SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Mezavant XL1200 mg, gastro-resistant, prolonged release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1200 mg mesalazine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant, prolonged release tablets.
Red-brown, ellipsoidal, film-coated tablet, debossed on one side with S476.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the induction of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis. For maintenance of remission.

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 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
Mezavant XL is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

Specific studies have not been performed to investigate Mezavant XL 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 of Mezavant XL.
Severe renal impairment (GFR <30 ml/min/1.73m^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 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 judgment taking baseline renal function into account. 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).

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

Mesalazine induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely with Mezavant and with other mesalazine containing preparations. Use caution 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.

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 Mezavant 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.

Patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema have reported severe photosensitivity reactions.

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-acetylaminosalicylic acid (N-Ac-5-ASA). Consider an alternative, selective assay for normetanephrine.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with a 100% mesalazine content. Ensure adequate fluid intake during treatment.

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 to investigate any effect of Mezavant on the pharmacokinetics and safety of three commonly used antibiotics. There were no clinically significant interactions of Mezavant 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 nonsteroidal 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 drugs 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 is recommended to be administered with food (see sections 4.2 and 5.2).

4.6 Pregnancy, Lactation and Fertility

<u>Pregnancy</u>

There are no adequate and well-controlled studies of mesalazine in pregnant women.
Mesalazine is known to cross the placental barrier.

Congenital malformations and other adverse outcomes (including one event of hydrops fetalis and fetal anaemia in one infant) were reported in infants born to mothers who were exposed to mesalazine during pregnancy. Mezavant should be only used during pregnancy if the benefits outweigh the risks.

<u>Breast-feeding</u>

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 breast-feeding 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. Mezavant 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, 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%.
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		
System/Organ Class	**Incidence Category**	**Adverse drug reaction**
Blood and lymphatic system disorder	Uncommon	Thrombocytopenia*
	Rare	Agranulocytosis*
	Not known	Aplastic anaemia*, Leukopenia*, Neutropenia*, Pancytopenia*
Immune system disorders	Rare	Face oedema
	Not known	Hypersensitivity*, Anaphylactic shock, Angioedema, Stevens-Johnson syndrome (SJS), Drug reaction with eosinophilia and systemic symptoms (DRESS), Toxic epidermal necrolysis (TEN)
Nervous system disorders	Common	Headache*
	Uncommon	Dizziness, Somnolence, Tremor
	Not known	Neuropathy *Intracranial pressure increased
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	Interstitial lung disease Hypersensitivity pneumonitis

		(including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis) Bronchospasm, Pleurisy
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, Cholelithiasis, Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Pruritus, Rash*
	Uncommon	Acne, Alopecia, Urticaria
	Not known	Photosensitivity
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Back pain
	Uncommon	Myalgia
	Not known	Lupus-like syndrome
Renal and urinary disorders	Uncommon	Nephrolithiasis
	Rare	Renal failure*
	Not known	Interstitial nephritis*, Nephrotic syndrome*, Nephrogenic diabetes insipidus, Chromaturia (urine discoloration caused by contact with surfaces treated with hypochlorite containing bleach and Mesalamine products, including its inactive metabolite).
Reproductive system and breast disorders	Not known	Oligospermia (reversible)
General disorders and administration site conditions	Common	Asthenia, Fatigue, Pyrexia*

*See section 4.4.

Descriptions of Selected Adverse Reactions:

Intracranial pressure increased:

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

Nephrogenic diabetes insipidus:

Cases of nephrogenic diabetes insipidus have been reported with mesalamine use.

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.

4.9 Overdose
Mezavant 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. Correct hypoglycaemia, fluid and electrolyte imbalance by the administration of appropriate therapy. Maintain adequate renal function.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Aminosalicyclic 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 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 was investigated in two similarly designed, Phase3, placebo controlled studies (SPD476-301 and SPD476-302) in 623 randomised patients with mild to moderate, active Ulcerative Colitis. Mezavant 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 2.4 g/day in two divided doses	Mezavant 4.8 g/day once daily	
% patients in remission	12.9	34.1*	29.2*	
Study SPD476-302 (n=341[#])				
	Placebo	Mezavant 2.4 g/day once daily	Mezavant 4.8 g/day once daily	Mesalazine pH 7-dependent modified release 2.4 g/day in three divided
% 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 ($p>0.05$)

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 Mezavant does not correlate with the pharmacokinetic profile. A major pathway of clearance of mesalazine is via metabolism to N- acetyl-5-aminosalicylic acid (Ac-5-ASA), which is pharmacologically inactive.

Absorption:

Gamma-scintigraphy studies have shown that a single dose of Mezavant 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 Mezavant and complete release of mesalazine occurred after approximately 17.4 hours.

The total absorption of mesalazine from Mezavant 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, Mezavant 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 Mezavant. 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 Mezavant, 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 Mezavant 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 Mezavant 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. Mezavant was administered with food in the Phase 3 trials.

In a single dose pharmacokinetic study of Mezavant, 4.8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young (18-35 yrs); 28 elderly (65-75 yrs); 15 elderly (>75 yrs)). 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.

Distribution:
Following dosing of Mezavant 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 Mezavant 2.4 g and 4.8 g were, on average, 7-9 hours and 8-12 hours, respectively.

Hepatic Impairment
There are no data in patients with hepatic impairment taking Mezavant. 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 Mezavant.

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

Elderly
The potential impact on the safe use of Mezavant 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 Mezavant, mesalazine plasma AUC in females appeared up to 2-fold higher than in males.
Based on limited pharmacokinetic data, 5-ASA and Ac-5-ASA pharmacokinetics appear comparable between Caucasian and Hispanic subjects.
Pharmacokinetics data have not been investigated in elderly people.

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 Special precautions for storage
Store at or below 30°C
Store in the original package in order to protect from moisture

6.4 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.

6.5 Special precautions for disposal
No special requirements.

7 MANUFACTURER
Cosmo SpA
Lainate-Milan, Italy

8 DATE OF REVISION OF THE TEXT
March 2023