, enteric coated prolonged released tablet. Such 10 tablets are packed in ALU-ALU blister. Such 3 ALU-ALU blister is packed in a printed carton along with insert.

**6.6 Special precautions for disposal and other handling**
Not Applicable.

**7. Marketing authorization holder**
**SANJEEVANI BIO-TECH EXIM PVT. LTD.**
**Address:** A-216, Siddhi Vinayak Tower, B/H ACP Office, Off. S.G. Highway, Nr. Kataria Motors, Makarba,Sarkhej, Ahmedabad – 380051, Gujarat, India
**Telephone No.:** +919724309703
**E-mail:** abhinav@sanjeevanibiotech.com
**Website:** www.sanjeevanibiotech.com

**8. Marketing authorization number(s)**
CTD10027

**9. Date of first authorization/renewal of the authorization**

06/04/2023

**10. Date of revision of the text**
13/09/2023

**11. Dosimetry**
Not Applicable

**12. Instructions for Preparation of Radiopharmaceuticals**
Not Applicable