PRODUCT INFORMATION

DIPENTUM®

NAME OF THE MEDICINE:-

Olsalazine sodium.

DESCRIPTION:-

Composition

Active ingredient:	olsalazine sodium
Excipients:	250 mg capsule - magnesium stearate, gelatin capsule shells; 500 mg tablet - magnesium stearate, silica - colloidal anhydrous, povidone, crospovidone.

Olsalazine sodium is a fine crystalline powder. The pH of an aqueous solution is in the range of 7 to 8. Solubility is poor in most solvents except water. Solubility is low at low pH.

PHARMACOLOGY:-

Pharmacodynamics

Olsalazine consists of two molecules of 5-amino-salicylic acid (5-ASA) covalently bound through an azo-bond. Olsalazine is activated exclusively in the colon. Colonic bacterial azoreductases split the azo-bond converting olsalazine into 5-ASA, the clinically active moiety. The mechanism of action of 5-ASA in the treatment of ulcerative colitis remains unknown.

Pharmacokinetics

The parent molecule is poorly absorbed from the gastrointestinal tract (approximately 2% of a 1 g oral dose) and its action is neither pH nor time release dependent. Thus there is no absorption of 5-ASA from the small bowel, and more than 95% of an oral dose will consistently reach the colon where it is completely transformed into 5-ASA. The 5-ASA formed is partially acetylated to acetyl-5-ASA (Ac-5-ASA). Partial colonic absorption of the resulting 5-ASA and acetyl-5-ASA thus explains the appearance of approximately 20% of the dose in urine.

The concentration of 5-ASA in the colon approaches 1000 times that found in the serum.

Olsalazine sulfate is formed as a minor metabolite following a single oral dose of olsalazine. However, with repeat dosing, this metabolite accumulates and becomes the major circulating metabolite at steady state.

In clinical studies Dipentum has been well tolerated and shows clinical efficacy similar to sulphasalazine.

INDICATIONS:-

Treatment of ulcerative colitis in patients intolerant of sulphasalazine.

CONTRAINDICATIONS:-

Known hypersensitivity to salicylates or to any other constituents in Dipentum.

Pathological bleeding tendency, peptic ulcer, erosive gastritis and concomitant anticoagulants.

PRECAUTIONS:-

Use in Renal Impairment
Although clinical trials with olsalazine have not shown any renal adverse effects, the possibility of renal tubular damage due to absorbed 5-ASA or its n-acetylated metabolite as noted in the Animal Toxicology section, must be kept in mind particularly for patients with pre-existing renal disease. In these patients, monitoring with urinalysis, blood urea nitrogen (BUN) and creatinine determinations is advised.

Use in hepatic impairment:Monitoring is advised.

It is recommended to monitor patients with impaired kidney or liver function.

It is recommended to monitor renal function in patients receiving olsalazine, by estimating serum creatinine before treatment, every 3 months for the first year, every 6 months for the next 4 years, and annually after 5 years of treatment.

Although rare, blood dyscrasias may develop during therapy. Practitioners should be aware of the possibility of this occurring and be prepared to cease treatment immediately.

Patients or their carers should be instructed how to recognize signs of haematotoxicity and should be advised to contact their treating doctor immediately if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Patients suffering from severe allergy or asthma should be observant to signs of worsening of these conditions.

Use in Pregnancy

Category C:.
Olsalazine has been shown to produce foetal developmental toxicity as indicated by reduced foetal weights, retarded ossifications and immaturity of the foetal visceral organs when given during organogenesis to pregnant rats in doses 5 to 20 times the human dose (100 to 400 mg/Kg).

There are no adequate and well-controlled studies in pregnant women. Olsalazine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation
Small amounts of the active metabolite of olsalazine (5-ASA) may pass into breast milk. There have been reports of infants developing diarrhoea when 5-ASA was used during breastfeeding. Unless the benefit of the treatment outweighs the risks, olsalazine should not be taken by breast-feeding women, or patients should be advised to discontinue breastfeeding if using olsalazine.

Use in Children
Safety and efficacy in children have not been established. Therefore, use in infants 2 years of age and under is not recommended.

Use in Elderly
Regular monitoring of renal function in the elderly is advisable as renal function deteriotates with age.

Animal Toxicology
Repeat dose toxicity studies in the rat have shown the kidney to be the major target organ. In a four week oral gavage study the 800 mg/kg/day dose level produced interstitial nephritis and tubular necrosis. In a six month oral gavage study the highest dose (400 mg/kg/day) caused no appreciable toxic changes. In a 12 month study using diet admixture the 400 mg/kg dose caused no appreciable toxic changes whilst at higher doses (800 and 1600 mg/kg) pelvic dilatation, focal mineral deposition, transitional cell hyperplasia, congestion and/or haemorrhage and fibrosis were seen.

Carcinogenicity/mutagenicity
In male rats, a low incidence of transitional cell carcinomas of the urinary bladder was observed following dietary administration of olsalazine sodium at 800 mg/kg/day for 2 years. These tumours appear to have developed as a result of irritating effects of urinary calculi, that were also observed at this dose level. No medicine-related tumours were observed in male rats treated with 400 mg/kg/day, in female rats treated with doses up to 800 mg/kg/day, or in mice treated with dietary doses up to 2000 mg/kg/day. There was no clear evidence of genotoxic activity in gene mutation assays in bacterial or cultured mammalian cells, or in chromosomal aberration studies in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

Interactions with Other Medicines
The coadministration of salicylates and low molecular weight heparins or haparinoids may result in an increased risk of bleeding, more specifically haematomas following neuraxial anaesthesia. Salicylates should be discontinued prior to the initiation of a low molecular weight heparin or heparinoid. If this is not possible, it is recommended to monitor patients closely for bleeding.

Increased prothrombin time in patients taking concomitant warfarin has been reported.

The coadministration of olsalazine and 6-mercaptopurine or thioguanine may result in an increased risk of myelosuppression. If coadministered with 6-mecaptopurine, it is recommended to use the lowest possible doses of each medicine and to monitor the patient, especially for leucopenia. In case of coadministration with thioguanine, careful monitoring of blood counts is recommended.

It is recommended not to give salicylates for six weeks after the varicella vaccine to avoid a possible increased risk of developing Reye's syndrome.

ADVERSE EFFECTS:-

Patients should be informed that about 17% of subjects receiving olsalazine during clinical studies reported diarrhoea some time during therapy. This diarrhoea resulted in withdrawal of treatment in 6% of patients. If diarrhoea occurs, patients should contact their physician.

Other commonly reported adverse effects have been gastrointestinal (nausea, abdominal pain, upset stomach). Patients who experience dose related watery (not bloody) diarrhoea, particularly those patients with extensive disease at the initiation of treatment, may be managed by dosage reduction. Experience has shown that, where necessary, subsequent small incremental doses taken directly after meals are often well tolerated in these patients.

In addition, there have been rare reports of the following adverse effects in patients receiving olsalazine. These are often difficult to distinguish from possible symptoms of the underlying disease and a causal relationship to the medicine has not been demonstrated:

Gastrointestinal:
Pancreatitis, increased blood in stool, rectal bleeding, exacerbation of symptoms, rectal discomfort, epigastric discomfort, dyspepsia, upper abdominal pain, vomiting, flatulence, nausea.

Hepatic:
Rare cases of granulomatous hepatitis and nonspecific reactive hepatitis have been reported in patients receiving olsalazine. One patient developed mild, cholestatic hepatitis during treatment with sulphasalazine and experienced the same symptoms two weeks later when the treatment was changed to olsalazine. Withdrawal of olsalazine led to complete recovery in these cases. Increased bilirubin levels and elevated liver enzyme levels have also been reported.

Renal and urinary disorders:
Interstitial nephritis.

Neurologic:
Paraesthesia, tremors, insomnia, mood swings, irritability, fever, chills, dizziness, peripheral neuropathy.

Dermatologic:
Erythema, photosensitivity, hot flushes, alopecia, angioneurotic oedema, pruritus, rash, urticaria.

Musculoskeletal:
Muscle cramps, myalgia, arthralgia.

Cardiovascular:
Pericarditis, second degree heart block, hypertension, orthostatic hypotension, peripheral oedema, chest pains, tachycardia, palpitations, myocarditis.

Pulmonary:
Bronchospasm, shortness of breath, dyspnoea, interstitial lung disease.

Genitourinary:
Frequency, dysuria, haematuria, proteinuria, impotence, menorrhagia.

Haematologic:
Leucopenia, neutropenia, lymphopenia, eosinophilia, thrombocytopenia, anaemia, aplastic anaemia, haemolytic anaemia, reticulocytosis, haemolysis, granulocytopenia, pancytopenia.

Psychiatric disorders:
Depression.

Other:
Dry mouth, dry eyes, watery eyes, blurred vision, headache.

DOSAGE AND ADMINISTRATION:-

Dipentum should be taken at regular intervals during the day, after meals.

Adults: Long Term Maintenance of Remission
Adults including the elderly: 1g/day (2 capsules or 1 tablet, twice daily), to be continued indefinitely.

Adults: Acute Ulcerative Colitis
Adults including the elderly: Normal dose 2 g/day, in divided doses.

For maximum compliance titration of the dose is recommended. If taking the capsules, commence treatment with 250 mg on the first day, gradually increasing the dose each day by 250 mg to 2 g/day in divided doses. If taking the tablets, commence treatment with 500mg on the first day, gradually increasing the dose each day by 500 mg to 2 g/day in divided doses.

As bioequivalence between the 250 mg capsule and 500 mg tablet has not been established, care should be taken when changing from one dosage form to the other to ensure an equivalent clinical effect. A dose of 250mg should be given as the 250 mg capsule; the 500 mg tablet should not be divided*.

If no response is achieved with 2 g and the medicine is well tolerated the total dose may be increased to 3 g/day. A single dose should not exceed 1g.

Should a patient experience a medicine related watery diarrhoea during escalation of the dose, reduce the dose to a previously tolerated level for three days and then increase again. Further subdivision of the dose may be beneficial.

Concomitant oral or rectal steroids may be used.

Paediatric:
Safety and efficacy in children have not been established. See under 'Precautions'.

OVERDOSAGE:-

The knowledge of overdosage is limited. Possible symptoms include nausea, vomiting and diarrhoea. It is recommended to check haematology, acid-base, electrolyte, liver and kidney status, and to provide symptomatic treatment. There is no specific antidote to Dipentum. Advice for the management of overdose may be obtained by contacting the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS:-

Store below 30^{O}C in a dry place. Keep container tightly closed.

Capsules, 250 mg (beige, marked DIPENTUM 250 mg one end) in polyethylene bottles: 100's.

Tablets 500 mg (yellow, capsule-shaped tablets, debossed with "D500" on one side and scored line on the other in polyethylene bottles: 50's and 100's.

POISON SCHEDULE OF THE MEDICINE:- Schedule 4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR:-

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