1 NAME OF THE MEDICINAL PRODUCT

Dipentum Tablets 500 mg
Olsalazine Sodium 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Olsalazine sodium 500.0mg
For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

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

Acute mild disease:
Adults including elderly: Commence on 1 g daily in divided doses and depending upon the patient response, titrate the dose upwards to a maximum of 3 g daily over one week.
A single dose should not exceed 1 g.
Olsalazine should be taken with food.
Remission:
Adults including the elderly: one tablet (0.5 g) twice daily, taken with food.
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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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:

<u>General disorders and administration site conditions:</u>

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 bilary 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 stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Colloidal silicon dioxide
Polyvidone 30
Crospovidone
Ethanol 99.5%

6.2 Incompatibilities

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

6.3 Shelf life

48 months, unopened.

6.4 Special precautions for storage

Store in a dry place.

6.5 Nature and contents of container

HD polyethylene securitainers with cap or HD polyethylene square section pots with child and tamper resistant cap.

Packs of 60 tablets

Packs of 100 tablets (not marketed)

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Atnahs Pharma UK Limited
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 43252/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/06/2005

10 DATE OF REVISION OF THE TEXT

15/11/2021