SUMMARY OF PRODUCT CHARACTERISTICS

MELANEZ 1 G

Mesalazine Suppositories BP 1 g

1. Name of the medicinal product

Melanez 1G (Mesalazine Suppositories BP 1g)

2. Qualitative and quantitative composition

Each Suppository contains:

Mesalazine Ph. Eur. ……1 g

Excipients…… …q.s

For detail list of excipients refer Section 6.1

3. Pharmaceutical form

Suppositories

Off white to light brown opaque bullet shaped suppository

4. Clinical particulars

4.1 Therapeutic indications

Treatment of acute mild to moderate ulcerative colitis that is limited to the rectum (ulcerative proctitis).the maintenance of remission of Crohn's ileo-colitis

4.2 Posology and method of administration

Posology

Adults and older people:

One Melanez 1g Suppository once daily (equivalent to 1g mesalazine daily) inserted into the rectum.

Paediatric population

There is little experience and only limited documentation for an effect in children.

Method of administration:

For rectal administration only.

Melanez 1g Suppositories should be administered preferably at bedtime.

Treatment with Melanez 1g Suppositories must be administered regularly and consistently, because only in this way can healing be successfully achieved.

Duration of treatment

The duration of use is determined by the physician.

4.3 Contraindications

Melanez 1g Suppositories are contraindicated in patients with:

- known hypersensitivity to salicylates or to the excipient listed in section 6.1
- Severe impairment of hepatic or renal function

4.4 Special warnings and precautions for use

Blood tests (differential blood count; liver function parameters such as ALT or AST; serum creatinine) and urinary status (dip-sticks) should be determined prior to and during treatment, at the discretion of the treating physician. 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 3 months. If additional symptoms occur, these tests should be performed immediately. Caution is recommended in patients with impaired hepatic function.

Melanez 1g Suppositories should not be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment.

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

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with Melanez 1g Suppositories.

Patients with a history of adverse drug reactions to preparations containing sulphasalazine should be kept under close medical surveillance on commencement of a course of treatment with Melanez 1g Suppositories. Should Melanez 1g Suppositories cause acute intolerance reactions such as abdominal cramps, acute abdominal pain, fever, severe headache and rash, therapy should be discontinued immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Specific interaction studies have not been performed. In patients, who are concomitantly treated with azathioprine, 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, 6- mercaptopurine or thioguanine should be taken

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of Melanez 1g Suppositories in pregnant women. However, data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the foetus/newborn child. To date no other relevant epidemiologic data are available.

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.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Melanez 1g Suppositories should only be used during pregnancy if the potential benefit outweighs the possible risk.

Breastfeeding

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. Only limited experience during lactation in women is available to date.

Hypersensitivity reactions such as diarrhoea in the infant cannot be excluded. Therefore, Melanez 1g Suppositories should only be used during breastfeeding if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

Melanez 1g Suppositories have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most commonly reported ADRs were headache, in approximately 0.8%, and gastrointestinal side effects (constipation in approximately 0.8%; nausea, vomiting and abdominal pain in 0.4% each).

The following side effects have been reported with the use of mesalazine:

Organ Class System	***Frequency According to MedDRA Convention***		
	rare ***(≥ 1/10,000; <1/1,000)***	***very rare*** ***(< 1/ 10,000)***	***not known***

			(cannot be estimated from the available data)
Blood and lymphatic system disorders		Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)	Blood and lymphatic system disorders
Nervous system disorders	Headache, dizziness	peripheral neuropathy	
Cardiac disorders	Myocarditis, pericarditis		
Respiratory, thoracic and mediastinal disorders		Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis)	
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation	Acute pancreatitis	
	Renal and urinary disorders	Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency	Nephrolithiasis*
Skin and subcutaneous tissue disorders	Photosensitivity	Alopecia	
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia	
immune system disorders		Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Hepatobiliary disorders		Changes in liver function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis	
Reproductive system disorders		Oligospermia (reversible)	

Photosensitivity

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

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:

There are rare data on overdosage (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminosalicylic acid and similar agents

ATC code: A07EC02

The mechanism of the anti-inflammatory action is unknown. The results of in vitro studies indicate that inhibition of lipoxygenase may play a role. Effects on prostaglandin concentrations in the intestinal mucosa have also been demonstrated. Mesalazine (5-Aminosalicylic acid / 5-ASA) may also function as a radical scavenger of reactive oxygen compounds. On reaching the intestinal lumen, rectally administered mesalazine has largely local effects on the intestinal mucosa and submucosal tissue.

Clinical efficacy and safety of Melanez 1 g suppositories was evaluated in a multicentre phase III study, which included 403 patients with endoscopically and histologically confirmed mild to moderately active ulcerative proctitis. The mean disease activity index (DAI) at base line was 6.2 ± 1.5 (range: 3 – 10). Patients were randomised to treatment with one Melanez 1 g suppository (1 g OD group) or 3 suppositories containing 0.5 g mesalazine (0.5 g TID group per day for 6 weeks. The primary efficacy variable was clinical remission defined as DAI < 4 at the final visit or withdrawal. At the final per protocol analysis, 87.9% of the patients in the 1 g OD group and 90.7% of the 0.5 g TID group were in clinical remission (Intention-to-treat analysis: 1 g OD group: 84.0%; 0.5 g TID group: 84.7%). The mean change in DAI from baseline was -4.7 in both treatment groups. No drug-related serious AEs occurred.

5.2 Pharmacokinetic properties

General considerations of mesalazine:

Absorption:

Mesalazine absorption is highest in proximal gut regions and lowest in distal gut areas.

Biotransformation:

Mesalazine is metabolised both pre-systemically by the intestinal mucosa and in the liver to the pharmacologically inactive N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA). The acetylation seems to be independent of the acetylator phenotype of the patient. Some acetylation also occurs through the action of colonic bacteria. Protein binding of mesalazine and N-Ac-5-ASA is 43% and 78%, respectively.

Elimination:

Mesalazine and its metabolite N-Ac-5-ASA are eliminated via the faeces (major part), renally (varies between 20 and 50 %, dependent on kind of application, pharmaceutical preparation and route of mesalazine release, respectively), and biliary (minor part). Renal excretion predominantly occurs as N-Ac-5-ASA. About 1 % of total orally administered mesalazine dose is excreted into the breast milk mainly as N-Ac-5-ASA.

Melanez 1g suppositories specific:

Distribution:

Scintigraphic studies with a similar medicinal product, technetium-labelled mesalazine 500mg suppositories showed peak spread of the suppository that had melted due to body temperature after 2 – 3 hours. The spread was limited primarily to the rectum and rectosigmoid junction. It is assumed that Melanez 1g suppositories act very similar and thus are particularly suitable for treating proctitis (ulcerative colitis of the rectum).

Absorption:

In healthy subjects mean peak plasma concentrations of 5-ASA after a single rectal dose of 1g mesalazine (Melanez 1 g Suppository) were 192 ± 125 ng/ml (range 19 –557 ng/ml), those of the main metabolite N-Ac-5-ASA were 402 ± 211 ng/ml (range 57 – 1070 ng/ml). Time to reach the peak plasma concentration of 5-ASA was 7.1 ±4.9 h (range 0.3 – 24 h).

Elimination:

In healthy subjects, after a single rectal dose of 1g mesalazine (Melanez 1g Suppository) approx. 14 % of the administered 5-ASA dose were recovered in the urine during 48 hours.

5.3 Preclinical safety data

With the exception of a local tolerance study in dogs, which demonstrated good rectal tolerance, no preclinical studies have been performed with Melanez 1g Suppositories. Preclinical data on mesalazine reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity (rat) or toxicity to reproduction.

Kidney toxicity (renal papillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine. The clinical relevance of this finding is unknown.

6. Pharmaceutical particulars

6.1 List of excipients

Hard Fat

6.2 Incompatibilities

Not available

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in dry place, below 30º C. Protect from light.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

Bliss GVS Pharma Ltd.
102, Hyde Park, Saki Vihar Road,
Andheri (East), Mumbai - 400 072.