PRODUCT MONOGRAPH

DIPENTUM ®

(olsalazine sodium)

250 mg Capsules

Lower gastrointestinal anti-inflammatory

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NAME OF DRUG

Dipentum

(olsalazine sodium)

THERAPEUTIC CLASSIFICATION

Lower gastrointestinal anti-inflammatory

ACTION AND CLINICAL PHARMACOLOGY

The conversion of olsalazine to 5-aminosalicylic acid (5-ASA) in the colon is similar to that of sulfasalazine (SASP), which is converted into sulfapyridine and 5-ASA. On a weight basis olsalazine delivers twice the amount of 5-ASA to the colon compared with SASP and there is no residual carrier molecule (sulfapyridine) following olsalazine administration. It is thought that the 5-ASA component is therapeutically active in ulcerative colitis. The usual dose of sulfasalazine for maintenance of remission in patients with ulcerative colitis is 2 grams daily, which would provide approximately 0.8 gram of mesalamine to the colon. More than 0.9 gram of mesalamine would usually be made available in the colon from 1 gram of olsalazine.

The mechanism of action of 5-ASA (and SASP) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways (i. e., prostanoids), and through the lipoxygenase pathways (i. e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids [HETEs]) is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

After oral administration olsalazine has limited systemic bioavailability. Based on oral and intravenous dosing studies approximately 2.4% of a single 1.0 g oral dose is absorbed. Less than 1% of olsalazine is recovered in the urine. The remaining 98-99% of an oral dose will reach the colon, where each molecule is rapidly converted into two molecules of 5-ASA by colonic bacteria and the low prevailing redox potential found in this environment. The liberated 5-ASA is absorbed slowly resulting in very high local concentrations in the colon.

Systemically absorbed olsalazine is rapidly cleared from plasma with a half-time of 0.9 hour. The plasma 5-ASA and acetylated-5-aminosalicylic acid (Ac-5-ASA) are rapidly cleared via the kidneys. The elimination half-times are 45 and 80 minutes, respectively. In urine less than 1% is recovered as olsalazine, 20% as Ac-5-ASA and less than 1% as 5-ASA. The remaining 80% is eliminated via the faeces as 5-ASA and Ac-5-ASA.

Geriatric use of DIPENTUM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, elderly patients should be treated with caution due to the greater frequency of decreased hepatic, renal, or cardiac function, co- existence of other disease, as well as concomitant drug therapy.

CLINICAL STUDIES

Two controlled studies have demonstrated the efficacy of olsalazine as maintenance therapy in patients with ulcerative colitis. In the first, ulcerative colitis patients in remission were randomized to olsalazine 500 mg B.I.D. or placebo, and relapse rates for a six-month period of time were compared. For the 52 patients randomized to olsalazine, 12 relapses occurred, while for the 49 placebo patients, 22 relapses occurred. This difference in relapse rates was significant ($p<0.02$).

In the second study, 164 ulcerative colitis patients in remission were randomized to olsalazine 500 mg B.I.D. or sulfasalazine 1 gram B.I.D., and relapse rates were compared after six months. The relapse rate for olsalazine was 19.5% while that for sulfasalazine was 12.2%, a non-significant difference.

INDICATIONS

Long-term 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.

CONTRAINDICATIONS

Hypersensitivity to olsalazine, other salicylates or any of the excipients.

WARNINGS

All 5-ASA preparations have been reported to cause an exacerbation of colitis symptoms in less than 1% of patients with ulcerative colitis. This reaction may also occur with olsalazine treatment due to the pharmacological similarities among these drugs.

Use in 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 fetus.

Nursing Mother
Small amounts of the active metabolite of olsalazine (5-ASA) may pass into breast milk. Harmful infant effects (diarrhea) 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.

Oral administration of olsalazine to lactating rats in doses 5 to 20 times the human dose produced growth retardation in their pups.

Use in Children
Safety and effectiveness in a pediatric population have not been established.

PRECAUTIONS

General
Overall, approximately 17% of patients reported diarrhea when olsalazine was initially administered, resulting in treatment withdrawal in 6%. This diarrhea appears to be dose related although it may be difficult to distinguish it from the underlying symptoms of the disease. The diarrhea is temporary and may depend on the extent of colonic involvement.

However, the severity of ulcerative colitis does not appear to influence its occurrence.

Drug-related diarrhea in patients in remission is defined as watery stools, four or more times a day, without blood or sigmoidoscopic signs of inflammation. Withdrawal of the drug results in prompt clinical improvement of the diarrhea.

Disease-induced diarrhea (i.e. relapse of the colitis) is defined as four or more bowel movements a day with visible blood in association with sigmoidoscopic evidence of inflammation.

Drug-induced hypersensitivity colitis presents with increasing diarrhea that is frequently bloody. Other signs of hypersensitivity such as fever, skin rash, cramping abdominal pain, or nausea are often part of this type of acute exacerbation. Sigmoidoscopy reveals the macroscopic changes of an active colitis. Withdrawal of the drug results in prompt improvement of this hypersensitivity reaction.

Dipentum can be used with or without concomitant steroids for treatment of acute ulcerative colitis of mild to moderate severity.

The following definitions may serve as guidelines for selection of patients:

Remission is defined as three or fewer bowel movements a day without macroscopic blood admixture and without sigmoidoscopic evidence of inflammation.

Mild disease is defined as three to five bowel movements a day or other symptoms of colitis including rectal bleeding, anorexia, or nausea.

Moderate disease includes patients with at least six and up to ten bowel movements per day, with or without rectal bleeding, anorexia or nausea.

Severe disease is indicated by ten or more bowel movements per day and one or more of the following signs: abdominal tenderness, pulse rate greater than 100 beats/minute, body temperature higher than 37.5° C.

Severe allergies and/or asthma
Patients with severe allergies or asthma should be monitored for signs of worsening of symptoms.

Renal
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 renal abnormalities were not reported in clinical trials with olsalazine, there have been rare reports from post-marketing experience (see under ADVERSE REACTIONS). Therefore, the possibility of renal tubular damage due to absorbed mesalamine 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, BUN and creatinine determinations is advised.

Hepatic
Patients with impaired hepatic function should be monitored (see under ADVERSE REACTIONS).

Blood
Patients and/or their caregivers should be instructed on 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.

Drug interactions
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.

In view of the inhibition of thiopurine methyl transferase (TPMT) by olsalazine, 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.

Drug / laboratory test interactions
None known.

Information for patients
Patients should be made aware that ulcerative colitis rarely remits completely and that the risk of relapse can be substantially reduced by continuous administration of olsalazine.

Patients should be instructed to take olsalazine regularly, not to take more than 4 capsules at any one dosing interval and to take the capsules with meals. The drug should be taken in evenly divided doses. Patients should be informed that in approximately 15% of cases, loose stool or diarrhea may result on initial administration and that they should contact their physician if severe diarrhea occurs.

ADVERSE REACTIONS

Olsalazine has been evaluated in ulcerative colitis patients in remission, as well as those with acute disease. Both sulfasalazine-tolerant and intolerant patients have been studied in controlled clinical trials. Overall, 10.4% of patients discontinued olsalazine because of an adverse experience as compared with 6.7% of placebo patients (Table l). In sulfasalazine-controlled trials in which all patients were already known to be sulfasalazine-intolerant, adverse experiences with this drug resulted in a similar rate of discontinuance of treatment (10.0%).

In general, olsalazine is well tolerated; adverse effects appear to be mild and transient, and may be difficult to differentiate from the symptoms of the underlying disease (Table 2). Olsalazine appears to induce loose stool in approximately 15% of patients. This incidence may be reduced if olsalazine is initially titrated and taken with food.

TABLE 1
Adverse Reactions Resulting in Withdrawal From Controlled Studies

	Total

	Olsalazine (N = 441)	Placebo (N = 208)
Diarrhea/ Loose Stools	26 (5.9%)	10 (4.8%)
Nausea	3	2
Abdominal Pain	5 (1.1%)	0
Rash/ Itching	5 (1.1%)	0
Headache	3	0
Heartburn	2	0
Rectal Bleeding	1	0
Insomnia	1	0
Dizziness	1	0
Anorexia	1	0
Light Headedness	1	0
Depression	1	0
Miscellaneous	4 (0.9%)	3 (1.4%)
Total Number of Patients Withdrawn	46 (10.4%)	14 (6.7%)

TABLE 2: Comparative incidence (%) of adverse effects reported by one percent or more of ulcerative colitis patients treated with olsalazine or placebo in double-blind controlled trials

Adverse Event	Olsalazine (N=441) %	Placebo (N=208) %
Gastrointestinal Disorders		
Diarrhea	11.1	6.7
Abdominal Pain/Cramps	10.1	7.2
Nausea	5.0	3.9
Dyspepsia	4.0	4.3
Bloating	1.5	1.4
Vomiting	1.0	-
Stomatitis	1.0	-
Increased Blood in Stool	-	3.4
Metabolism and Nutrition Disorders		
Anorexia	1.3	1.9
Nervous System Disorders		
Headache	5.0	4.8
Insomnia	-	2.4
General Disorders and Administration Site Conditions		
Fatigue/Drowsiness/Lethargy	1.8	2.9
Psychiatric Disorders		
Depression	1.5	-
Ear and Labyrinth Disorders		
Vertigo/Dizziness	1.0	-
Skin and Subcutaneous Tissue Disorders		
Rash	2.3	1.4
Itching	1.3	-
Musculoskeletal and Connective Tissue Disorders		
Arthralgia/Joint Pain	4.0	2.9
Infections and Infestations		
URTI/ Runny Nose	1.5	-

Over 2,500 patients have been treated with olsalazine in various controlled and uncontrolled clinical studies. In these studies, olsalazine was administered mainly to patients intolerant to sulfasalazine. The adverse effects related to olsalazine reported in uncontrolled studies were similar to those seen in controlled clinical trials. There have been rare reports of the following adverse effects in patients receiving olsalazine. Several of these adverse effects were often

difficult to distinguish from possible symptoms of the underlying disease or from the effects of prior and/ or concomitant therapy. A causal relationship to the drug has not been demonstrated for some of these events.

Blood and Lymphatic System Disorders
Anemia, eosinophilia, hemolytic anemia, interstitial pulmonary disease, leucopenia, lymphopenia, neutropenia, reticulocytosis, thrombocytopenia.

Cardiac Disorders
Chest pains, edema, heart block second degree, palpitations, pericarditis, peripheral edema, shortness of breath, tachycardia, tightness in chest.

A patient who developed thyroid disease 9 days after starting DIPENTUM was given propranolol and radioactive iodine and subsequently developed shortness of breath and nausea. The patient died 5 days later with signs and symptoms of acute diffuse myocarditis.

Ear and Labyrinth Disorders
Tinnitus.

Eye Disorders
Dry eyes, vision blurred, watery eyes.

Gastrointestinal Disorders
Abdominal pain upper, diarrhea with dehydration, dry mouth, epigastric discomfort, flare in symptoms, flatulence, increased blood in stool, pancreatitis, rectal bleeding, rectal discomfort.

In a double- blind, placebo- controlled study, increased frequency and severity of diarrhea were reported in patients randomized to olsalazine 500 mg B. I. D. with concomitant pelvic radiation.

General Disorders and Administration Site Conditions
Fever chills, hot flashes, irritability, rigors.

Hepatobiliary Disorders
Rare cases of granulomatous hepatitis and nonspecific, reactive hepatitis have been reported in patients receiving olsalazine. Additionally, a patient developed mild cholestatic hepatitis during treatment with sulfasalazine and experienced the same symptoms two weeks later after the treatment was changed to olsalazine. Withdrawal of olsalazine led to complete recovery in these cases.

Immune System Disorders
Bronchospasm, erythema nodosum.

Laboratory
ALT (SGPT) or AST (SGOT) elevated beyond the normal range.

Musculoskeletal and Connective Tissue Disorders
Muscle cramps.

Nervous System Disorders
Insomnia, paresthesia, tremors.

Psychiatric Disorders
Mood swings.

Renal and Urinary Disorders
Dysuria, hematuria, interstitial nephritis, nephrotic syndrome, proteinuria, urinary frequency.

Reproductive System and Breast Disorders
Impotence, menorrhagia.

Skin and Subcutaneous Tissue Disorders
Alopecia, erythema, photosensitivity.

Vascular Disorders
Hypertension, orthostatic hypotension.

POSTMARKETING

The following events have been identified during post-approval use of products that contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Blood and Lymphatic System Disorders
Agranulocytosis, aplastic anaemia, pancytopenia.

Cardiac Disorders
Myocarditis.

General Disorders and Administration Site Conditions
Pyrexia.

Hepatobiliary Disorders
Hepatic enzyme increased, hepatitis, increased bilirubin.

Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases

were fatal. One case of Kawasaki-like syndrome, which included hepatic function changes, was also reported.

Immune System Disorders
Anaphylactic reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Musculoskeletal and Connective Tissue Disorders
Myalgia.

Nervous System Disorders
Peripheral neuropathy.

Respiratory, Thoracic and Mediastinal Disorders
Dyspnoae, interstitial lung disease.

Skin and Subcutaneous Tissue Disorders
Angioneurotic oedema, urticaria, pruritus, Stevens-Johnson Syndrome.

DRUG ABUSE AND DEPENDENCY

Abuse:	None reported
Dependence:	Drug dependence has not been reported with chronic administration of olsalazine.

OVERDOSAGE

For management of suspected drug overdose, contact your Regional Poison Control Centre.

No overdosage has been reported in humans. The knowledge of overdosage is limited. Possible overdose symptoms include nausea, vomiting and diarrhoea. It is recommended to check hematology, acid-base, electrolyte**,** liver and kidney status, and to provide supportive treatment. There is no specific antidote to Dipentum.

Maximum single oral doses of 5g/kg in mice and rats and 2 g/kg in dogs were not lethal. Symptoms of acute toxicity were decreased motor activity and diarrhea in all species tested. In addition, vomiting was reported in dogs.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the disease. Increase the dose gradually over a one-week period, starting with 500 mg (2 capsules) per day. If no response is achieved

with 2 g and the drug is well tolerated, the dose may be increased to 3 g daily. A single dose should not exceed 1 g.

The drug should be taken at regular intervals, together with meals.

Patients experiencing watery diarrhea associated with increasing dosage can reduce the dose to the previously tolerated dose, for a two-day period.

The dose may then be increased again. Further sub-division of the dose may be necessary.

USUAL ADULT DOSE (INCLUDING ELDERLY)

Acute:	500 mg (2 capsules), 4 times daily
Prophylaxis:	500 mg (2 capsules), 2 times daily

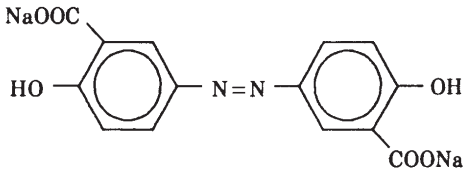
General Remarks
Concomitant therapy with oral or rectal steroids may be used.

Long-term maintenance therapy with Dipentum is recommended in order to avoid relapse and remain free from symptoms.

PHARMACEUTICAL INFORMATION

Drug substance
Proper name: Olsalazine
Chemical name: Olsalazine sodium (I.N.N. and USAN)
Disodium 3,3'-azobis-(6-hydroxybenzoate)
Disodium 5,5'-azodisalicylate

Structural formula:



Molecular formula: $C_{14}H_8N_2Na_2O_6$
Molecular weight: 346.21
Physical form: Olsalazine sodium is a yellow odorless crystalline fine powder.
Solubility: Olsalazine sodium is sparingly soluble to soluble in water, soluble in dimethylsulfoxide and insoluble in most common organic solvents.
Composition:

The inert ingredient in each 250 mg capsule of olsalazine sodium is magnesium stearate. The capsule shell contains the following inactive ingredients: black iron oxide, caramel, gelatin, and titanium dioxide.

AVAILABILITY

Each opaque, beige, hard gelatin capsule contains 250 mg Olsalazine sodium. Bottles of 100.

Store in a well closed container at room temperature (15°C to 30°C).

PHARMACOLOGY

Olsalazine is delivered to the colon, where it is bioconverted through bacterial reduction into 2 molecules of 5-amino-salicylic acid (5-ASA). Subsequently 5-ASA, generated in high concentrations, acts topically on the colonic mucosa either to keep the inflammation in remission or to act as an anti-inflammatory drug in acute Ulcerative Colitis (UC).

As this mode of action and site-specific delivery involves unusual pharmacodynamics and pharmacokinetics, standard calculations such as for absorption, bioavailability, etc. must be interpreted differently than for a systematically acting drug. However, many of the properties of olsalazine are shared by sulfasalazine, which has been used in the treatment of UC for more than 30 years.

Animal Pharmacodynamics

In vitro
Olsalazine has been tested for anti-inflammatory effects *in vitro* against activated neutrophils and lymphocytes. With two exceptions, effects were seen only at extraordinarily high concentrations i.e. 1000 times the level found in human plasma. However, olsalazine could effectively (Ki=20 μm) inhibit Xanthine Oxidase, an enzyme responsible for the generation of destructive oxygen free radicals and could inhibit neutrophil activation by the bacterial cell wall derived tri-peptide f-MLP.

In vivo
Primary pharmacologic effects:
No studies with olsalazine have been performed, due to the lack of adequate animal models for studies of inflammatory bowel disease. In other inflammatory models small or insignificant effects were seen at very high doses.

Secondary pharmacological effects:
Gastrointestinal effects: high doses of olsalazine have induced diarrhea in animals and man. Watery stool was induced in rats on a regular diet with 500 mg/kg. A similar response is seen in rats on a fiber free diet with 150 mg/kg. In the latter case the diarrhea disappeared within 3-4

days upon continued daily administration and could not be provoked by increasing the dose by 50 mg/kg. Such adaptation has been noticed in other species including man.

Although the mechanism of olsalazine-induced diarrhea is not fully understood, it is known that olsalazine can induce water secretion from the small intestinal mucosa without affecting the absorption. The effect is due to the intact olsalazine molecule through a local mechanism on the mucosa. No similar effect is seen with systemic olsalazine. The effect is rapidly reversible. The secretion is not mediated by a prostaglandin pathway. No intestinal damage has been noted in long term studies of experimental animals regardless of the dose.

Animal Pharmacokinetics
Relevant information on absorption, bioavailability and excretion is found under the pharmacokinetic section on man.

Distribution:
Whole body autoradiography of rats of both sexes including pregnant females following both oral and i.v. administration showed the following distribution: p.o. administration: major part is found in the gastrointestinal tract; traces seen in kidney pelvis. No radioactivity seen in placenta or fetus i.v. administration: rapid appearance in bile duct and duodenum as a sign of pronounced biliary excretion. Olsalazine did not cross the blood-brain barrier and was not found in testes. With both routes of administration the radioactivity was eliminated within 48 hours.

Excretion:
Isotope-labelled olsalazine given to rats and dogs showed a total elimination within 48 - 96 hours measured by both radioactivity as well as chemical analysis. Olsalazine and its metabolites were eliminated exclusively through faeces and urine. In rat and dog a large fraction of i.v. olsalazine was eliminated via bile excretion (25-70%).

Human Pharmacodynamics

Secondary pharmacological effects:
The only pharmacological effect noticed with olsalazine is the increased incidence of loose stool seen at high doses. In patients with a total colectomy the 24 hour output of ileostomy fluid increased from 500 mL to 900 mL following administration of 2 g olsalazine. This is a minor increase (80%), which a normal healthy colon could easily absorb.

In cases of an abrupt volume load or a decreased absorption capacity, such an increase might still lead to the development of loose stool. Since every dose appears to be a single event (no cumulative effect is seen) an initial division of doses will be of benefit. Adaptation to olsalazine induced loose stool has been noted in two studies. In one study with refractive patients the dose was gradually increased to 4 g/day. During scale up 9 patients reported diarrhea but in 7 this was of a transient nature. In another study the dose was increased to 3 g/day during one week. Two out of 27 patients reported loose stool, one of whom had the same problem on previous therapy with sulfasalazine.

Human Pharmacokinetics:
Absorption:
A minute amount of olsalazine is absorbed. In healthy male volunteers taking a single dose of 1 - 2 g, the average olsalazine recovery in urine was 0.25 - 0.39%. The bioavailability was extremely low. After a single 1 g oral dose a value of 1.7% with food and 2.4% without food was calculated. In healthy volunteers an olsalazine plasma peak level of 3.6 - 4.0 μm appeared after 1 hour in fasting subjects following a 1 g single dose. With food the same dose gave rise to a peak of 2.3 μM at 1.7 hours. These levels emphasize the low absorption of olsalazine and indicate that the stomach and upper small intestine are the major absorption sites.

Distribution.
In vitro studies showed that olsalazine was unable to penetrate erythrocytes during a 30 minute incubation at 37°C. The association of olsalazine with human plasma proteins is extraordinarily high, i.e. human serum 99.5% bound, human albumin 98-99% bound. Consequently the plasma level of free olsalazine is negligible. The olsalazine binding was not affected by other drugs known to be strongly bound to protein, i.e. up to 600 μM of Warfarin, Naproxen, diazepam and digitoxin did not decrease the olsalazine binding.

Biotransformation (metabolism):
Olsalazine is bioconverted to 5-ASA only in the colon. No studies in animal or man have indicated any systemic conversion. The site where olsalazine splits has been verified in a number of studies. 1) In coloctomized patients - no 5-ASA was formed. 2) No 5-ASA or acetyl-5-ASA (Ac-5-ASA) appears in plasma until after 4 hours, corresponding to the transit time from mouth to caecum. 3) Ingested, passable dialysis capsules showed high levels of 5-ASA and Ac-5-ASA (5 - 40 mM) but no olsalazine.

Thus the highly reductive bacterial environment with azoreductases found in the caecum and colon is needed for the bioconversion of olsalazine to 5-ASA. Once generated, 5-ASA can be acetylated to Ac-5-ASA by bacteria and more importantly by the colonocytes. This leads to a progressive increase in the level of Ac-5-ASA in the colon. The 5-ASA slowly absorbed from the colon is rapidly acetylated in the liver. Thus very low circulating levels of 5-ASA are measured and in the urine Ac-5-ASA is found almost exclusively. Systemically absorbed olsalazine is metabolized to a limited degree (≈10%) in the liver into olsalazine-O-sulfate (OLZ-S). This corresponds to 0.1-0.4% of a given olsalazine dose. As will be explained subsequently the only noticeable aspect of this minor metabolite is its long half life in plasma. Olsalazine-S accumulates to steady state within 2 to 3 weeks. Patients on daily doses of 1.0 g olsalazine for 2 to 4 years show a stable plasma concentration of olsalazine-S (3.3 to 12.4 μmol/L).

Excretion:
Olsalazine is eliminated via 4 different pathways i.e. kidney, bile, faeces and metabolism.

Systemically absorbed olsalazine is rapidly cleared from plasma with a half-time of 0.9 hour. Corresponding elimination of OLZ-S metabolite is 120 hours, which will cause this metabolite to accumulate to reach a steady state after 10-14 days. Beyond 14 days and for more than a year the plasma level of OLZ-S was constant. The reason for the slow elimination of OLZ-S is mainly a strong association with plasma protein.

In the colon olsalazine is rapidly and totally bioconverted to 5-ASA. The plasma 5-ASA and Ac-5-ASA is rapidly cleared via the kidneys. The elimination half-times are 45 and 80 minutes, respectively. In urine 20% Ac-5-ASA and less than 1% 5-ASA is found.

Bile clearance of olsalazine in man is at least 5% as judged from i.v. studies. Due to technical difficulties with bile collection such studies in man often yield a minimum value.

From studies with a 1 g single dose of olsalazine we can make the following conclusion about its elimination: in urine less 1% is recovered as olsalazine, 20% as Ac-5-ASA, and less than 1% as 5-ASA.

The remaining 80% is eliminated via the faeces as 5-ASA and Ac-5-ASA. Due to the site specific delivery of 5-ASA to the colon where the absorption of 5-ASA is low, very limited amounts of 5-ASA will reach the kidneys and then almost exclusively as the inert metabolite Ac-5-ASA. As a consequence of the pharmacokinetic properties of olsalazine approximately 99% of a given dose will reach the colon where it is totally bioconverted into 5-ASA.

Factors influencing the pharmacodynamics and pharmacokinetics of olsalazine
Being a weak acid, olsalazine is mainly absorbed in an acid environment. Factors decreasing the acidity of the stomach will decrease its absorption, thus delivering more olsalazine to the colon. Since olsalazine needs a reductive bacterial environment in the colon, strong enterically confined antibiotics might transiently decrease the rate of bioconversion to 5-ASA. Likewise laxatives or severe diarrhea might temporarily decrease the formation of 5-ASA due to limited transit time of olsalazine in the colon.

TOXICOLOGY

The toxicity studies performed with olsalazine sodium and summarized below confirm that this drug has low toxicity.

Single dose toxicity
The oral toxicity was low for all three species examined, LD_{50} being greater than the maximum practical dose, i.e. 5000 mg/kg for the mouse and rat and 2000 mg/kg for the dog.

The intravenous toxicity was also low, LD_{50} for the mouse and rat being 233-266 mg/kg and 521 mg/kg respectively. Studies in the dog showed that the lethal dose was approximately 300 mg/kg.

Repeated dose toxicity

Route of administration	Species	Duration of administration	Dose levels mg/kg bw/day
po	Rat	4 weeks	5, 50, 100, 200, 400, 800
po	Dog	4 weeks	0, 250, 500, 1000
po	Rat	6 months	0, 100, 200, 400
po	Dog	6 months	0, 250, 500, 1000
po	Rat 1)	8 weeks	0, 600, 800, 1100, 1500 (diet administration)
po	Rat 1)	4 weeks	0, 2000, 2500, 3000 (diet administration)
po	Rat 1)	4 weeks	0, 800, 1100, 1500, 2000 (gavage)
po	Rat	12 months	0, 400, 800, 1600
po	Dog	12 months	0, 250, 500, 1000
(iv)	Rat	2 weeks	0, 10, 30, 90) 2)

1) Range finding study
2) Olsalazine sulphate

In the rat the dose level of 400 mg/kg caused no appreciable changes when administered for long time periods. At 800 and 1600 mg/kg the kidney was the target organ when examined morphologically (pelvic dilatation and focal mineral deposits, transitional cell hyperplasia, congestion and/or hemorrhages and fibrosis). This was not reflected in clinical or other parameters.

In the dog the dose level of 250 mg/kg did not cause any appreciable effects while doses of 500 and 1000 mg/kg were associated with transient gastrointestinal effects (loose faeces and vomiting). No morphological changes were observed.

Carcinogenicity

Route of administration	Species	Duration of administration	Dose levels mg/kg bw/day
po	Mouse	18 months	0, 500, 1000, 2000
po	Rat	24 months	0, 200, 400, 800

In an eighteen month oral mouse carcinogenicity study, olsalazine was tested in male and female CD- 1 mice at daily doses of 500, 1000 and 2000 mg/kg/day (approximately 25 to 100 times the human maintenance dose). Liver hemangiosarcomata were found in two male mice (4%) receiving olsalazine at 100 times the human dose, while no such tumor occurred in the other treated male mice groups or any of the treated female mice. The observed incidence of this tumor is within the 4% incidence in historical controls.

Even in the rat study using dose levels of 200, 400 and 800 mg/kg over 24 months the incidence of tumours and non-neoplastic lesions were rare for all groups. The kidneys seemed to be the target organs, as reflected in an increased incidence of mineralization and transitional cell hyperplasia but these changes were not associated with increased incidence of neoplasms of the kidneys. At dose levels of 400 and 800 mg/kg in the males there was also an increased incidence of mineralization and focal transitional cell hyperplasia of the urinary bladder (calculi in the vesical lumen). In three cases this was associated with urinary bladder carcinoma. A similar carcinoma was also found in one control rat.

The occurence of these carcinoma is interpreted as being the ultimate response of the transitional cell epithelium to the chronic exposure to / irritation by the calculi. They are accordingly of a mechanical origin and are consequently not chemically induced.

Mutagenicity
Studies performed:

Bacterial mutagenicity
Mutation in mouse lymphoma cells
Metaphase analysis *in vitro*
Metaphase analysis *in vivo*

A comprehensive mutagenicity testing program was performed covering gene mutation and chromosome aberration studies. Gene mutation studies were performed in pro-caryotic cells (bacteria) and in eucaryotic cells (cultured mammalian cells). The chromosome aberration studies were performed *in vitro* (human lymphocytes) and *in vivo* (rat bone marrow cells).

The results showed that olsalazine was neither a gene mutagen nor a clastogenic agent.

Teratology

Route of administration	Species	Duration of administration (days)*	Dose levels mg/kg bw/day
po	Rat	15 ac--20 pp	0, 100, 200, 400
po	Rat	6--15 pc	0, 100, 200, 400
po	Rabbit 1)	6--18 pc	0, 200, 400, 800
po	Rabbit	Adaptation study to increasing dose levels	
po	Rabbit 1)	7 ac--18 pc after adaptation	0, 50, 100, 200, 300, 400
po	Rabbit	7 ac--18 pc after adaptation	0, 50, 100, 150
po	Mouse	6--15 pc	0, 250, 500, 1000
po	Rat	15 pc--20 pp	0, 100, 200, 400

* ac = ante coitus; pc = post coitus; pp = post-partum

1) Range finding study

In the rat fertility study using dose levels of 100, 200 and 400 mg/kg there were no adverse reactions.

In the rat teratology study the influence at dose levels of 100 and 200 mg/kg was negligible while at 400 mg/kg, a slight influence on growth development was suspected.

In the rabbit teratology study, dose range finding experiments showed maternal toxicity (gastrointestinal disturbances) at dose levels above 150 mg/kg.

A teratology study was performed modifying the protocol (i.e. adaptation of the animals to increasing dose levels before mating and splitting the daily dose) and using dose levels of 50, 100 and 150 mg/kg. No materno-toxic effect was seen nor any effect on the progeny.

In the mouse teratology study using dose levels of 250, 500 and 1000 mg/kg, there was no effect either on the females nor on the progeny.

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).

Autoradiography confirmed that olsalazine does not pass the rat placental barrier.

Oral administration of olsalazine to lactating rats in doses 5 to 20 times the human dose produced growth retardation in their pups.

CONCLUSION

Based on extensive toxicological studies, olsalazine has been proven to be a safe drug for the use in acute and long-term treatment of ulcerative colitis.

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