

1. Name of the medicinal product

Dipentum Capsules 250 mg
Olsalazine Sodium 250 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250mg olsalazine sodium.
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral treatment of mild active ulcerative colitis and maintenance of remission.

4.2 Posology and method of administration

Oral.

General

Olsalazine taken on an empty stomach may sometimes lead to loose stools or diarrhoea. By taking the drug at the end of a meal, this may be avoided.

Acute Mild Disease

Adults including the elderly: Commence on 1 g daily in divided doses taken at the end of meals. Depending on the patient's response, the dose may be titrated upwards over a period of one week to a maximum of 3g daily.

A single dose should not exceed 1 g.

Remission

Adults including the elderly: A dose of 0.5g should be taken twice daily, at the end of meals.

Olsalazine has been used concomitantly with gluco-corticosteroids.

4.3 Contraindications

Hypersensitivity to olsalazine or other salicylates or any other of the excipients listed in section 6.1.

There is no experience of the use of olsalazine in patients with significant renal

impairment. Olsalazine is contra-indicated in patients with significant renal impairment.

4.4 Special warnings and precautions for use

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.

Baseline renal function measurement is required in all patients initiating treatment with olsalazine.

For patients with baseline renal impairment, treatment with olsalazine should only be initiated if the benefits are considered to outweigh risk. In addition, periodic renal function monitoring, especially in the early months of treatment, should be conducted based on clinical judgment taking baseline renal function into account. 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. Treatment should be discontinued if renal function deteriorates.

Serious blood dyscrasias have been reported very rarely with olsalazine. Haematological investigations should be performed if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever, sore throat or mouth ulcers. Treatment should be stopped if there is a suspicion or evidence of a blood dyscrasia.

Patients or their carers should be instructed how to recognise the signs of haematotoxicity and should be advised to contact their physicians immediately if the symptoms develop.

4.5 Interaction with other medicinal products and other forms of interaction

The coadministration of salicylates and low molecular weight heparins or heparinoids may result in an increased risk of bleeding, more specifically hematomas following neuraxial anesthesia. 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 leukopenia. 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:

Olsalazine has been shown to produce fetal developmental toxicity as indicated by reduced fetal weights, retarded ossifications and immaturity of the fetal 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.

There is a reported risk of stillborn or pre-term birth but with no substantial risk of malformation.

Breast-feeding:

Small amounts of the active metabolite of olsalazine (5-ASA) may pass into breast milk. Harmful infant effects (diarrhoea) have been reported 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

On the basis of the pharmacodynamic profile and reported adverse events, olsalazine has minor or moderate influence on the ability to drive and use machines in patients that experience dizziness and /or blurred vision when taking olsalazine. Caution is recommended in patients that experience these symptoms.

4.8 Undesirable effects

Frequency estimate: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

The most common side effect is diarrhoea which is usually transient. Where it does not, taking the drug at the end of a more substantial meal, dose titration or dose reduction are usually effective. Withdrawal in clinical studies when the drug was taken at the end of meals was around 3%. Where diarrhoea persists, the drug should be stopped.

In addition, the following undesirable effects have been

reported:General disorders and administration site conditions:

Common: headache

Uncommon: pyrexia

Blood and lymphatic system disorders:

Uncommon: thrombocytopenia

Not known: aplastic anaemia, eosinophilia, haemolytic anemia, leukopenia, neutropenia, pancytopenia

Gastrointestinal disorders:

Common: diarrhoea, nausea

Uncommon: vomiting, dyspepsia

Not known: abdominal pain upper, pancreatitis

Hepatobiliary disorders:

Uncommon: hepatic enzyme increased

Not known: hepatitis, increased bilirubin

Skin and subcutaneous tissue disorders:

Common: rash

Uncommon: pruritus, alopecia, photosensitivity reaction, urticaria

Not known: angioneurotic oedema

Cardiac disorders:

Uncommon: tachycardia

Not known: myocarditis, palpitations, pericarditis

Renal and urinary disorders:

Not known: interstitial nephritis

Respiratory, thoracic and mediastinal disorders:

Uncommon: dyspnoea

Not known: interstitial lung disease

Musculoskeletal and connective tissue disorders:

Common: arthralgia

Uncommon: myalgia

Nervous system disorders:

Uncommon: dizziness, paraesthesia

Not known: peripheral neuropathy

Psychiatric disorders

Uncommon: depression

Eye disorders:

Not known: vision blurred

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The knowledge of overdosage is limited. Possible overdose symptoms include nausea, vomiting and diarrhoea. It is recommended to check haematology, acid-base,

electrolyte, liver and kidney status, and to provide supportive treatment. There is no specific antidote to olsalazine sodium.

As a salicylate, interference in biochemical and other tests characteristic of salicylates may occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminosalicylic acid and similar agents, ATC Code: A07E C 03.

Olsalazine is itself a relatively inert compound. Absorption in the small intestine is slight. On entering the colon it is split by bacteria into two molecules of 5-amino salicylate (5-ASA, mesalazine). 5-ASA is believed to be principal active fragment of sulphasalazine, which has been in use for 40 years in the treatment of ulcerative colitis. 5-ASA is believed to be the active form of olsalazine sodium as olsalazine has little effect in in-vitro tests or on experimental animals. The clinical benefits of sulphasalazine, 5-ASA and olsalazine are evident in ulcerative colitis, but the pharmacological mechanism is not established.

5.2 Pharmacokinetic properties

Studies in man and animals indicate a low uptake of olsalazine and its metabolites, which is in keeping with the desired aim to deliver a high local concentration of 5-ASA to the colon.

In man an oral dose of olsalazine is negligibly absorbed in the gut. Bacteria split olsalazine in the colon into two molecules of 5-ASA. Local concentrations of 5-ASA in the colon can be 1000 times the plasma levels. Uptake by colonic mucosal cells leads to acetyl 5-ASA generation (the principle metabolite), traces of 5-ASA and olsalazine-O-SO₄ also being found in plasma. 500 mg b.d. in 6 volunteers gave a steady state level of amino salicylate of 0.8-2.9 mcg/ml after 6-9 days. In ileostomised patients almost all the olsalazine could be recovered in ileal fluid. Intravenous administration of olsalazine showed biliary excretion and traces of Ac-5-ASA in the urine and a half life of 56 minutes. Olsalazine given with or without food was taken up to the extent of 1.3 or 1.6% respectively. After a 1 g dose p.o. a maximum plasma level of 12.2 mcg/ml was noted at 1 hour of olsalazine. 22-33% of an oral dose appears in the urine almost all as Ac-5-ASA. The metabolite olsalazine-O-SO₄ is 99% plasma bound and has a half life of 6-10 days. Olsalazine does not penetrate red cells nor displace warfarin, naproxen, diazepam or digitoxin from plasma binding.

Autoradiography in rats showed no activity in the brain, testes, placenta or foetus, some activity in the bile duct and kidney and high activity in the gut.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents

Magnesium stearate

Capsule Shell

Gelatin

Caramel (E150)

Titanium dioxide (E171)

Printing Ink

Shellac

Iron oxide black (E172)

Propylene glycol

6.2 Incompatibilities

As a salicylate, interference in biochemical and other tests characteristic of salicylates may occur.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at room temperature in a dry place.

6.5 Nature and contents of container

White, square, polyethylene bottles with knurled tamper-evident cap containing 112 capsules, with a label incorporating a pull-out leaflet.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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SS14 3FR
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8 MARKETING AUTHORISATION NUMBER(S)

PL 43252/0001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

09/06/2005

10 DATE OF REVISION OF THE TEXT

15/11/2021