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# Australian Product Information – DIPENTUM® (olsalazine sodium)

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## 1. NAME OF THE MEDICINE

olsalazine sodium

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of olsalazine sodium.

Each tablet contains 500 mg of olsalazine sodium.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

## 3. PHARMACEUTICAL FORM

Capsules, 250 mg (beige, opaque, hard gelatin capsule shells, size 1, radially printed "DIPENTUM 250mg" in black).

Tablets 500 mg (yellow, capsule-shaped tablets, debossed with "D500" on one side and score line on the other).

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Treatment of ulcerative colitis in patients intolerant of sulphasalazine.

### 4.2 DOSE AND METHOD OF 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.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

### 4.3 CONTRAINDICATIONS

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

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

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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 hepatic impairment**

Monitoring is advised.

##### **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.

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

##### **Use in the elderly**

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

##### **Paediatric use**

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

##### **Effects on laboratory tests**

No data available.

#### **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 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.

#### **4.6 FERTILITY, PREGNANCY AND LACTATION**

##### **Effects on fertility**

No data available.

##### **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.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

#### **4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at <https://www.tga.gov.au/reporting-problems>.

## **4.9 OVERDOSE**

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

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.

#### **Clinical trials**

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

### **5.2 PHARMACOKINETIC PROPERTIES**

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.

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

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*.

## **Carcinogenicity**

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.

## **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.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

#### **250 mg capsule**

Magnesium stearate

Gelatin capsule shells:

Caramel

Gelatin

Titanium dioxide

Printing ink:

OPACODE monogramming ink S-1-27794 BLACK (ARTG No. 12390)

OPACODE monogramming ink S-1-17823 BLACK (ARTG No. 12108)

OPACODE monogramming ink S-1-17822 BLACK (ARTG No. 12104)

#### **500 mg tablet**

Magnesium stearate

Colloidal anhydrous silica

Povidone

Ethanol

Crospovidone

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Tablets: Store below 30°C.

Capsules: Store below 30°C in a dry place. Keep container tightly closed/airtight.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

The 250 mg capsules are supplied in HDPE bottles containing 100 capsules.

The 500 mg tablets are supplied in HDPE bottles with a PP cap containing 50 or 100 tablets

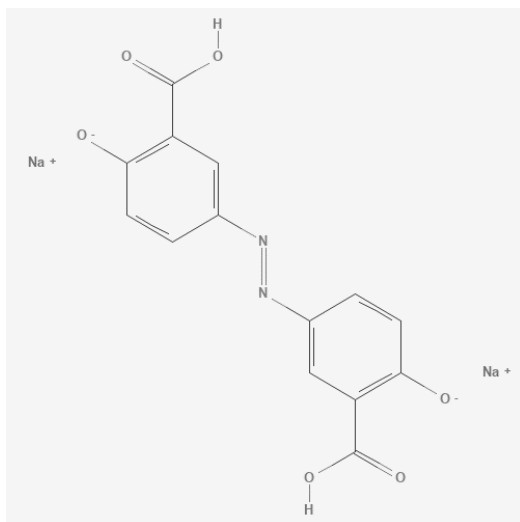
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

## 6.7 PHYSICOCHEMICAL PROPERTIES

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.

### Chemical structure



### CAS number

6054-98-4

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

## 8. SPONSOR

Atnahs Pharma Australia Pty Ltd

Level 10 / 10 Shelley Street,

Sydney, NSW, 2000, Australia

Ph: 1800 899 005

## 9. DATE OF FIRST APPROVAL

14 September 1995

## 10. DATE OF REVISION

22 March 2021

### Summary table of changes

| Section changed | Summary of new information                    |
|-----------------|---|
| All             | Reformat                                      |
| 6.1             | Update ingredients to AANs                    |
| 6.7             | Addition of chemical structure and CAS number |