PRODUCT MONOGRAPH

[Pr] pms-ALLOPURINOL

Allopurinol Tablets, USP
100 mg, 200 mg and 300 mg

Xanthine Oxidase Inhibitor

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PRODUCT MONOGRAPH

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THERAPEUTIC CLASSIFICATION
Xanthine Oxidase Inhibitor

ACTIONS AND CLINICAL PHARMACOLOGY

Allopurinol is a structural analogue of hypoxanthine. Reduction in both the serum and urinary uric acid levels is brought about by allopurinol inhibiting the action of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid. Allopurinol is metabolized to the corresponding xanthine analogue, oxypurinol, which is also an inhibitor of xanthine oxidase. The action of allopurinol in blocking formation of urate differs from that of uricosuric agents which lower the serum uric acid level by increasing urinary excretion of uric acid.

INDICATIONS AND CLINICAL USE

Treatment of gout, either primary, or secondary to hyperuricemia which occurs in blood dyscrasias and their therapy.

Treatment of primary or secondary uric acid nephropathy, with or without accompanying signs or symptoms of gout.

Prophylactically, to prevent tissue urate deposition or renal calculi in patients with leukemias, lymphomas or other malignancies, receiving antineoplastic treatment (radiation or cytotoxic drugs) which might induce increased uricemia levels. Also in the therapy and prophylaxis of acute urate nephropathy and resultant renal failure in patients with neoplastic disease who are particularly susceptible to hyperuricemia and uric acid stone formation (especially after radiation therapy or use of antineoplastic drugs).

Prevention of the occurrence and recurrence of uric acid stones or gravel and renal calcium lithiasis in patients with hyperuricemia and/or hyperuricosuria.

CONTRAINDICATIONS

Should not be given to patients who are hypersensitive to allopurinol or who have previously developed a severe reaction to this drug or to any components of the formulation. pms-

ALLOPURINOL (allopurinol) is contraindicated in nursing mothers and in children (except in those with hyperuricemia secondary to malignancy).

WARNINGS

Allopurinol should be discontinued immediately at the appearance of a skin rash, as the rash may be, in some instances, followed by a more severe hypersensitivity reaction, including Stevens-Johnson Syndrome, DRESS, and Toxic Epidermal Necrolysis (see ADVERSE REACTIONS).

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

Reduced doses should be administered to patients with renal or hepatic impairment. The drug should be withdrawn if increased abnormalities in hepatic or renal functions appear. 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 this group.

Occupational Hazards

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

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

Asymptomatic hyperuricemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.

Mercaptopurine or Azathioprine with Allopurinol

In patients receiving mercaptopurine or azathioprine, the concomitant administration of 300 to 600 mg of allopurinol/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.

Pregnancy

Allopurinol is not recommended for use during pregnancy or in women of childbearing potential unless in the judgment of the physician, the potential benefits outweigh the possible risk to the fetus.

Children

Allopurinol should not be given to children with the exception of those with hyperuricemia secondary to malignancy or with Lesch-Nyhan syndrome, because safety and effectiveness have not been established in other conditions.

PRECAUTIONS

Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated.

Acute gout attacks may be precipitated at the start of treatment with allopurinol 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 allopurinol (100 and 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 (see DOSAGE AND ADMINISTRATION). If acute gouty attacks develop in patients receiving allopurinol, treatment should continue at the same dosage while the acute attack is treated with a suitable anti-inflammatory agent.

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 minimized by adequate hydration to achieve optimal urine dilution.

Lactation

Reports indicate that allopurinol and oxipurinol are excreted in human breast milk. Concentrations of 1.4 mg/L allopurinol and 53.7 mg/L oxipurinol have been demonstrated in breast milk from woman taking allopurinol 300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on breast-fed babies.

Drug Interactions

Mercaptopurine or Azathioprine: (see WARNINGS).

Uricosurics and Salicylates

Renal clearance of oxypurinol, the major therapeutically active metabolite of allopurinol, is increased by uricosuric agents such as probenecid or large doses of salicylate and as a consequence the addition of a uricosuric agent may reduce the extent of inhibition of xanthine oxidase by oxypurinol. However, such combined therapy may be useful in achieving minimum serum uric acid levels provided that total urinary uric acid load does not exceed the competence of the patient's renal function.

Coumarin Anticoagulants

It has been reported that under experimental conditions allopurinol prolongs the half-life of the anticoagulant, dicumarol. The clinical significance of this has not been established, but this interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Chlorpropamide
In the presence of allopurinol, there may be competition in the renal tubule for the excretion of chlorpropamide. When renal function is poor, the recognized risk of prolonged hypoglycemic activity of chlorpropamide may be increased if allopurinol is given concomitantly.

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

Phenytoin
Allopurinol may inhibit hepatic oxidation of phenytoin but the 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 b.i.d.) under experimental conditions. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. 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 is used where available.

Cyclophosphamide, Doxorubicin, Bleomycin, Procarbazine and Mechloroethamine
Enhanced bone marrow suppression reported among patients with neoplastic disease, (other than leukemia), in the presence of allopurinol. However, in a well-controlled study of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechloroethamine (mustine HCl) allopurinol did not appear to increase the toxic reaction of the cytotoxic agents.

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 coadministered.

ADVERSE REACTIONS

Adverse reactions in association with allopurinol are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder. (See WARNINGS).

Skin Reactions
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. The rash has been followed by severe hypersensitivity reactions. Allopurinol should be withdrawn **immediately** should such reactions occur. After recovery from mild reactions allopurinol may, if desired, be cautiously reintroduced at a small dose (e.g., 50 mg/day) and gradually increased. If the rash recurs, allopurinol should be **permanently** withdrawn.

Generalized Hypersensitivity
Skin reactions associated with exfoliation, fever, chills, nausea and vomiting, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson Syndrome, DRESS, and Toxic Epidermal Necrolysis have occurred. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and very rarely, epilepsy. If they do occur, it may be at any time during treatment. Allopurinol should be withdrawn **immediately** and **permanently.**

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

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

Granulomatous Hepatitis
Very rarely granulomatous hepatitis, without overt evidence of more generalized hypersensitivity has been described. It appears to be reversible on withdrawal of allopurinol.

Gastrointestinal Disorders
Diarrhea, intermittent abdominal pain, nausea and vomiting were reported. Gastrointestinal disorders diminish if allopurinol is taken after meals. Recurrent hematemesis has been reported as an extremely rare event, as has steatorrhea.

Blood and Lymphatic System
There have been occasional reports of reduction in the number of circulating formed elements of the blood, including agranulocytosis, thrombocytopenia and aplastic anemia, usually in association with renal and/or, hepatic disorders or in whom concomitant drugs have been administered which have a potential for causing these reactions.

Miscellaneous:
The following adverse effects have been reported occasionally: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesiae, taste perversion, stomatitis, changed bowel habit, infertility, hepatic necrosis, abnormal liver function tests, rise in BUN, hyperlipemia, visual disorder, cataracts, macular changes, neuropathy, impotence, diabetes mellitus, furunculosis, alopecia, discolored hair, angina, hypertension, bradycardia, hematuria, edema, uremia, drowsiness, peripheral neuritis, angioedema and gynecomastia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Ingestion of up to 22.5 g allopurinol without adverse effect has been reported. Symptoms and signs including nausea, vomiting, diarrhea, and dizziness have been reported in a patient who ingested 20 g allopurinol. 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 affecting concomitant medication, especially with mercaptopurine and/or azathioprine. No treatment is normally required provided the drug is withdrawn and adequate hydration is maintained to facilitate excretion of the drug. If considered necessary hemodialysis may be used. If, however, other forms of acute distress are observed, gastric lavage should be considered, otherwise the treatment is symptomatic.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Adults

General Considerations: pms-ALLOPURINOL (allopurinol) is administered orally. The total daily requirement should be divided into 1 to 3 doses. Daily doses up to and including 300 mg of pms-ALLOPURINOL may be taken once a-day after a meal. Larger doses should be administered as divided doses of not more than 300 mg. It should be noted that allopurinol is generally better tolerated if taken following meals.

Treatment of Gout

The dose of pms-ALLOPURINOL (allopurinol) varies with the severity of the disease. The minimum effective dose is 100 to 200 mg. The average is 200 to 300 mg/day for patients with mild gout, 400 to 600 mg/day for patients with moderately severe tophaceous gout, and 700 to 800 mg in severe conditions. The maximal recommended dose is 800 mg/day in patients with normal renal function.

Since allopurinol and its metabolites are excreted only by the kidney, accumulation of the drug can occur in renal failure and the dose of pms-ALLOPURINOL should consequently be reduced. With a creatinine clearance of 20 to 10 mL/min, a daily dosage of 200 mg of pms-ALLOPURINOL is suitable. When the creatinine clearance is less than 10 mL/min, the daily dosage should not exceed 100 mg. With extreme renal impairment (creatinine clearance less than 3 mL/min), the interval between doses may also need to be lengthened. As no simple method of measuring the blood concentrations of allopurinol is available, the correct size and frequency of dosage for maintaining the serum uric acid just within the normal range is best determined by using the serum uric acid level as an index.

Once the daily dose of pms-ALLOPURINOL necessary to produce the desired serum uric acid level has been determined, this dose should be continued until the serum uric acid level indicates a need for dosage adjustment.

Normal serum urate levels are achieved in 1 to 3 weeks. The upper limit of normal is about 6 mg % for men and postmenopausal women and 5 mg % for premenopausal women. By the selection of the appropriate dose, together with the use of uricosurics agents in certain patients, it is possible to reduce the serum uric level to normal and, if desired, to hold it as low as 2 to 3 mg %. Combined therapy of pms-ALLOPURINOL and uricosurics will often result in a reduction in dosage of both agents.

To reduce the possibility of an increase in acute attacks of gout during the early stages of pms-ALLOPURINOL administration, it is recommended that the patient start with a low dose of pms-ALLOPURINOL (100 to 200 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of about 6 mg % or less is attained. Also, a maintenance dose of colchicine should be given prophylactically when allopurinol is begun, and a high fluid intake is advisable.

In patients who are being treated with uricosuric agents, colchicine and/or anti-inflammatory agents, it is wise to continue this therapy while adjusting the dosage of allopurinol until a normal serum uric acid level and freedom from acute attacks have been maintained for several months. If desired, the patient may then be transferred to allopurinol therapy exclusively.

For the Prevention of Uric Acid Nephropathy During the Vigorous Therapy of Neoplastic Disease

Treatment with 600 to 800 mg daily for 2 or 3 days prior to chemotherapy of X-irradiation is advisable. Treatment should be continued at a dosage adjusted to the serum uric acid level until there is no longer a threat of hyperuricemia and hyperuricosuria.

pms-ALLOPURINOL (allopurinol) treatment can be maintained during the antimitotic therapy for prophylaxis of the hyperuricemia which may arise during the natural crises of the disease. In prolonged treatment, 300 to 400 mg of pms-ALLOPURINOL daily is usually enough to control the serum uric acid level.

It is essential that a daily urinary output of 2 L or more be maintained during allopurinol therapy, and neutral or alkaline urine is desirable.

Prophylaxis of Renal Calcium Lithiasis

The recommended starting dose of pms-ALLOPURINOL (allopurinol) for the prevention of recurrent calcium stones is 200 to 300 mg daily as one dose or individual doses. Therapy should be continued indefinitely. Some patients have received maintenance dosages of 200 to 300 mg daily for more than 7 years. In some patients, the maintenance dosage may be reduced to 100 to 200 mg daily.

Children (6 to 10 years of age)
For the treatment of secondary hyperuricemia associated with malignancies and in the Lesch-Nyhan syndrome, pms-ALLOPURINOL should be given in doses of 10 mg/kg/day. The response should be evaluated after approximately 48 hours by monitoring serum uric acid and/or urinary uric acid levels and adjusting the dose if necessary.

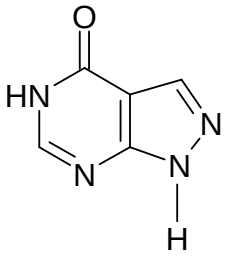
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Allopurinol

Chemical name: 4*H*-Pyrazolo [3,4-*d*]pyrimidin-4-one.

Structural formula:



Molecular formula: $C_5H_4N_4O$

Molecular mass: 136.11 g/mol

Description: Allopurinol is a position isomer of the natural purine base hypoxanthine in which the carbon and nitrogen at the number 7 and number 8 positions in the purine nucleus are transferred. It is a white, odorless, tasteless powder, insoluble in cold water, soluble in about 250 parts of hot water and in dilute sodium hydroxide.

Composition

In addition to allopurinol, each tablet also contains the non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and povidone.

pms-ALLOPURINOL 200 & 300 mg: In addition to the non-medicinal ingredients listed under composition, pms-ALLOPURINOL 200 and 300 mg tablets also contain the dye FD & C Yellow #6 Lake 40%.

Stability and Storage Recommendations

Store at room temperature (15°C – 30°C). Preserve in well-closed containers.

CLINICAL TRIALS

Comparative Bioavailability Studies

Comparative Bioavailability Study with 100 mg

A single center, pivotal, double-blind, balanced, randomized, two-sequence, two-treatment, two-period, single dose, crossover design comparative bioavailability study of pms-ALLOPURINOL 100 mg tablets (Pharmascience Inc.) was performed versus [Pr]ZYLOPRIM® 100 mg tablets (AA Pharma Inc.) administered as a 1 x 100 mg dose to 30 healthy male volunteers under fasting conditions. Bioavailability data were measured and the results are summarized on 28 subjects in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Allopurinol (1 × 100 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	1464.2 1583.5 (40.3)	1626.7 1701.8 (30.7)	90.0	84.1 - 96.3
AUC_I (ng.h/mL)	1484.3 1608.2 (41.2)	1642.8 1717.9 (30.8)	90.4	84.4 - 96.8
C_{max} (ng/mL)	573.2 627.9 (49.3)	647.7 680.7 (31.3)	88.5	80.6 - 97.2
T_{max} (h)§	1.75 (0.50 – 5.00)	1.13 (0.50 – 5.00)		
$T_{½}$ € (h)	0.90 (20.1)	0.93 (11.1)		

* pms-ALLOPURINOL 100 mg tablets; Manufactured by Pharmascience Inc., Montreal, Canada

† [Pr]ZYLOPRIM® (Allopurinol USP 100 mg tablets); Manufactured by AA Pharma Inc., Vaughan, ON, Canada and was purchased in Canada

§ Expressed as the median value (range) only

€ Expressed as the arithmetic mean (CV %) only

Comparative Bioavailability Study with 300 mg

A single center, randomized, single oral dose, double-blind, two-treatment, two-period, two-sequence, crossover bioequivalence study comparing pms-ALLOPURINOL 300 mg tablets (Pharmascience Inc.) to the Canadian reference product, ^{Pr}ZYLOPRIM® (allopurinol 300 mg tablets) (AA Pharma Inc.). The study drugs were administered as a single 300 mg dose to 32 healthy, adult male subjects under fasting conditions with 31 subjects completing the study. The bioavailability data were measured in plasma and the results are summarized on 31 subjects in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Allopurinol (1 × 300 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	6883.6 7550.3 (50.3)	6238.1 6884.8 (53.4)	110.3	105.2 – 115.7
AUC_I (ng.h/mL)	7187.5 8027.7 (56.8)	6573.6 7434.9 (62.0)	109.3	104.0 – 115.0
C_{max} (ng/mL)	2006.3 2199.0 (46.6)	1681.2 1831.0 (47.8)	119.3	111.6 – 127.7
T_{max} (h)§	1.75 (0.33 – 4.50)	2.00 (0.67 – 4.50)		
$T_{½}$ϵ (h)	1.28 (29.3)	1.35 (37.4)		

* pms-ALLOPURINOL 300 mg tablets; Manufactured by Pharmascience Inc., Montreal, Canada

† ^{Pr}ZYLOPRIM® (Allopurinol 300 mg tablets); Manufactured by AA Pharma Inc., Vaughan, ON, Canada and was purchased in Canada

§ Expressed as the median value (range) only

ϵ Expressed as the arithmetic mean (CV %) only

AVAILABILITY OF DOSAGE FORMS

pms-ALLOPURINOL 100 mg: Each white, round, biconvex tablet is debossed with "ALL" above "100" on each side of the score on one side and nothing on the other side. Available in bottles of 100 tablets.

pms-ALLOPURINOL 200 mg: Each orange, round, biconvex tablet is debossed with "ALL" above "200" on each side of the score on one side and nothing on the other side. Available in bottles of 100 tablets.

pms-ALLOPURINOL 300 mg: Each orange, round, biconvex tablet is debossed with "ALL" above "300" on each side of the score on one side and nothing on the other side. Available in bottles of 100 tablets.

PHARMACOLOGY

When taken orally, allopurinol is rapidly absorbed and rapidly metabolized. The main metabolite is oxypurinol, which is itself a xanthine oxidase inhibitor. Allopurinol and its metabolites are excreted by the kidney. The renal handling is such that allopurinol has a plasma half-life of about one hour, whereas that of oxypurinol exceeds 18 hours. Thus, the therapeutic effect can be achieved by a once-a-day dosage of allopurinol in patients taking 300 mg or less per day.

Administration of allopurinol generally results in a fall in both serum and urinary uric acid within 2 to 3 days. The magnitude of the decrease can be adjusted to a certain extent by varying the dose of allopurinol. The serum uric acid levels fall gradually and therefore a week or more of allopurinol treatment may be necessary before the full effect is obtained. Uric acid returns to pre-treatment levels slowly, usually after a cessation of therapy. This is due primarily to the accumulation and slow clearance of oxypurinol. In some patients, particularly those with tophoceous gout, a significant fall in urinary uric acid excretion may not occur, possibly due to the mobilization of urate from tissue deposits as the serum uric acid levels begins to fall.

The combined increase in hypoxanthine and xanthine excreted in the urine is usually, but not always, considerably less than the accompanying decline in urinary uric acid. This may be due to pseudofeedback inhibition of purine biosynthesis by allopurinol ribotide.

It has been shown that reutilization of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by allopurinol. This reutilization and the normal feedback inhibition which would result from an increase in available purine nucleotides serve to regulate purine biosynthesis, and, in essence, the defect of the over-producer of uric acid is thereby compensated.

Innate deficiency of xanthine oxidase, which occurs in patients with xanthinuria, as in inborn error of metabolism has been shown to be compatible with comparative well being. While urinary levels of oxypurines attained with full doses of allopurinol may in exceptional cases equal those (250-

600 mg/day) which in xanthinuric subjects have caused formation of urinary calculi, they usually fall in the range of 50-200 mg and no evidence of renal damage has been clinically observed. Xanthine crystalluria has been reported in a few exceptional cases. The serum concentration of oxypurines in patients receiving allopurinol is usually in the range of 0.3 mg to 0.4 mg % compared to a normal level of approximately 0.15 mg %. A maximum of 0.9 mg % was observed when the serum urate was lowered to less than 2 mg % by high doses of the drug. In one exceptional case, a value of 2.7 mg % was reached. These are far below the saturation level at which precipitation of xanthine or hypoxanthine would be expected to occur so that tissue deposition is unlikely and has not been observed to date. The solubilities of uric acid and xanthine in the serum are similar (about 7 mg %) while hypoxanthine is much more soluble. The finding that the renal clearance of oxypurines is at least ten times greater than that of uric acid explains the relatively low serum oxypurine concentration at a time when the serum uric acid level has decreased markedly. At serum oxypurine levels of 0.3 to 0.9 mg %, oxypurine: inulin clearance ratios were between 0.7 and 1.9. The glomerular filtration rate and urate clearance in patients receiving allopurinol do not differ significantly from those obtained prior to therapy. The rapid renal clearance of oxypurines suggests that allopurinol therapy should be of value in allowing a patient with gout to increase his total purine excretion.

TOXICOLOGY

ACUTE ORAL TOXICITY (LD50)

Rats: greater than 1100 mg/kg
Mice: greater than 953 mg/kg

SUBACUTE TOXICITY

In a 13-week feeding experiment in rats at a drug level of 72 mg/kg/day, 2 of 10 rats died; at 225 mg/kg/day, 4 to 10 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 dose described above.

Dogs survived oral dosing at 30 mg/kg/day for one year with nil 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 the 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 concentrations 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.

TERATOGENICITY

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 malformations.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

pms-ALLOPURINOL
Allopurinol Tablets, USP

Read this carefully before you start taking pms-ALLOPURINOL and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about pms-ALLOPURINOL.

What is pms-ALLOPURINOL used for?
pms-ALLOPURINOL is used for the:

- treatment of gout, a painful form of arthritis caused by high levels of uric acid in the blood;
- treatment of kidney problems due to high uric acid levels;
- treatment or prevention of uric acid build-up in tissues or kidneys in patients receiving certain cancer treatments (which may cause high levels of uric acid in the blood);
- prevention of kidney stones in patients with high levels of uric acid in the blood or urine.

How does pms-ALLOPURINOL work?
pms-ALLOPURINOL works by reducing the production of uric acid in the body.

What are the ingredients in pms-ALLOPURINOL?
Medicinal ingredients: allopurinol
Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone and FD & C Yellow #6 Lake 40% (dye, in 200 mg and 300 mg tablets only).

pms-ALLOPURINOL comes in the following dosage forms:
Tablets: 100 mg, 200 mg and 300 mg

Do not use pms-ALLOPURINOL:

- you are allergic to any of the ingredients in pms-ALLOPURINOL;
- you are breastfeeding;
- you are under the age of 18 (except in children with a high level of uric acid in the blood due to cancer or Lesch-Nyhan syndrome).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-ALLOPURINOL. Talk about any health conditions or problems you may have, including if you:

- have kidney problems;
- have liver problems;
- have heart disease;
- are pregnant or plan to become pregnant.

Other warnings you should know about:

Serious skin and allergic reactions: Some serious skin and allergic reactions such as rash, skin reddening, pain, swelling or blistering of lips, eyes or mouth, skin peeling and flu-like symptoms have been reported in patients taking pms-ALLOPURINOL. If you experience skin reactions of any kind (e.g., skin rash), stop taking pms-ALLOPURINOL **immediately** and contact your physician. Some skin reactions could lead to life-threatening allergic reactions.

pms-ALLOPURINOL should not be started until a gout attack has completely settled down.

In new patients, pms-ALLOPURINOL may cause gout attacks at the start of treatment.

pms-ALLOPURINOL may cause drowsiness. Do not drive or use machines until you know how pms-ALLOPURINOL affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-ALLOPURINOL:

- mercaptopurine - a drug used to treat leukemia;
- azathioprine - a drug that reduces the strength of the immune system (immunosuppressant);
- uricosurics (e.g., probenecid) - drugs that help remove uric acid from the body through the urine;
- salicylates (e.g., Aspirin) - anti-inflammatory drugs;
- coumarin anticoagulants (e.g., dicumarol) - a type of blood-thinner;
- chlorpropamide - a drug used to control blood-sugar levels;
- vidarabine - an anti-viral drug;
- phenytoin - a drug used to control seizures;
- theophylline - a drug used to treat certain breathing problems;
- ampicillin/amoxicillin - types of antibiotics;
- cyclophosphamide, doxorubicin, bleomycin, procarbazine and mechloroethamine - drugs used to treat cancer; and
- cyclosporine - a drug used to treat autoimmune conditions or to prevent organ rejection after transplantation.

How to take pms-ALLOPURINOL:
Follow the directions given to you by your healthcare professional.

Take pms-ALLOPURINOL:

- by mouth;
- with food;
- with plenty of fluids during treatment.

Usual dose:
Your dose will depend on your medical condition and the recommendations of your healthcare professional. If you take 300 mg or less of pms-ALLOPURINOL each day, you may take it as a

single dose, once a day. If you take more than 300 mg of pms-ALLOPURINOL each day, it should be divided in 2 or 3 doses per day (of not more than 300 mg per dose). Your dose may be adjusted depending on how well pms-ALLOPURINOL is working.

Overdose:

If you think you have taken too much pms-ALLOPURINOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as you remember. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed dose.

What are possible side effects from using pms-ALLOPURINOL?

These are not all the possible side effects you may feel when taking pms-ALLOPURINOL. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- diarrhea;
- abdominal pain;
- nausea;
- vomiting;
- change in normal bowel habits;
- changes in taste sensation;
- mouth ulcers;
- headache;
- dizziness;
- drowsiness;
- unsteadiness when walking.

Your doctor will perform regular kidney and liver function tests when you are taking pms-ALLOPURINOL.

pms-ALLOPURINOL may cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Skin reactions: itchy or flaky skin, reddening of skin, raised skin rash			√
RARE			
Allergic reaction: difficulty breathing, swelling of the face and throat, rash, skin reddening, pain, swelling or blistering of lips, eyes or mouth, hives, skin peeling, flu-like symptoms			√
Lymphadenopathy (swollen glands): swollen glands in the neck, armpit or groin			√
VERY RARE			
Vomiting blood			√
Liver problems: yellowing of the skin and the whites of eyes, nausea and vomiting, a general sense of feeling unwell, abdominal pain and swelling, a tendency to bruise and bleed easily and mental disorientation or confusion		√	
Kidney problems: any change in the amount, frequency or colour of urine.		√	
Steatorrhea (excessive fat in stool): pale, bulky, foul-smelling stool	√		
UNKNOWN			
Depression		√	
Infertility		√	
Changes in vision		√	
Feeling of weakness, pain, numbness, prickling or tingling in hands or feet		√	
Impotence		√	
Too much sugar in the blood (diabetes)		√	
Red, swollen, painful bumps under the skin (boils)		√	
Chest pain		√	
High blood pressure		√	

Slow heart beat		√	
Buildup of fluid leading to swelling in the arms or legs		√	
Hair loss	√		
Discoloration of hair	√		
Enlarged breasts in men	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adversereactionreporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 -30°C). Preserve in well-closed containers

Keep out of reach and sight of children.

If you want more information about pms-ALLOPURINOL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) the manufacturer's website (https://www.pharmascience.com) or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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