

# New Zealand Datasheet

## Name of Medicine

DIPENTUM®

Olsalazine sodium 250mg capsules, 500mg tablets.

## Presentation

250 mg capsules: Beige, opaque, hard, gelatin capsules size 1, filled with yellow powder and without print or radially printed "DIPENTUM 250mg".

500 mg tablets: Yellow, capsule-shaped tablets, with the letters 'KPh' on one side and the product code '110' and a score line on the other. The tablets are 16mm long and 7mm wide.

## Uses

### Actions

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 1g 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 sulphate 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

Maintenance of patients with ulcerative colitis in remission.

Treatment of acute ulcerative colitis of mild to moderate severity with or without the concomitant use of steroids.

### 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: 1 g/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.

To ensure maximum tolerability, commence treatment with 0.5g the first day and increase the dose each day by 0.5g to 2g daily in divided doses.

As bioequivalence between the 250mg capsule and 500mg 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 250mg capsule; the 500mg tablet should not be divided.

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

Should a patient experience a drug 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 'Warnings and Precautions'

**Contraindications**

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

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

**Warnings and Precautions**

Caution should be exercised in patients with compromised renal function or impaired renal reserve. These patients should be monitored.

Regular monitoring of renal function in the elderly is advisable as renal function deteriorates with age.

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.

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

Patients suffering from severe allergy or asthma should be observed for signs of worsening of these conditions.

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.

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

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.

### **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 drug-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*.

### **Use in Pregnancy**

#### **Category B2**

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.

### **Effects on Ability to Drive and Use Machines**

On the basis of the pharmacodynamic profile and reported adverse events, olsalazine does not appear to produce any effects on ability to drive and use machines.

## **Adverse Effects**

The most common side effect is diarrhoea, which is usually transient.

In addition, the following undesirable effects have been reported:

*General disorders and administration site conditions:* headache, pyrexia

*Blood and lymphatic system disorders:* aplastic anaemia, eosinophilia, haemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia

*Gastrointestinal disorders:* abdominal pain upper, diarrhoea, dyspepsia, nausea, pancreatitis, vomiting

*Hepatobiliary disorders:* hepatic enzyme increased, hepatitis, increased bilirubin

*Skin and subcutaneous tissue disorders:* alopecia, angioneurotic oedema, photosensitivity reaction, pruritus, rash, urticaria,

*Cardiac disorders:* myocarditis, palpitations, pericarditis, tachycardia

*Renal and urinary disorders:* interstitial nephritis

*Respiratory, thoracic and mediastinal disorders:* dyspnoea, interstitial lung disease

*Musculoskeletal and connective tissue disorders:* arthralgia, myalgia

*Nervous system disorders:* dizziness, paraesthesia, peripheral neuropathy

*Psychiatric disorders:* depression

*Eye disorders:* vision blurred

## **Interactions**

The coadministration of salicylates and low molecular weight heparins or heparinoids 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-mercaptopurine, it is recommended to use the lowest possible doses of each drug 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.

## **Overdosage**

The knowledge of overdosage with Dipentum is limited. Possible symptoms are nausea, vomiting, diarrhoea. It is recommended to check haematology, the status of

the acid-base balance, electrolyte levels and the liver and kidney. There is no specific antidote to Dipentum.

### **Pharmaceutical Precautions**

Store below 30°C in a dry place. Keep container tightly closed.

### **Medicine Classification**

Prescription Medicine

### **Package Quantities**

250mg capsules are available in polyethylene bottles: 100's

500mg tablets are available in polyethylene bottles: 100's

### **Further Information**

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.

### **Excipients**

250 mg capsule - magnesium stearate, gelatin capsule shells

500 mg tablet - magnesium stearate, silica - colloidal anhydrous, povidone, crospovidone.

### **Name and Address**

Pharmabroker Sales Limited  
PO Box 302-234  
North Harbour Postal Centre  
Auckland  
NEW ZEALAND  
Phone: (09) 415 5050

### **Date of Preparation**

20 May 2010

CCDS 20.4.2010