SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mezavant XL 1200 mg, gastro-resistant, prolonged-release tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1200 mg mesalazine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant, prolonged-release tablets.

Red-brown, ellipsoidal, film-coated tablet (dimensions 20.5 × 9.5 × 7.5 mm), debossed on one side with S476.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults, including the elderly (>65 years)
For the induction and maintenance of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis.

Children and adolescents (weighing more than 50 kg and age 10 years or older)
For the induction and maintenance of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis.

4.2 Posology and method of administration

Mezavant XL is intended for once daily, oral administration. The tablets must not be crushed or chewed and should be taken with food.

Adults, including the elderly (>65 years)
For induction of remission: 2.4 g to 4.8 g (two to four tablets) should be taken once daily. The highest dose of 4.8 g/day is recommended for patients not responding to lower doses of mesalazine. When using the highest dose (4.8 g/day), the effect of the treatment should be evaluated at 8 weeks.

For maintenance of remission: 2.4 g (two tablets) should be taken once daily.

Children and adolescents (weighing more than 50 kg and age 10 years or older)
For induction of remission (initial 8 weeks): 2.4 g to 4.8 g (two to four tablets) should be taken once daily.

For maintenance of remission: 2.4 g (two tablets) should be taken once daily.

Mesalazine 1200-mg tablets should not be used by paediatric patients weighing 50 kg or less and should not be used in paediatric patients below the age of 10 years due to a lack of data on safety and efficacy in these patients.

Hepatic and renal impairment
Specific studies have not been performed to investigate mesalazine in patients with hepatic or renal impairment (see sections 4.3 and 4.4).

4.3 Contraindications

History of hypersensitivity to salicylates (including mesalazine) or any of the excipients listed in section 6.1.

Severe renal impairment (GFR < 30 mL/min/1.73 m^2) and/or severe hepatic impairment.

4.4 Special warnings and precautions for use

Reports of renal impairment, including minimal change nephropathy, acute/chronic interstitial nephritis and renal failure have been associated with preparations containing mesalazine and pro-drugs of mesalazine. Mezavant XL should be used with caution in patients with confirmed mild to moderate renal impairment. It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and at least twice a year, while on treatment, based on clinical judgement taking baseline renal function into account. **Mesalazine treatment should be discontinued if renal function deteriorates.**

Patients with chronic lung function impairment, especially asthma, are at risk of hypersensitivity reactions and should be closely monitored.

Following mesalazine treatment, serious blood dyscrasias have been reported rarely. If the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat, haematological investigations should be performed. If there is suspicion of blood dyscrasia, treatment should be terminated (see sections 4.5 and 4.8).

Mesalazine induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely with Mezavant XL and with other mesalazine containing preparations. Caution should be used in prescribing this medication to patients with conditions predisposing to the development of myo- or pericarditis. If such hypersensitivity reaction is suspected, products containing mesalazine must not be reintroduced.

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. Mesalazine 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.

Mesalazine 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 mesalazine or sulphasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required and products containing mesalazine must not be reintroduced.

There have been reports of increased liver enzyme levels in patients taking preparations containing mesalazine. Caution is recommended if mesalazine is administered to patients with hepatic impairment.

Caution should be exercised when treating patients allergic to sulphasalazine due to the potential risk of cross sensitivity reactions between sulphasalazine and mesalazine.

Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of the product.

Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

This medicine contains less than 1 mmol sodium (23 mg) per the maximum recommended dose (4 tablets), that is to say essentially 'sodium-free'.

Interference with laboratory tests
Use of mesalazine may lead to falsely 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-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g. in toilets cleaned with sodium hypochlorite contained in certain bleaches).

4.5 Interaction with other medicinal products and other forms of interaction

Drug-drug interaction studies in healthy adult subjects have been conducted with Mezavant XL to investigate any effect of mesalazine on the pharmacokinetics and safety of three commonly used antibiotics. There were no clinically significant interactions of mesalazine with amoxicillin, metronidazole or sulfamethoxazole.

However, the following drug-drug interactions have been reported for products containing mesalazine.

- Caution is recommended for the concomitant use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine as these may increase the risk of renal adverse reactions.

- Mesalazine 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 mesalazine as this can increase the potential for blood dyscrasias, bone marrow failure, and associated complications (see sections 4.4 and 4.8).

- 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.

Mezavant XL is recommended to be administered with food (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited experience with mesalazine in pregnancy. Mesalazine crosses the placental barrier, but provides foetal concentrations much lower than those seen with adult therapeutic use. Animal studies do not indicate harmful effects of mesalazine in pregnancy, embryonal/foetal development, parturition or postnatal development. Adverse outcomes (including disturbances in blood counts such as leukopenia, thrombocytopenia, and anaemia) were reported in infants born to mothers who were exposed to mesalazine during pregnancy. Mesalazine should be used during pregnancy only when the benefits outweigh the risks. Caution should be exercised when using high doses of mesalazine.

Breastfeeding
Mesalazine is excreted in breast milk at low concentration. Acetylated form of mesalazine is excreted in breast milk at higher concentration. Caution should be exercised if using Mesalazine while

breastfeeding and only if the benefit outweighs the risks. Sporadically acute diarrhoea has been reported in breast fed infants.

Fertility
Data on mesalazine show no sustained effect on male fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Mesalazine is considered to have negligible influence on these abilities.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) within the pooled safety analysis of clinical studies with Mezavant XL, including 3,611 patients, 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).

Adverse drug reactions (ADRs) associated with Mezavant XL		
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
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)*, drug reaction with eosinophilia and systemic symptoms (DRESS)
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*

*See section 4.4.

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), including Drug reaction with eosinophilia and systemic symptoms (DRESS), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

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 the national reporting system:

Malta

ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Mezavant XL is an aminosalicylate, and signs of salicylate toxicity include tinnitus, vertigo, headache, confusion, drowsiness, pulmonary oedema, dehydration as a result of sweating, diarrhoea 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: Aminosalicylic acid and similar agents

ATC code: A07E C02

Mechanism of action
Mesalazine is an aminosalicylate. The mechanism of action of mesalazine is not fully understood, but appears to have a topical anti-inflammatory effect on the colonic epithelial cells. 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 mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. Mesalazine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key proinflammatory cytokines. More recently, it has been proposed that impairment of PPAR-γ nuclear receptors, (γ-form of the peroxisome proliferator-activated receptors) may be implicated in ulcerative colitis. PPAR-γ receptor agonists have shown efficacy in ulcerative colitis and evidence has been accumulating that the mechanism of action of mesalazine may be mediated by PPAR-γ receptors.

Pharmacodynamic effects
The Mezavant XL tablet contains a core of mesalazine (5-aminosalicylic acid) 1.2 g formulated in a multi-matrix system. This system is coated with methacrylic acid – methyl methacrylate copolymer (1:1) and methacrylic acid–methyl methacrylate copolymer (1:2), which are designed to delay release of mesalazine until exposure to approximately pH 7.

Clinical efficacy and safety
Mezavant XL was investigated in two similarly designed, Phase 3, placebo-controlled studies (SPD476-301 and SPD476-302) in 623 randomised patients with mild to moderate, active ulcerative colitis. Mezavant XL 2.4 g/day and 4.8 g/day administered with food achieved statistical superiority over placebo in terms of the number of patients achieving remission from ulcerative colitis after 8 weeks treatment. Using the Ulcerative Colitis Disease Activity Index (UC-DAI), remission was defined as a UC-DAI score of ≤1 with a score of 0 for rectal bleeding and stool frequency and at least a 1-point reduction in sigmoidoscopy score from baseline. Study SPD476-302, included a comparator,

mesalazine pH 7-dependent modified release 2.4 g/day (0.8 g administered in 3 divided doses), as an internal reference arm. On the primary variable of remission, the following results were achieved:

Study SPD476-301 (n=262[#])				
	Placebo	Mezavant XL 2.4 g/day in two divided doses	Mezavant XL 4.8 g/day once daily	
% patients in remission	12.9	34.1*	29.2*	
Study SPD476-302 (n=341[#])				
	Placebo	Mezavant XL 2.4 g/day once daily	Mezavant XL 4.8 g/day once daily	Mesalazine pH 7-dependent modified release 2.4 g/day in three divided doses
% patients in remission	22.1	40.5*	41.2*	32.6[NS]

[#]Based on the ITT Population; * Statistically different from placebo ($p < 0.025$); [NS] Not significant ($p > 0.05$)

A Phase 3, multicentre, randomized, double-blind, parallel-group study was conducted in 107 paediatric patients aged 5 to 17 years (inclusive) with mild to moderate ulcerative colitis to evaluate the safety and efficacy of Mezavant XL in both double-blind acute (Double-Blind Acute, DBA) and double-blind maintenance (Double-Blind Maintenance, DBM) phases. Subjects received a low or a high weight-based dose of mesalazine in four weight groups: 18 kg to ≤23 kg (n=3), >23 kg to ≤ 35 kg (n=9), > 35 kg to ≤ 50 kg (n=29), and > 50 kg to ≤ 90 kg (n=66). The low dose ranged from 900 mg/day to 2,400 mg/day and the high dose ranged from 1,800 mg/day to 4,800 mg/day. Clinical effects of 1200 mg mesalazine tablets were evaluated in 66 subjects > 50 kg to ≤ 90 kg in the age range 10 to 17 years.

Primary endpoint of the double-blind treatment phases was defined in terms of clinical response. Clinical response was defined as a partial Ulcerative Colitis Disease Activity Index (UC-DAI) score of ≤1 with a score of 0 for rectal bleeding and ≤1 for stool frequency and physician's global assessment = 0.

After 8 weeks of treatment in the DBA phase, 37.0% of subjects achieved a clinical response in the low-dose arm compared to 65.4% of subjects in the high-dose arm. The response rates at Week 8 in these dose arms were 50.0% and 56.3% respectively in subjects weighing >50 kg to ≤ 90 kg who received 1200 mg mesalazine tablets. In the DBM phase, after 26 weeks of treatment, 54.8% of subjects maintained a clinical response in the low-dose arm compared to 53.3% in the high-dose arm. The response rate at Week 26 was 50% in both dose arms in subjects weighing >50 kg to ≤ 90 kg who received 1200 mg mesalazine tablets. The study was not powered to assess differences between the low dose and high dose.

5.2 Pharmacokinetic properties

The mechanism of action of mesalazine (5-ASA) is not fully understood but appears to be topical, and therefore the clinical efficacy of mesalazine does not correlate with the pharmacokinetic profile. A

major pathway of clearance of mesalazine is via metabolism to N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), which is pharmacologically inactive.

Absorption

Gamma-scintigraphy studies have shown that a single dose of mesalazine 1.2 g 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 mesalazine had spread throughout this region of the gastrointestinal tract. Complete disintegration of mesalazine and complete release of mesalazine occurred after approximately 17.4 hours.

The total absorption of mesalazine from mesalazine 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, mesalazine 1.2 g, 2.4 g, and 4.8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalazine 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. Mesalazine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was dose proportional between 1.2 g and 4.8 g mesalazine. Maximum plasma concentrations (C_{max}) of mesalazine 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 mesalazine, 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 mesalazine 2.4 and 4.8 g administered with standard meals in 56 healthy volunteers, plasma concentrations of mesalazine 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 mesalazine 4.8 g with a high-fat meal resulted in further delay in absorption and mesalazine plasma levels were detectable after approximately 4 hours following dosing. However, a high-fat meal increased systemic exposure of mesalazine (mean C_{max} by 91%; mean AUC 16%) compared to results in the fasted state. Mesalazine was administered with food in the Phase 3 trials.

In a single-dose pharmacokinetic study of mesalazine, 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 AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) to mesalazine and its metabolite N-acetyl-5-aminosalicylic acid but did not affect the percentage of mesalazine absorbed. Increased age resulted in a slower apparent elimination of mesalazine, 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 mesalazine 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 mesalazine 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 AUC_{ss} and $C_{max,ss}$, increased in a dose-proportional manner between 30 and 60 mg/kg/day of mesalazine. Between 60 and 100 mg/kg/day, systemic exposure of mesalazine increased in a sub-proportional manner. The mean percentage of mesalazine 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 mesalazine 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 mesalazine 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 mesalazine the distribution profile of mesalazine is presumed to be the same as that of other mesalazine containing products. Mesalazine has a relatively small volume of distribution of approximately 18 L confirming minimal extravascular penetration of systemically available drug. Mesalazine 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 mesalazine 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 mesalazine 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 mesalazine and its major metabolite after administration of mesalazine 2.4 g and 4.8 g were, on average, 7-9 hours and 8-12 hours, respectively.

In adults, the mean renal clearances (CL_R) 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 mesalazine 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 CL_R to decrease with increasing dose, and individual CL_R estimates were highly variable. The mean CL_R 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 mesalazine. Systemic exposure to mesalazine 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 4.8-g single dose of mesalazine.

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 mesalazine 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 mesalazine may constitute an increased risk of nephrotoxic adverse reactions (see section 4.4).

In different clinical studies with mesalazine, mesalazine plasma AUC in females appeared up to 2-fold higher than in males.

Based on limited pharmacokinetic data, 5-ASA and N-Ac-5-ASA pharmacokinetics appear comparable between Caucasian and Hispanic subjects.

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

Tablet core
Carmellose sodium
Carnauba wax
Stearic acid
Silica, colloidal hydrated
Sodium starch glycolate (Type A)
Talc
Magnesium stearate

Film-coating
Talc
Methacrylic acid – methyl methacrylate copolymer (1:1)
Methacrylic acid – methyl methacrylate copolymer (1:2)
Triethylcitrate
Titanium dioxide (E171)
Red ferric oxide (E172)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Tablets are packed in polyamide/aluminium/PVC foil blister packs with aluminium push-through foil.

Packs contain 60 or 120 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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19th August 2011/19th December 2012

10. DATE OF REVISION OF THE TEXT

03/2023