1. **Trade Name and Pharmaceutical Form**

ORAL FORMULATIONS:
- Pentasa® prolonged release Tablets, 500 mg
- Pentasa® prolonged release Tablets, 1000 mg
- Pentasa® Sachet prolonged release granules, 1g and 2g

RECTAL FORMULATIONS:
- Pentasa® Suppositories, 1g
- Pentasa® Rectal suspension (enema), 1g

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Active ingredient: Mesalazine (INN) (5–ASA)
- One Tablet contains: 500 mg mesalazine.
- One Tablet contains: 1000 mg mesalazine.
- One Sachet contains: 1g, 2g mesalazine.
- One Suppository contains: 1g mesalazine
- One Rectal suspension (enema) contains: 1g mesalazine

For full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

ORAL FORMULATIONS:
- Prolonged release tablets 500 mg
- Prolonged release tablets 1 g
- Prolonged release granules 1 g
- Prolonged release granules 2 g

Appearance of PENTASA prolonged release tablets 500 mg: White grey to pale brown, speckled round tablets. Break mark and embossing: 500 mg on one side, PENTASA on the other side.

Appearance of PENTASA prolonged release tablets 1 g: White-grey to pale brown, Speckled, oval tablets. Embossing on both sides: PENTASA.

Appearance of PENTASA Sachet prolonged release granules 1 g and 2 g: White grey to pale white-brown granules.

RECTAL FORMULATIONS:
- Suppositories 1 g
- Rectal suspension 1 g

Appearance of PENTASA suppositories 1 g: White to tan, spotted, oblong suppositories.

Appearance of PENTASA rectal suspension 1 g: White to slightly yellow suspension with a pH value between 4.4 and 5.0.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Tablet 500 mg, 1000 mg, Granules 1 g, 2g
Treatment of mild to moderate ulcerative colitis and Crohn’s disease.

**Suppositories 1g**

Treatment of Ulcerative Proctitis.

**Enema 1 g**

Treatment of Ulcerative Colitis and Crohn’s disease.

### 4.2 Posology and method of administration

#### 4.2.1 Tablets 500 mg, 1000 mg, Granules 1g, 2g:

**Ulcerative Colitis**

**Adults:**

Active treatment: Individual dosage, up to 4 g mesalazine once daily or in two or three divided doses.

Maintenance treatment: Recommended dosage, 2 g mesalazine once daily.

**Crohn’s Disease**

**Adults:**

Active treatment: Individual dosage, up to 4 g mesalazine daily in two or three divided doses.

Maintenance treatment: Individual dosage, up to 4 g mesalazine daily in two or three divided doses.

**Paediatric population**

There is only limited documentation for an effect in children (age 6-18 years)

**Ulcerative colitis**

Treatment of active disease:

**Children 6 years of age and older:** To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance treatment:

**Children 6 years of age and older:** To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

**Crohn’s disease**

Treatment of active disease:

**Children 6 years of age and older:** To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).

Maintenance treatment:

**Children 6 years of age and older:** To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (recommended adult dose).
It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

**Method of Administration**

Pentasa® Tablets or Granules must not be chewed. To facilitate swallowing the tablets may be dispersed in 50ml of cold water. Stir and drink immediately. The contents of the sachet should be emptied onto the tongue and washed down with some water or juice.

**4.2.2 Suppositories 1 g**

1 suppository 1-2 times daily.

**4.2.3 Enema 1g**

1 enema at bedtime

A visit to the toilet is recommended before administration of enemas and suppositories. Instructions for use appear in the Patient Leaflet. Shake the enema container well before use. The enema is protected by an aluminium foil bag and should be used immediately after opening.

**4.3 CONTRAINDICATIONS**

Hypersensitivity to mesalazine, any of the excipients, or salicylates
Severe liver and/or renal impairment

**4.4 Special warnings and precautions for use**

Most patients who are intolerant or hypersensitive to sulphasalazine are able to take Pentasa without risk of similar reactions. However, caution is recommended when treating patients allergic to sulphasalazine (risk of allergy to salicylates). In case of acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

Caution is recommended in patients with impaired liver function. Liver function parameters like ALT or AST should be assessed prior to and during treatment, at the discretion of the treating physician.

The drug is not recommended for use in patients with renal impairment. The renal function should be monitored regularly (e.g. serum creatinine), especially during the initial phase of treatment. Urinary status (dip sticks) should be determined prior to and during treatment at the discretion of the treating physician. Mesalazine induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment. The concurrent use of other known nephrotoxic agents should increase monitoring frequency of renal function.

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment.
Mesalazine induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have been reported rarely. Serious blood dyscrasias have been reported very rarely with mesalazine. Blood test for differential blood count is recommended prior to and during treatment, at the discretion of the treating physician. As stated in the interaction section 4.5, concomitant treatment with mesalazine can increase the risk of blood dyscrasia in patients receiving azathioprine, 6-mercaptopurine or thioguanine.

Treatment should be discontinued on suspicion or evidence of these adverse reactions. As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional symptoms occur, these tests should be performed immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Combination therapy with Pentasa and azathioprine, 6-mercaptopurine or thioguanine, have in several studies shown a higher frequency of myelosuppressive effects, and an interaction seems to exist, however, the mechanism behind the interaction is not fully established. Regular monitoring of white blood cells is recommended and dosage regime of thiopurines should be adjusted accordingly.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

4.6 Fertility, pregnancy and lactation

Pentasa should be used with caution during pregnancy and lactation and only if the potential benefits outweigh the possible hazards in the opinion of the physician.

Mesalazine is known to cross the placental barrier, and its concentration in umbilical cord plasma is one tenth of the concentration in maternal plasma. The metabolite acetyl-mesalazine is found in the same concentration in umbilical cord and maternal plasma. From several observational studies no teratogenic effects are reported and there is no evidence of significant risk of use in humans. Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Blood disorders (pancytopenia, leucopenia, thrombocytopenia, anaemia) have been reported in new-borns of mothers being treated with Pentasa.

In one single case after long-term use of a high dose of mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.

Mesalazine is excreted in breast milk. The mesalazine concentration in breast milk is lower than in maternal blood, whereas the metabolite, acetyl-mesalazine appears in similar or increased concentrations. There is limited experience of the use of oral mesalazine in lactating women. No controlled studies with Pentasa during breast-feeding have been carried out. Hypersensitivity reactions like diarrhoea in the infant can not be excluded. If the infant develops diarrhoea, breast-feeding should be discontinued.
Animal data on mesalazine show no effect on male and female fertility. Oligospermia (reversible) has been reported after use of mesalazine, see section 4.8.

4.7 Effects on ability to drive and use machines
No adverse effects.

4.8 Undesirable effects
The most frequent adverse reactions seen in clinical trials are diarrhoea, nausea, abdominal pain, headache, vomiting and rash. Hypersensitivity reactions and drug fever may occasionally occur. Following rectal administration local reactions such as pruritis, rectal discomfort and urge may occur.

Frequency of adverse effects, based on clinical trials and reports from post-marketing surveillance

<table>
<thead>
<tr>
<th>SOC</th>
<th>Common &gt;1/100 to &lt; 1/10</th>
<th>Rare &gt;1/10,000 to &lt;1/1,000</th>
<th>Very rare &lt;1/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td></td>
<td>Eosinophilia (as part of an allergic reaction), altered blood counts (anaemia, aplastic anaemia, leucopenia (incl. granulocytopenia and neutropenia)), Thrombocytopenia, Agranulocytosis, Pancytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Pancolitis, Hypersensitivity reactions such as allergic exanthema</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>dizziness</td>
<td>Peripheral neuropathy Benign intracranial hypertension in adolescents</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Allergic and fibrotic lung reactions (incl. dyspnoea, coughing, bronchospasm, allergic alveolitis, pulmonary eosinophilia, interstitial lung disease, pulmonary infiltration, pneumonitis)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea, Abdominal pain, Nausea, Vomiting</td>
<td>Increased amylase, acute pancreatitis*, flatulence</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
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<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>Increased liver enzymes, cholestatic parameters and bilirubin, Hepatotoxicity (incl. hepatitis*, cholestatic hepatitis, cirrhosis, hepatic failure)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash (incl. urticaria, erythematous rash)</td>
<td>Alopecia (Reversible) Quincke's oedema</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal connective tissue and bone disorders</td>
<td>Myalgia, Arthralgia Lupus erythematosus-like reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal function impairment (incl. acute and chronic interstitial nephritis*, nephrotic syndrome, renal insufficiency), Urine discolouration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system disorders</td>
<td>Oligospermia (reversible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Drug fever</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The mechanism of mesalazine induced myocarditis, pericarditis, pancreatitis, nephritis and hepatitis is unknown, but it might be of allergic origin.

It is important to note that several of these disorders can also be attributed to be the inflammatory bowel disease itself.

**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 to the Ministry of Health according to the National Regulation by using an online
form
(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

Acute experience in animals:
Single oral doses of mesalazine of up to 5g/kg in pigs or a single intravenous dose of mesalazine at 920mg/kg in rats were not lethal.

Human experience:
There is limited clinical experience with overdose of Pentasa which does not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive. There have been reports of patients taking daily doses of 8 grams for a month without any adverse events.

Management of overdose in man:
Symptomatic treatment at hospital. Close monitoring of renal function. Intravenous infusion of electrolytes may be used to promote diuresis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agents.
ATC Code: A07 EC02

Mechanism of action and pharmacodynamic effects:
Mesalazine is recognised as the active moiety of sulphasalazine in the treatment of ulcerative colitis. It is thought to act locally on the gut wall in inflammatory bowel disease, although its precise mechanism of action has not been fully elucidated.

Increased leucocyte migration, abnormal cytokine production, increased production of arachidonic acid metabolites, particularly leukotriene B4 and increased free radical formation in the inflamed intestinal tissue are all present in patients with inflammatory bowel disease. Mesalazine has in-vitro and in-vivo pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leukotriene production and scavenge for free radicals. It is currently unknown which, if any of these mechanisms play a predominant role in the clinical efficacy of mesalazine.

The risk of colorectal cancer (CRC) is slightly increased in ulcerative colitis. Observed effects of mesalazine in experimental models and patient biopsies support the role of mesalazine in prevention of colitis-associated CRC, with down regulation of both inflammation dependent and non-inflammation dependent signalling pathways involved in the development of colitis-associated CRC. However data from meta-analyses, including both referral and non-referral populations, provide inconsistent clinical information regarding the benefit of mesalazine in the carcinogenesis risk associated with ulcerative colitis.
5.2 Pharmacokinetic Properties

General characteristics of the active substance:

**Disposition and local availability:**
Pentasa tablets consist of ethylcellulose-coated microgranules of mesalazine. Following administration and tablet disintegration the microgranules act as discrete slow-release formulations which allow a continuous release of drug from duodenum to rectum at all enteral pH conditions. The microgranules enter the duodenum within an hour of administration, independent of food co-administration. In healthy volunteers the average small intestinal transit time is approximately 3-4 hours.

**Biotransformation:** Mesalazine is metabolised both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl mesalazine (acetyl mesalazine). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Acetyl mesalazine is thought to be clinically as well as toxicologically inactive, although this remains to be confirmed.

**Absorption:** Based on urinary recovery data in healthy volunteers, 30-50% of the ingested dose is absorbed following oral administration, predominantly from the small intestine. Mesalazine is detectable in plasma approximately 15 minutes following administration. Maximum plasma concentrations are seen 1-4 hours post-dose. After a gradual decrease, mesalazine will no longer be detectable 12 hours post-dose. The plasma concentration curve for acetyl mesalazine follows the same pattern, but the concentrations are generally higher and the elimination is slower.

The metabolic ratio of acetyl mesalazine to mesalazine in plasma after oral administration ranges from 3.5 to 1.3 after daily doses of 500mg x 3 and 2g x 3 respectively, implying a dose-dependent acetylation which may be subject to saturation.

Mean steady-state plasma concentrations of mesalazine are approximately 2 micromoles/l, 8 micromoles/l and 12 micromoles/l after daily doses of 1.5g, 4g and 6g respectively. For acetyl mesalazine the corresponding concentrations are 6 micromoles/l 13 micromoles/l and 16 micromoles/l respectively.

The transit and release of mesalazine after oral administration are independent of food co-administration, whereas the systemic absorption is reduced.

**Distribution:** Mesalazine and acetyl mesalazine do not cross the blood-brain barrier. Protein binding of mesalazine is approximately 50% and of acetyl mesalazine about 80%.

**Elimination:** The plasma half-life of pure mesalazine is approximately 40 minutes and for acetyl mesalazine approximately 70 minutes. Due to continuous release of mesalazine from Pentasa throughout the gastrointestinal tract, the elimination half-life
cannot be determined after oral administration. However, steady-state is reached after a treatment period of 5 days following oral administration. Both substances are excreted in urine and faeces. The urinary excretion consists mainly of acetyl mesalazine.

Characteristics in patients:
The delivery of mesalazine to its site of action after oral administration is only slightly affected by pathophysiological changes such as diarrhoea and increased bowel activity observed during active inflammatory bowel disease. A reduction in systemic absorption to 20 – 25% of the daily dose has been observed in patients with accelerated intestinal transit. A corresponding increase in faecal excretion has been seen.

In patients with impaired liver and kidney functions, the resultant decrease in the rate of elimination and increased systemic concentration of mesalazine may constitute an increased risk of nephrotoxic adverse reactions.

5.3 Preclinical Safety Data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of excipients

Tablets 500 mg & 1000mg
Magnesium stearate, talc, ethylcellulose, povidone, microcrystalline cellulose.
Granules 1g, 2g
Ethylcellulose, Povidone.
Suppositories 1g
Magnesium stearate, talc, povidone, macrogol 6000
Enema 1g
Disodium edetate dihydrate, sodium metabisulphite, sodium acetate trihydrate, purified water, concentrated hydrochloric acid ad pH 4.8.

Incompatibilities
None known

6.2 Shelf Life
Tablets 500 mg, 1000 mg
3 years
Granules 1g, 2g
2 years
Suppositories 1g
3 years
Enema 1g
3 years

6.3 **Storage Conditions**
Store below 25°C in the original package, Protect from light.
Enema 1g: do not freeze.

6.4 **Nature and Contents of Container**
Tablets 500 mg, 1000 mg
Double aluminium foil blisters, each containing 10 tablets.
Granules 1g, 2g
Individually packed sachets of aluminium foil
Suppositories 1g
Aluminium foil.
Enema 1g
Polyethylene bottles with a tip with a valve for rectal application. The bottles are supplied in nitrogen-filled aluminium foil bags.

6.5 **Instructions for use/handling**
*No special requirements.*

6.6 **Legal Category**
Prescription only.

6.7 **License Number**
Tablets 500 mg: 064 73 26905 00
Tablets 1000 mg: 147-06-33401-00
Granules 1g: 114 57 29591 00
Granules 2g: 138 91 31560 00
6.8 **Manufacturer**

Tablets 500mg, 1000mg and Granules 1g, 2g: Ferring, St-Prex, Switzerland
Suppositories and Enema: Ferring GmbH, Germany

6.9 **Importer**

A. Lapidot Pharmaceuticals Ltd
8, Hashita Street, Industrial Park Caesarea 38900
ISRAEL

6.10 **License Holder**

Ferring Pharmaceuticals Ltd
8, Hashita Street, Industrial Park Caesarea 38900
ISRAEL

6.11 **Date of revision of the text**

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in November 2014.