PREScribing INFORMATION

PrALLOPRIN TABLETS

100 mg, 200 mg, 300 mg

(Allopurinol Tablets, USP)

XANTHINE OXIDASE INHIBITOR
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XANTHINE OXIDASE INHIBITOR

ACTION AND CLINICAL PHARMACOLOGY

Allopurinol inhibits xanthine oxidase, the enzyme that catalyzes the conversion of hypoxanthine to xanthine and of xanthine to uric acid. Oxypurinol, a metabolite of allopurinol, also inhibits xanthine oxidase. By inhibiting xanthine oxidase, allopurinol and its metabolite block conversion of the oxypurines (hypoxanthine and xanthine) to uric acid, thus decreasing serum and urine concentrations of uric acid. The drug differs, therefore, from uricosuric agents which lower serum urate concentrations by promoting urinary excretion of uric acid. Xanthine oxidase concentrations are not altered by long-term administration of the drug.

By lowering both serum and urine concentrations of uric acid below its solubility limits, allopurinol prevents or decreases urate deposition, thereby preventing the occurrence or progression of both gouty arthritis and urate nephropathy. In patients with chronic gout, allopurinol may prevent or decrease tophi formation and chronic joint changes, promote resolution of existing urate crystals and deposits, and, after several months of therapy, reduce the frequency of acute gout attacks. Also, reductions in urine urate concentration prevent or decrease the formation of uric acid or calcium oxalate calculi.

PHARMACOKINETICS

Absorption

Following oral administration, approximately 80-90% of a dose of allopurinol is absorbed from the GI tract. Peak plasma concentrations of allopurinol are reached 2 to 6 hours after a usual dose. Because allopurinol concentrations are difficult to determine and because serum concentrations may not adequately reflect the amount of drug bound to xanthine oxidase in the tissues, serum urate concentrations should be used to monitor therapy. After beginning allopurinol therapy, serum urate concentrations begin to decrease slowly within
24 to 48 hours and reach the lowest point after 1-3 weeks of therapy. During allopurinol therapy, serum urate concentrations remain relatively constant, however, serum urate concentrations usually return to pretreatment levels within 1 to 2 weeks after discontinuation of the drug. Because of the continued mobilization of urate deposits, substantial reduction of uric acid may be delayed 6 to 12 months or may not occur in some patients, particularly in those with tophaceous gout and in those who are underexcretors of uric acid.

**Distribution**

Allopurinol is uniformly distributed in total tissue water with the exception of the brain, where concentrations of the drug are approximately 50% those of other tissues. Small amounts of oxypurinol and allopurinol crystals have been found in muscle. Allopurinol and oxypurinol are not bound to plasma proteins. Allopurinol and oxypurinol are distributed into milk.

**Elimination**

Allopurinol is metabolized by xanthine oxidase to oxypurinol. The half-lives of allopurinol and oxypurinol are about 1 to 3 hours and 18-30 hours, respectively, in patients with normal renal function and are increased in patients with renal impairment. Patients genetically deficient in xanthine oxidase are unable to convert allopurinol to oxypurinol. About 5 to 7% of an allopurinol dose is excreted in urine unchanged within 6 hours after ingestion. After this time, the drug is excreted by the kidneys as oxypurinol and in small amounts as allopurinol and oxypurinol ribonucleosides. Unlike allopurinol, a large part of oxypurinol is reabsorbed by the renal tubules, therefore, its renal clearance is much lower than that of allopurinol. About 70% of the administered daily dose is excreted in urine as oxypurinol and an additional 20% appears in feces as unchanged drug within 48-72 hours. Allopurinol and oxypurinol are dialysable.

**INDICATIONS AND CLINICAL USE**

**Gout** (gouty arthritis): Allopurinol is indicated for the long-term management of hyperuricemia associated with primary or secondary gout. Allopurinol is not effective in the treatment of acute gout attacks because it has no anti-inflammatory action, and may intensify and prolong inflammation during the acute phase. However, after several months of treatment, allopurinol may prevent attacks.

**Uric acid nephropathy** (prophylaxis and treatment): Allopurinol is indicated in the treatment of primary or secondary uric acid nephropathy (with or without accompanying symptoms of gout) to prevent progression of the condition. Allopurinol will not reverse severe renal damage that has already occurred.

**Hyperuricemia** (prophylaxis and treatment): Allopurinol is indicated to control hyperuricemia secondary to blood dyscrasias, such as polycythemia vera or myeloid metaplasia, or their treatment. It is also indicated to prevent or treat hyperuricemia
secondary to tumorlysis induced by cancer chemotherapy with cytotoxic antineoplastic agents or radiation therapy in patients suffering from leukemia, lymphomas, or other neoplastic disease. Allopurinol prevents complications of hyperuricemia (e.g., acute uric acid nephropathy or renal calculi, tissue urate deposition, or gouty arthritis) in these patients. However, allopurinol may increase the toxicity of some antineoplastic agents.

**Uric acid renal calculi** (prophylaxis): Allopurinol is indicated to prevent recurrence of uric acid stone formation in patients with a history of uric acid calculi.

**Calcium oxalate renal calculi** (prophylaxis): Allopurinol is indicated to prevent recurrence of calcium stone formation in patients with a history of recurrent calcium oxalate calculi associated with hyperuricosuria (i.e., uric acid excretion > 800 mg per day in males or 750 mg per day in females).

**CONTRAINDICATIONS**

Allopurinol should be discontinued at the first appearance of rash or any sign that may indicate an allergic reaction, since severe hypersensitivity reactions that may be fatal have been reported following appearance of rash. Although, in some patients with rash, allopurinol may be reinstated at a lower dosage without untoward incident, the drug should **NOT** be reinstituted in patients who have had a severe reaction.

Allopurinol is rarely indicated in children except in those with hyperuricemia secondary to neoplastic disease, cancer chemotherapy, or genetic disorders of purine metabolism.

**Pregnancy, Fertility and Lactation**

The effect of allopurinol on the human fetus is not known, and the drug should be used during pregnancy only when clearly needed.

Since allopurinol and oxypurinol are distributed into milk, allopurinol should be used with caution in nursing mothers.

**WARNINGS**

Periodic liver function tests should be performed in all patients on Alloprin therapy.

Patients with impaired renal or hepatic functions should be carefully observed during the early stages of Alloprin administration and the drug should be withdrawn if increased abnormalities in hepatic or renal functions appear.

Due to occasional occurrence of drowsiness, patients should be alerted to the need for precautions when engaging in activities where alertness is mandatory.

In patients receiving **mercaptothione** (Purinethol) or **azathioprine** (Imuran), the concomitant administration of 300-600 mg of Alloprin per day will require a reduction in dose to approximately one-third or one-fourth of the usual dose of mercaptopurine or
azathioprine. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and any toxic effects.

**PRECAUTIONS**

Acute gouty attacks may be precipitated at the beginning of the treatment with Alloprin in new patients, and these may continue even after serum uric acid levels begin to fall. Prophylactic administration of colchicine is advisable, particularly in new patients and in those where the previous attack rate has been high. In addition, it is recommended that the patient start with a low dose of Alloprin (100 to 200 mg daily) and the dose be built up slowly until a serum uric acid level of 6 mg/100 mL or less is attained.

**Drug Interactions**

**Antineoplastic Agents:** in dosages of 300-600 mg daily, alloprin inhibits the oxidative metabolism of azathioprine and mercaptopurine by xanthine oxidase, thus increasing the possibility of toxic effects from these drugs, particularly bone marrow depression.

**Drugs that increase serum urate concentration:** many drugs may increase serum urate concentrations, including most diuretics, pyrazinamide, diazoxide, alcohol, and mecamylamine. If these drugs are administered during alloprin therapy, dosage of alloprin may need to be increased.

**Anticoagulants:** alloprin inhibits the hepatic microsomal drug metabolism of dicumarol. In one study, the half-life of dicumarol was increased from 51 to 152 hours when taken concurrently with alloprinol. Although the clinical importance of this effect may vary, patients taking alloprin with dicumarol should be observed for increased anticoagulant effects. Allopurinol has not been shown to substantially potentiate the anticoagulant effect of warfarin.

**Ampicillin and Amoxicillin:** an increased incidence of rash has been reported in patients with hyperuricemia who received allopurinol and concomitant ampicillin or amoxicillin as compared with those receiving allopurinol, ampicillin or amoxicillin alone. The clinical importance of this effect has not been determined, however, it has been suggested that concomitant use of the drugs should be avoided if possible.

**Uricosuric Agents and Diuretics:** uricosurics promote urinary excretion of oxypurinol and may thereby reduce the inhibition of xanthine oxidase produced by allopurinol therapy. The effects of allopurinol and a uricosuric are generally additive, and the combination is usually used to therapeutic advantage. Renal precipitation of oxypurines has not occurred to date in patients receiving allopurinol alone or in combination with a uricosuric, but the possibility should be kept in mind. Diuretics such as thiazide and ethacrynic acid, when given with allopurinol, may increase serum oxypurinol concentrations and may thereby increase the risk of serious allopurinol toxicity, including hypersensitivity reactions particularly in patients with decreased renal function, however, allopurinol has been used safely with thiazide to reduce hyperuricemia.
induced by the diuretics. Although a causal mechanism and relationship have not been definitely established, the evidence suggests that renal function should be monitored in patients receiving allopurinol and a thiazide concomitantly and that dosage of allopurinol in such patients should be adjusted even more conservatively than usual if decreased renal function is detected.

**Chlorpropamide:** allopurinol and chlorpropamide cause adverse hepatorenal reactions. Although the combination does not enhance the occurrence of these reactions, caution is indicated if these two drugs are administered concomitantly. Because allopurinol or its metabolites may compete with chlorpropamide for renal tubular secretion, patients who receive these drugs concomitantly should be observed for signs of excessive hypoglycemia.

**Other drugs:** concurrent administration of cotrimoxazole with allopurinol has been associated with thrombocytopenia in a few patients.

**ADVERSE REACTIONS**

**Note:** following initiation of allopurinol therapy for gouty arthritis, the most commonly encountered adverse effect is a temporary increase in the frequency of acute gout attacks. The occurrence of such reactions may be reduced by initiating therapy with a low dose that is gradually increased until the desired effect is obtained and by administration of prophylactic doses of colchicine or a nonsteroidal anti-inflammatory drug.

In addition to the listed adverse reactions, bone marrow depression has been reported to occur from 6 weeks to 6 years after initiation of allopurinol therapy. Anemia, aplastic anemia, and agranulocytosis have been reported. However, a definite causal relationship has not been established.

The following adverse reactions occur more frequently:

- allergic dermatitis (skin rash, hives, or itching)
- agranulocytosis (chills, fever, sore throat)
- angitis (vasculitis)
- hypersensitivity (chills, fever, sore throat; muscle aches, pains, or weakness; shortness of breath, troubled breathing, tightness in chest, or wheezing)
- exfoliative dermatitis (possible prodrome of chills, fever, sore throat, muscle aches or pains, and/or nausea with or without vomiting; red, thickened, scaly skin)
- erythema multiforme (possible prodrome of chills, fever, sore throat, muscle aches or pains, and/or nausea with or without vomiting; sores, ulcers, or white spots in mouth or on lips; skin rash or sores, hives, and/or itching)
- hepatotoxicity (swelling in upper abdominal area; yellow eyes or skin) - may be hypersensitivity-mediated; hepatic necrosis, granulomatous hepatitis, and cholestatic jaundice have been reported.
Allopurinol-induced hypersensitivity reaction (initially skin rash immediately preceding or concurrent with chills, fever, and sore throat; muscle aches or pains; and/or nausea with or without vomiting; followed by signs and symptoms of angiitis, hepatotoxicity, and/or acute renal failure)

- peripheral neuritis (numbness, tingling, pain, or weakness in hands or feet)
- xanthine renal calculus (blood in urine, difficult or painful urination, pain in lower back and/or side)
- acute renal failure (sudden decrease in amount of urine; swelling of face, fingers, feet, and/or lower legs; rapid weight gain)
- thrombocytopenia (usually asymptomatic; rarely, unusual bleeding or bruising; black, tarry stools; blood in urine or stools; pinpoint red spots on skin)
- unexplained nosebleeds
- diarrhea
- drowsiness
- headache
- indigestion
- nausea and vomiting
- stomach pain
- unusual hair loss

SYMPTOMS AND TREATMENT OF OVERDOSAGE

**Symptoms:** Overdosage of allopurinol is usually manifested by nausea and vomiting.

**Treatment:** No treatment is normally required provided the drug is withdrawn and adequate hydration is maintained to facilitate excretion of the drug. If, however, other forms of acute distress are observed, gastric lavage should be considered, otherwise the treatment is symptomatic.

DOSAGE AND ADMINISTRATION

**Administration:** Allopurin is administered orally, usually in a single daily dose—preferably after meals to lessen gastrointestinal irritation. Oral doses greater than 300 mg should be administered in divided doses.

**Dosage:**

**Usual adult and adolescent dose:**
Antihyperuricemic - **Gout: initial** - 100 mg once a day, to be increased by 100 mg per day at one-week intervals until the desired serum uric acid concentration is attained, not to exceed the maximum recommended dosage of 800 mg per day.

**Maintenance:** 100 to 200 mg two or three times a day; or 300 mg as a single dose once a day. The usual maintenance dose is 200 to 300 mg
per day in mild gout or 400 to 600 mg per day in moderately severe tophaceous gout.

Neoplastic disease therapy: initial 600 mg to 800 mg per day starting twelve hours to three days (preferably two to three days) prior to initiation of chemotherapy or radiation therapy.

**Maintenance:** dosage should be based on serum uric acid determinations performed approximately forty-eight hours after initiation of allopurin therapy and periodically thereafter. Allopurin should be discontinued after tumor regression.

Antiurathic (uric acid calculi): 100 to 200 mg one to four times a day; or 300 mg as a single daily dose.

Antiurathic (calcium oxalate calculi): 200 to 300 mg a day as a single dose or in divided doses.

**NOTE:** Because oxipurinol is excreted primarily by the kidneys, accumulation may occur in patients with renal failure. Patients receiving dialysis may require usual therapeutic doses of allopurinol; however, in patients not receiving dialysis, it is recommended that the dosage be reduced as follows:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
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<tbody>
<tr>
<td>10 to 20</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>3 to 10</td>
<td>no more than 100 mg daily</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>100 mg at intervals of more than 24 hours may be necessary</td>
</tr>
</tbody>
</table>

Some patients with renal function impairment may require even lower doses or longer intervals between doses. In some cases, 300 mg twice a week, or even less, may suffice.

**Usual adult prescribing limit:** 300 mg per dose or 800 mg per day

**Usual pediatric dose:**

Anti hyperuricemic, in neoplastic disease therapy - Children up to 6 years of age: 50 mg three times a day. Children 6 to 10 years of age: 100 mg three times a day; or 300 mg as a single dose once a day. **NOTE:** dosage adjustment may be necessary after approximately 48 hours of therapy, depending on the patient's response.
PHARMACEUTICAL INFORMATION

Drug Substance:   Allopurinol, USP

Chemical Name:   
   (1) 4H-Pyrazalo[3,4-d]pyrimidin-4-one, 1,5-dihydro-;
   (2) 1,5-Dihydro-4H-pyrazalo [3,4-d]pyrimidin-4-one;
   (3) 1H-Pyrazolo[3,4-d] pyrimidin-4-ol

Structural Formula:

Molecular Formula:   C₅H₄N₄O

Molecular Weight :   136.11

Description:   allopurinol occurs as a fluffy white to off-white powder having a slight odor and is very slightly soluble in water and in alcohol. The pKₐ of allopurinol is 9.4 and its active metabolite, oxypurinol, has a pKₐ of 7.7.

Composition:   Alloprin 100 mg tablets contain:
   * Allopurinol, USP
   * Microcrystalline cellulose
   * Lactose
   * Starch
   * Silicon dioxide
   * Magnesium stearate

   Alloprin 200 & 300 mg tablets contain:
   * Allopurinol, USP
   * Starch
   * Lactose
   * Alcohol
   * Magnesium stearate
   * F D&C Yellow # 6

Storage:   Alloprin tablets should be stored in well closed containers at controlled room temperature (15 - 30 °).

An oral suspension of allopurinol containing 20 mg/mL can be prepared extemporaneously from Alloprin tablets. The tablets are crushed, mixed with a volume of suspending agent equal to one-third the final volume, and then the suspension brought to a final volume with
a 2:1 mixture of simple syrup and wild cherry syrup. The resulting suspension is stable for at least 14 days when stored in an amber glass bottle at room temperature or 5°C.

AVAILABILITY

**Alloprin 100 mg:** Each white, scored compressed tablet, imprinted ICN A21 contains allopurinol, USP 100 mg. Available in bottles of 100 and 1000 tablets.

Alloprin 200 mg: Each orange, rectangular scored tablet, imprinted ICN A22, contains allopurinol, USP 200 mg. Available in bottles of 100 and 500 tablets.

**Alloprin 300 mg:** Each orange, round scored tablet, imprinted ICN A23, contains allopurinol, USP 300 mg. Available in bottles of 100 and 500 tablets.

PHARMACOLOGY

Allopurinol does not directly interfere with purine nucleotide or nucleic acid synthesis. The drug, however, indirectly increases oxypurine and allopurinol ribonucleotide concentrations and decreases phosphoribosylpyrophosphate concentrations, thus decreasing de novo purine biosynthesis by pseudofeedback inhibition. In addition, allopurinol increases the incorporation of hypoxanthine and xanthine into DNA and RNA, thereby further decreasing serum urate concentrations. Allopurinol may produce a deficit of total purines (uric acid and oxypurine) amounting to several hundred mg daily. Accompanying the decrease in uric acid produced by allopurinol is an increase in serum and urine concentrations of hypoxanthine and xanthine. Plasma concentrations of these oxypurines do not, however, rise commensurately with the fall in serum urate concentrations and are often 20-30 G less than would be expected in view of urate concentrations prior to allopurinol therapy. This discrepancy occurs because renal clearance of the oxypurines is at least 10 times greater than that of uric acid. In addition, normal urinary purine output is almost exclusively uric acid, but after treatment with allopurinol, it is composed of uric acid, xanthine, and hypoxanthine, each having independent solubility. Thus, the risk of crystalluria is reduced. Alkalization of the urine increases the solubility of the purines, further minimizing the risk of crystalluria. Decreased tubular transport of uric acid also results in increased renal reabsorption of calcium and decreased calcium excretion.

Allopurinol also interferes with de novo pyrimidine nucleotide synthesis by inhibiting oratidine 5'-phosphate decarboxylase. Secondary orotic aciduria and orotidinuria result. Orotic acid is highly soluble and could form a heavy sediment of urinary crystals; however, the increased excretion of orotic acid and oratidine rarely exceeds 10 % of the total pyrimidines synthesized by the body. In addition, enhanced conversion of uridine to uridine 5'-monophosphate usually occurs and, therefore, this partial inhibition of pyrimidine synthesis is considered innocuous.
In rats, allopurinol reportedly increases liver storage of iron by inhibiting the ferritin-xanthine oxidase system responsible for mobilization of iron from the liver; however, this effect has not been demonstrated clinically. Allopurinol may also inhibit hepatic microsomal enzymes. Allopurinol is not cytotoxic. The drug has no analgesic, anti-inflammatory, or uricosuric activity.

**TOXICOLOGY**

In mice, the LD$_{50}$ is 600-704 mg/kg per oral. In rats, the acute LD$_{50}$ is greater than 9 mg/kg per oral.

In a 13-week feeding experiment in rats at a drug level of 72 mg/kg/day, 2 of 10 rats died before the completion of the experiment. Both groups exhibited renal tubular damage due to the deposition of xanthine that was more extensive at the higher dose. In chronic feeding experiments, rats showed no toxic effects at a level of 14 mg/kg/day after one year. At a level of 24 mg/kg/day for one year, the rats showed very slight depression of weight gain and food intake, and five out of ten of the animals showed minor changes in the kidney tubules of the type exhibited by the rats on the higher doses described above.

Dogs survived oral dosing at 30 mg/kg/day for one year with no to minor changes in the kidney and no other significant abnormalities. At 90 mg/kg/day for one year, there was some accumulation of xanthine in kidneys with resultant chronic irritation and slight tubular changes. Occasional hemosiderin-like deposits were seen in the reticuloendothelial system. A higher dose (270 mg/kg/day) resulted in large concretions in the renal pelves, with severe destructive changes in the kidney secondary to xanthine accumulation. The deposit of xanthine appears to be a function of both the metabolic turnover of purines (which is proportionately larger in the smaller animals) and the degree of inhibition of xanthine oxidase.

Reproductive studies in rats and rabbits indicated that allopurinol did not affect litter size, the mean weight of the progeny at birth or at three weeks postpartum, nor did it cause an increase in animals born dead or with malformation.
REFERENCES