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PROGOUT

Allopurinol 100 mg & 300 mg Tablets



Presentation

Progout 100 mg Tablet: white, round, biconvex tablet, 3/8" in diameter, imprinted "AL" above "100" on one side. Each tablet contains 100 mg of allopurinol.

Progout 300 mg Tablet: white, round, biconvex tablet, 11mm in diameter, imprinted "AL" above "300" on one side. Each tablet contains 300 mg of allopurinol.

Uses

Actions

Allopurinol inhibits xanthine oxidase, the enzyme which catalyses the conversion of hypoxanthine to xanthine, and of xanthine to urate/uric acid.

Allopurinol decreases urate formation in two ways:

1. The inhibition of xanthine oxidase reduces the amount of hypoxanthine and xanthine converted to urate/uric acid.
2. This action makes more hypoxanthine and xanthine available for re-utilisation in the purine metabolic cycle, which in turn, by a feedback mechanism, decreases overall *de novo* purine formation.

Since allopurinol decreases urate formation, it reduces urate/uric acid concentrations in both body fluids and urine. In contrast, the uricosuric agents, which increase urate/uric acid excretion via the kidney, will reduce the urate concentration in body fluids, but increase urate/uric acid concentrations in urine. Reduction of the urate concentrations in body fluids by allopurinol permits mobilisation and dissolution of urate deposits anywhere in the body, the commonest sites being those in the skin, bones, joints and kidney interstitial tissue.

Therapeutic effects therefore include: the resolution of skin tophi and the healing of urate sinuses; eventual reduction in the frequency of attacks of acute gouty arthritis, improvement in joint mobility; reduction of the urate load to be excreted via the kidney; prevention and treatment of acute uric acid nephropathy; and, in the long-term, reduced risk of renal impairment by urate/uric acid and prevention and dissolution of uric acid renal stones.

Pharmacokinetics

Absorption:

Allopurinol is approximately 90% absorbed from the gastrointestinal tract.

Distribution:

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

Metabolism:

Allopurinol is rapidly converted in the body to the pharmacologically active principal metabolite oxypurinol and other metabolites including allopurinol riboside and oxypurinol-7-riboside. Peak

plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively. Oxypurinol is also an inhibitor of xanthine oxidase.

Excretion:

The renal clearance of hypoxanthine and xanthine is at least 10 times greater than that of uric acid. The increased xanthine and hypoxanthine in the urine have not been accompanied by problems of nephrolithiasis.

Approximately 20% of the ingested allopurinol is excreted in the faeces. Due to its rapid oxidation to oxypurinol and a renal clearance rate approximately that of glomerular filtration rate, allopurinol has a plasma half-life of about 1 to 2 hours. Allopurinol and oxypurinol are mainly excreted in the urine and little allopurinol is found in the urine 6 hours after administration. Oxypurinol, however, has a longer plasma half-life (approximately 15.0 hours) and therefore effective xanthine oxidase inhibition is maintained over a 24-hour period with single daily doses of allopurinol. Allopurinol is cleared essentially by glomerular filtration; oxypurinol is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

Indications

PROGOUT is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, or nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy).

The main clinical conditions where urate/uric acid deposition may occur are:

Idiopathic gout; uric acid lithiasis; acute uric acid nephropathy.

Neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously, or after cytotoxic therapy.

Overproduction of urate due to disorders of such enzymes as: hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome; glucose-6-phosphatase, including glycogen storage disease; phosphoribosylpyrophosphate synthetase; phosphoribosylpyrophosphate amidotransferase; adenine phosphoribosyltransferase.

PROGOUT is indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase.

PROGOUT is indicated for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary and similar measures have failed.

Dosage and Administration

Dosage in Adults:

PROGOUT should be introduced at low dosage, e.g. 100 mg/day to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor (see Dosage in Renal Impairment).

The following dosage schedules are suggested:

- 100 to 200 mg daily in mild conditions
- 300 to 600 mg daily in moderately severe conditions
- 700 to 900 mg daily in severe conditions.

If dosage on a mg/kg bodyweight basis is required, 2 to 10 mg/kg body weight/day should be used.

Dosage in Children:

Children under 15 years: 10 to 20 mg/kg body weight/day up to a maximum of 400 mg daily. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Dosage in Elderly:

In the absence of specific data, the lowest dosage that produces satisfactory urate reduction should be used. Particular attention should be paid to advice in Dosage in Renal Impairment and Warnings and Precautions.

Dosage in Renal Impairment:

Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the drug and/or its metabolites with consequent prolongation of plasma half-lives. In severe renal insufficiency, it may be advisable to use less than 100 mg/day or to use single doses of 100 mg at longer intervals than one day. If facilities are available to monitor plasma oxypurinol concentrations, the dose should be adjusted to maintain plasma oxypurinol levels below 100 micromol/litre (15.2 mg/l).

Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required 2 or 3 times per week, consideration should be given to an alternative dosage schedule of 300 to 400 mg immediately after each dialysis with none in the interim.

Dosage in Hepatic Impairment:

Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Treatment of high urate turnover conditions (neoplasia, Lesch-Nyhan syndrome):

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with allopurinol before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinisation of urine to increase solubility of urinary urate/uric acid. Dosage of PROGOUT should be at the lower end of the recommended dosage schedule.

If urate nephropathy or other pathology has compromised renal function, the advice given in Dosage in Renal Impairment should be followed.

These steps may reduce the risk of xanthine and/or oxypurinol deposition complicating the clinical situation. See also Interactions and Adverse Effects.

Monitoring Advice:

The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Instructions for Use:

Allopurinol may be taken orally once a day after a meal. It is well tolerated, especially after food. Should the daily dosage exceed 300 mg and gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

Contraindications

Allopurinol should not be administered to individuals known to be hypersensitive to allopurinol or to any components of the formulation (see Further Information).

Allopurinol should not be given concomitantly with iron salts to patients with idiopathic haemochromatosis, nor should it be given to the immediate relatives of such patients.

Warnings and Precautions

Asymptomatic hyperuricaemia *per se* is generally **not** considered an indication for use of PROGOUT. Fluid and dietary modifications with management of the underlying cause may correct the condition. If other clinical conditions suggest a need for PROGOUT it must be introduced at low dosage (50 to 100 mg/day) to reduce the risk of adverse reactions, and increased only if the serum urate response is unsatisfactory. Extra precaution should be exercised if renal function is poor (see also Dosage and Administration).

PROGOUT must be withdrawn immediately and permanently at the first signs of intolerance.

A fluid intake sufficient to yield a daily urinary output of at least two litres and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to help prevent renal precipitation of urates in hyperuricemic patients whether or not they are on allopurinol therapy.

Dermatological Effects:

PROGOUT should be **discontinued at the first appearance of skin rash or other signs, which may indicate an allergic reaction**. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme exudativum), and/or generalised vasculitis, irreversible hepatotoxicity and on rare occasions death.

Hepatic Effects:

A few cases of reversible clinical hepatotoxicity have been noted in patients taking allopurinol, and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develop in patients on allopurinol, evaluation of liver function should be part of their diagnostic workup. In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy.

Reduced doses should be used in patients with hepatic impairment.

Haematological Effects:

Bone marrow depression has been reported in patients receiving allopurinol, most of whom receive concomitant drugs with potential for causing this reaction. This has occurred as early as six weeks to as long as six years after the initiation of therapy of allopurinol. Rarely a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone.

Acute Gouty Attacks:

Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated. In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine (0.5 mg three times a day) for at least one month.

Xanthine Deposition:

In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Hypersensitivity Effects:

The occurrence of hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazides and allopurinol concurrently. For this reason, in this

clinical setting, such combinations should be administered with caution and patients should be observed closely.

Renal Effects:

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in serum urea during administration of allopurinol. Although the mechanism responsible for this has not been established, patients with impaired renal function should be carefully observed during the early stages of allopurinol administration, and dosage decreased or the drug withdrawn if increased abnormalities in renal function appear and persist. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in these patients.

Renal failure in association with administration of allopurinol has been observed among patients with hyperuricaemia secondary to neoplastic diseases. Concurrent conditions such as multiple myeloma and congestive myocardial disease were present among those patients whose renal dysfunction increased after allopurinol was begun. Renal failure is also frequently associated with gouty nephropathy and rarely with hypersensitivity reactions associated with allopurinol. Albuminuria has been observed among patients who developed clinical gout following chronic glomerulonephritis and chronic pyelonephritis.

A dose reduction will be required in patients with renal impairment (see Dosage and Administration).

Impaction of Uric Acid Renal Stones:

Adequate therapy with allopurinol will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

Carcinogenicity, Mutagenicity, Impairment of Fertility:

No data is available on whether or not allopurinol has mutagenic or carcinogenic effects within humans or animals. Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100 micrograms/mL and in vivo at doses up to 600 mg/day for mean period of 40 months. Reproduction studies in rabbits and rats using dosages up to 20 times the usual human dosage have not revealed any evidence of impaired fertility.

Only rarely has infertility in human males and impotence occurred during allopurinol therapy, however a casual relationship to the drug has not been established.

Use in Pregnancy (Category B2):

There is inadequate evidence of safety of allopurinol in human pregnancy, although it has been in wide use for many years without apparent ill consequence.

One study in mice receiving a high intraperitoneal dose on days 10 or 13 of pregnancy resulted in foetal abnormalities but extensive studies of high oral doses in mice, rats and rabbits during days 8 to 16 produced none.

Use in pregnancy only when there is no safer alternative and when the disease itself carries risks for the mother or child.

Use in Lactation:

Reports indicate that allopurinol and oxypurinol are excreted in human breast milk. Concentrations of 1.5 mg/litre allopurinol and 53.7 mg/litre oxypurinol have been demonstrated in breast milk from a woman taking allopurinol 300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed baby.

Effects on Ability to Drive and Use Machinery:

Since adverse reactions such as somnolence, vertigo and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities where alertness is mandatory until they are reasonably certain that allopurinol does not adversely affect performance.

Adverse Effects

Adverse effects are usually reversed by the reduction of dosage or complete withdrawal of allopurinol. Taking allopurinol after meals may minimise gastrointestinal disturbances. When hypersensitivity reactions occur, allopurinol should be withdrawn immediately.

Adverse effects in association with allopurinol are rare in the overall treated population and are mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorders.

Dermatological:

These are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Allopurinol should be withdrawn IMMEDIATELY should such reactions occur. After recovery from mild reactions, allopurinol may, if desired, be reintroduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, allopurinol should be PERMANENTLY withdrawn as more severe hypersensitivity reactions may occur.

Generalised Hypersensitivity:

Skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson and/or Lyell syndrome occur rarely. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. If such reactions do occur, it may be at any time during treatment. Allopurinol should be withdrawn IMMEDIATELY and PERMANENTLY.

Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

Very rarely acute anaphylactic shock has been reported.

Angioimmunoblastic Lymphadenopathy:

Angioimmunoblastic lymphadenopathy has been described rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

Hepatic Function:

Rare reports of hepatic dysfunction ranging from asymptomatic rises in liver function tests to hepatitis (including hepatic necrosis and granulomatous hepatitis) have been reported without overt evidence of more generalised hypersensitivity. Granulomatous hepatitis appears to be reversible on withdrawal of allopurinol.

Gastrointestinal:

In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking allopurinol after meals. Recurrent haematemesis has been reported as an extremely rare event, as has steatorrhoea.

Haematological:

Bone marrow suppression has been reported in patients during allopurinol therapy. However most patients were also receiving other drugs with myelosuppressive potential concomitantly. There have been occasional reports of transient reduction in the numbers of circulating formed elements of the blood, usually in association with renal and/or hepatic disorder. Adverse effects such as leukocytosis,

leukopenia, eosinophilia, thrombocytopenia and granulocytopenia have occurred very rarely. The clinical significance has yet to be demonstrated.

Other:

The following complaints have been reported occasionally: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesiae, neuropathy, visual disorder, cataract, macular changes, taste perversion, stomatitis, changed bowel habit, infertility, impotence, nocturnal emission, diabetes mellitus, hyperlipidaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia, haematuria, angioedema, gynaecomastia.

Interactions

6-Mercaptopurine and Azathioprine:

Allopurinol inhibits the enzymatic oxidation of 6-mercaptopurine and azathioprine. Therefore, when 6-mercaptopurine or azathioprine is given concurrently with allopurinol, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects.

Adenine Arabinoside:

Evidence suggests that the plasma half-life of adenine arabinoside is increased in the presence of allopurinol. When the two products are used concomitantly, extra vigilance is necessary to recognise enhanced toxic effects.

Salicylates and Uricosuric Agents:

Oxypurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxypurinol. This may decrease the therapeutic activity of allopurinol, but the significance needs to be assessed in each case.

Chlorpropamide:

If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity.

Coumarin Anticoagulants:

There is no evidence that interaction between allopurinol and the coumarins seen under experimental conditions has any clinical significance. However, all patients receiving anticoagulants must be carefully monitored.

Phenytoin:

Allopurinol may inhibit hepatic oxidation of phenytoin but clinical significance has not been demonstrated.

Theophylline:

Inhibition of the metabolism of theophylline has been reported in normal subjects given relatively high doses of allopurinol (300 mg twice daily) under experimental conditions. Although there have been no clinical reports of interaction, theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Ampicillin/Amoxicillin:

An increase in the frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The

cause of the reported association has not been established, however, it is recommended that in patients receiving allopurinol, an alternative to ampicillin or amoxicillin be used where available.

Cyclosporin:

Reports suggest that the plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporin toxicity should be considered if the drugs are co-administered.

Overdosage

Accidental or deliberate ingestion of up to 5 g of allopurinol or very rarely 20 g has been reported.

Symptoms: These include nausea, vomiting, diarrhoea and dizziness.

Treatment: Recovery followed general supportive measures. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine and/or azathioprine is being taken concomitantly. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary, haemodialysis may be used.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Progout 100 mg: Bottles of 500 tablets.

Progout 300 mg: Bottles of 500 tablets.

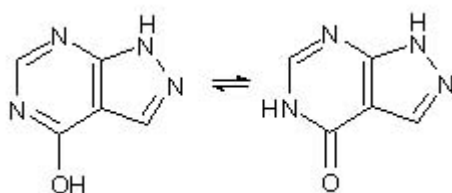
Further Information

Active ingredient

The active ingredient of Progout tablets is allopurinol.

Chemical name: 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one.

Structural formula:



Molecular formula: C₅H₄N₄O

Molecular weight: 136.1

CAS Registry no.: 315-30-0

Allopurinol is a white or off-white, almost odourless powder. It is very slightly soluble in water and in alcohol, and is practically insoluble in chloroform and in ether. It dissolves in dilute solutions of alkali hydroxides.

Other components

Progout tablets also contain the following inactive ingredients: lactose monohydrate, maize starch, povidone, sodium starch glycollate and magnesium stearate. The tablets are gluten free.

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2 February 2009