PRODUCT MONOGRAPH

PrNTP-5-AMINOSALICYLIC ACID

(5-aminosalicylic acid)
400 mg Enteric Coated Tablets

Lower Gastrointestinal, Anti-inflammatory

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THERAPEUTIC CLASSIFICATION

Lower Gastrointestinal, Anti-inflammatory

ACTION AND CLINICAL PHARMACOLOGY

NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) is thought to be the major active component of sulphasalazine for the treatment of inflammatory bowel disease. Its mechanism of action is not fully elucidated, however, evidence suggests that it has a topical anti-inflammatory effect on the colon, where it may inhibit prostaglandin and leukotriene synthesis.

NTP-5-AMINOSALICYLIC ACID tablets have an acrylic based resin coating, which does not allow the drug to be released below pH 5.5. Thus the coating delays release of the 5-aminosalicylic acid until it reaches the terminal ileum and colon. Once released in the colon, 5-aminosalicylic acid is minimally absorbed and plasma levels are similar to those found following rectal administration. The absorbed drug is rapidly acetylated through the gut mucosal wall and by the liver. The drug is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid.

A randomized, double-blind, parallel, multi-center clinical study was conducted in 201 patients diagnosed with ulcerative colitis of mild to moderate intensity to compare the efficacy and safety of two oral formulations of 5-aminosalicylic 400 mg enteric coated tablet products. The study demonstrated therapeutic equivalence of NTP-5-AMINOSALICYLIC ACID 400 mg tablets and ASACOL® 400 mg tablets when administered at a daily dose of 3.2 gm for up to 8 weeks. Both treatments were well tolerated and there was no evidence of a difference between the two treatments for intercurrent events in nature, severity, or frequency.

INDICATIONS

NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) is indicated for the treatment of mild to moderate active ulcerative colitis. Long-term treatment may be necessary to prevent recurrent relapses of active colitis. Abrupt discontinuation may result in relapse.

CONTRAINDICATIONS

NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) is contraindicated in patients with: a history of sensitivity to salicylates, existing gastric or duodenal ulcer, urinary tract obstruction and in infants under 2 years of age.

WARNINGS

NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) should be discontinued if toxic or hypersensitivity reactions occur. In assessing liver and joint complications, it should be kept in mind that these are frequently associated with ulcerative colitis (See PRECAUTIONS).

PRECAUTIONS

General

Caution should be exercised in patients with impaired renal function and/or hepatic dysfunction.

Patients with pyloric stenosis may have prolonged gastric retention of NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) tablets, which may delay release of active drug in the colon.

Drug Interactions

There are no known drug interactions with 5-aminosalicylic acid. A clinical study was conducted to observe the effects of co-administration of 5-aminosalicylic acid tablet with cimetidine, with an antacid containing activated dimethicone and aluminum hydroxide, or with an antacid accompanied by a high fat meal. There were no significant *in vivo* effects on 5-aminosalicylic acid release or the extent of drug absorption by any of the three treatments. Simultaneous administration of famotidine, a potent H_2-antagonist, and 5-aminosalicylic acid tablets does not influence the absorption and urinary excretion of 5-aminosalicylic acid. Interactions similar to aspirin cannot be excluded.

NTP-5-AMINOSALICYLIC ACID should not be administered with preparations which lower the stool pH, such as lactulose.

Interactions analogous to those seen with ASA cannot be excluded.

If toxic or hypersensitivity reactions occur, the drug should be discontinued.

Use in Pregnancy and Lactation

No evidence of impaired female fertility or harm to the fetus due to therapy with 5-aminosalicylic acid was observed in reproduction studies conducted in pregnant rats and rabbits administered oral doses of 480 mg/kg/day. However, the safety of 5-aminosalicylic acid in pregnant women has not been established yet, hence it should not be administered to pregnant women, unless in the judgement of the physician the potential benefit to the mother outweighs the risk to the fetus. Small amounts of 5-aminosalicylic acid and higher concentrations of acetyl-5-aminosalicylic acid were detected in one case. Therefore, caution should be exercised when 5-aminosalicylic acid is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of 5-aminosalicylic acid therapy in children have not been established.

Information for the Patient

1. Swallow tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact, to protect the active ingredient until it reaches the terminal ileum, where the tablet coating dissolves and the contents of the tablet are released into the terminal ileum and colon.

2. Take NTP-5-AMINOSALICYLIC ACID only as prescribed. Do not change the number or frequency of tablets ingested without first consulting your physician.

3. What appears to be intact or partially intact tablets may infrequently appear in the stool. If this occurs repeatedly, consult your physician.

ADVERSE EFFECTS

NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) is generally well tolerated. It does not contain a sulfa moiety, hence the side effects encountered are mild and reversible, much less frequent and less severe than with sulphasalazine. Cross-reactions to sulfasalazine have not been seen with NTP-5-AMINOSALICYLIC ACID, based on clinical usage to date.

The most frequently reported side effects (5% of the patients or greater) have been headache, rhinitis, fever, chills, weakness, dizziness, nausea, abdominal pain, dyspepsia, diarrhea, joint pain and rash. Other less frequently reported events (fewer than 5% of patients) include alopecia, pruritis, urticaria, acne, anxiety, insomnia, depression, tinnitus, vertigo, paresthesia, muscle cramps, anorexia, dyspnea and flatulence. The relationship of the reported events to 5-aminosalicylic acid is unclear in many cases, particularly for reported events which could be considered part of the clinical presentation of ulcerative colitis.

Allergic
An acute hypersensitivity reaction characterized by cramping, abdominal pain, bloody diarrhea and occasionally by fever, headache, malaise, pruritis, rash and conjunctivitis has been infrequently reported to occur shortly after the initiation of 5-aminosalicylic acid. Therapy should be discontinued if these symptoms occur. Symptoms usually disappear after discontinuation.

Hepatic
Asymptomatic elevations of liver function tests have occurred in patients taking 5-aminosalicylic acid tablets. These elevations usually resolve during continued therapy or with the discontinuation of administration of 5aminosalicylic acid. It should be kept in mind that hepatic complications are frequently associated with inflammatory bowel disease.

Rare Events
The following events have been reported rarely during 5-aminosalicylic acid use: pancreatitis, pericarditis, transverse myelitis, peripheral neuropathy, intestinal perforation, hepatitis, interstitial pneumonitis, leukopenia, agranulocytosis, minimal change nephropathy and acute and chronic interstitial nephritis.

SYMPTOMS AND TREATMENT OF OVERDOSE

Acute overdose with 5-aminosalicylic acid has not been reported in humans. If a large amount is ingested, induce vomiting with ipecac syrup unless the patient is convulsing, comatose, or has lost the gag reflex, in which case perform gastric lavage using a large bore tube. If indicated, follow with activated charcoal and a saline cathartic. There is no specific antidote for overdosage. Treatment is symptomatic and supportive.

DOSAGE AND ADMINISTRATION

The usual adult dose is 0.8 g to 3.2 g NTP-5-AMINOSALICYLIC ACID (5-aminosallcyllc acid) 400 mg tablets, taken orally in divided doses. In patients with severe active disease, the dose may be increased to 12 tablets daily. The dose should be continued indefinitely, since discontinuance may result in relapse.

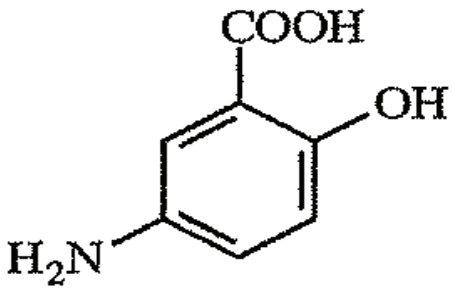
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: 5-aminosallcyllc acid

Chemical Name: 5-amino-2-hydroxybenzoic acid

Structural Formula:



Molecular Formula: $C_7H_7NO_3$

Molecular Weight: 153.1

Description: 5-aminosallcyllc acid is an off-white to light-brown powder, that decomposes at 280°C and is slightly soluble in water. It darkens upon exposure to air, high humidity or light over a period of several months.

Pka values: $pk_1 = 2.74$, $pk_2 = 5.80$.

STABILITY AND STORAGE RECOMMENDATIONS

Store bottles between 15°C - 30°C and protect from light.

AVAILABILITY OF DOSAGE FORMS

NTP-5-AMINOSALICYLIC ACID (5-aminosalicylic acid) is available as brown-red capsule shaped enteric-coated tablets each containing 400 mg of 5-aminosalicylic acid coated with an acrylic based resin supplied in bottles of 100, 500.

PHARMACOLOGY

Pharmacokinetics

NTP-5-AMINOSALICYLIC ACID tablets have an acrylic based resin coating, which does not allow the drug to be released below pH 5.5. Thus the coating delays release of the 5-aminosalicylic acid until it reaches the terminal ileum and colon.

In a randomized, double-blind, placebo controlled clinical trial, a 4.8 g/day dose of 5-aminosalicylic acid in divided doses was highly effective in inducing remission in ulcerative colitis patients with active disease.

Similar trials of 16, 24 and 52 weeks duration have shown 5-aminosalicylic acid in doses ranging from 0.8 to 4.4 g/day to be as effective as sulfasalazine for maintenance of remission. Patients intolerant or allergic to sulfasalazine can be effectively maintained in remission on 5-aminosalicylic acid as demonstrated in open-labeled clinical trials. In addition, male infertility that resulted from sulfasalazine therapy has been shown to be reversible upon treatment with 5-aminosalicylic acid.

TOXICOLOGY

Acute Toxicity

The acute oral LD_{50} for 5-aminosalicylic acid was found to be 5000 mg/kg in mice and 4595 mg/kg in rats.

Long-term Toxicity

Rats (2/sex/group) were orally administered dosages of 0, 40, 120, 360 and 1080 mg/kg/day for 14 days. At the highest dose, one female rat died probably as a result of renal failure complicated by gastric mucosal injury. Drug related histomorphologic effects were present in the kidneys at the 1080 mg/kg/day dose level and gastrointestinal tracts at the 360 and 1080 mg/kg/day level in the treated rats. Clinical chemistry assays showed drug related changes in increased serum urea nitrogen, serum creatinine and serum total proteins and decreased albumin/globulin ratios occurred only at the 1080 mg/kg/day level.

A similar study conducted in rabbits resulted in diarrhea during the first week in male rabbits at the 1080 mg/kg/day dose level. Urinalysis revealed slight increases in proteinuria, bilirubinuria and urinary acetone in the high dose group. No drug related effects were observed when rabbits were given 227.3 mg/kg/day rectally for 12 days.

Dogs (2/sex/group) were administered 5-aminosalicylic acid at oral dosages of 40, 120 and 200 mg/kg/day for one year. Control dogs received placebo tablets. Histopathology and clinical chemistry tests showed no evidence of drug related effects.

Teratology Studies

No evidence of teratogenicity was observed when 5-aminosalicylic acid was administered orally at a dosage of 480 mg/kg/day to pregnant rats and rabbits.

Reproduction Studies
No effects on fertility or gestation parameters were observed in rats at doses of 5-aminosalicylic acid up to 480 mg/kg/day.

Carcinogenesis and Mutagenesis
The long term carcinogenicity of 5- aminosalicylic acid has not been investigated in animals, but sulfasalazine, containing the 5- aminosalicylic acid moiety, identical to NTP-5-AMINOSALICYLIC ACID, was not carcinogenic in rodent studies.

5- aminosalicylic acid was not mutagenic in the Ames assay and K. pneumoniae test with and without metabolic activation.

Special Studies
The potential renal toxicity of 5-aminosalicylic acid was studied in two rat model studies. In the acute study, rats were given a single massive intravenous injection, at dose levels between 214 and 872 mg/kg. The animals sacrificed 24 to 96 hours after the injection presented lesions in the proximal cortical tubules as well as renal papillary necrosis. The former lesion was reversible by one week post-administration. In the second study, rats were dosed up to 200 mg/kg orally for 4 weeks. No drug related effects were observed.

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