NEW ZEALAND DATA SHEET

1. DIPENTUM® 250 mg capsules and 500 mg tablets

DIPENTUM 250 mg capsules and 500 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIPENTUM capsules contain 250 mg olsalazine sodium.

DIPENTUM tablets contain 500 mg olsalazine sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dosage and method of administration

Dose

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 0.5 g to 2 g daily 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 250 mg 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 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 'Section 4.4 Special warnings and precautions for use'.

Method of Administration

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

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

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

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.

Use in renal impairment

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 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.

Use in hepatic impairment

It is recommended to monitor patients with impaired liver function.

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.

Paediatric Use

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

4.5 Interactions with other medicines and other forms of interaction

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 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.

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding

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 breasfeeding if using olsalazine.

Fertility

No Data Available.

4.7 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.

4.8 Undesirable effects

a. Summary of the safety profile

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

b. Tabulated list of adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, ATC code: A07EC03

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.

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.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

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.

5.3 Preclinical safety data

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/Genotoxicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

250 mg capsule - magnesium stearate, gelatin capsule shells

500 mg tablet - magnesium stearate, colloidal silicon dioxide, povidone, crospovidone.

6.2 Incompatibilities

6.3 Not applicable.Shelf life

60 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

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

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

NEW ZEALAND

Telephone: 0800 138 803

9. DATE OF FIRST APPROVAL

24 September 1987

10. DATE OF REVISION OF THE TEXT

21 February 2019

Summary Table of Changes

Section Changed	Summary of New Information
All	Movement and addition of text to align with Medsafe Data Sheet guidance