

ALLOPURINOL TABLETS BP 100 MG



Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

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INN (GENERIC NAME)

ALLOPURINOL TABLETS BP 100 mg

1.2 Strength :- 100 mg

1.3 Pharmaceutical form :- Tablets

ALLOPURINOL TABLETS BP 100 mg



2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALLOPURINOL TABLETS BP 100 mg

Each uncoated tablet contains:

Allopurinol BP 100 mg

Excipients q.s.

Batch Size: 100000 Tablets

Sr. No.	Ingredients	Specification	Label amount mg	% Overages	Qty. / Tablet Mg	Reason for Inclusion
1.	Allopurinol	BP	100 mg	--	100.0	Active
2.	Maize Starch	BP	--	--	87.00	Diluent
3.	Dibasic Calcium Phosphate	BP	--	--	20.00	Diluent
4.	Microcrystalline Cellulose	BP	--	--	10.00	Diluent
5.	PVPK 30	BP	--	--	5.000	Binder
6.	Methylene Chloride#	BP	--	--	--	Solvent
	LUBRICATION					
7.	Purified Talc	BP	--	--	10.00	Lubricant
8.	Magnesium Stearate	BP	--	--	3.000	Lubricant
9.	Sodium Starch Glycolate	BP	--	--	5.000	Disintegrant

#Not a part of finished product (Methylene Chloride(Methylene Chloride evaporates during the manufacturing process))

BP = British Pharmacopoeia

3. PHARMACEUTICAL FORM. :

White coloured, elongated, biconvex, uncoated tablets, having a breakline on one side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Allopurinol is mainly used in the management of primary gout or secondary hyperuricaemia associated with chronic gout. It is not, however, used to treat an acute attack of gout as it has no analgesic, anti-inflammatory or uricosuric activity and may prolong the attack. It is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition may occur such as: uric acid nephropathy; recurrent uric acid stone formation; certain enzyme disorders or blood disorders which lead to overproduction of urate (e.g. Lesch-Nyhan syndrome; haemolytic anaemia); hyperuricaemia associated with malignancy and cytotoxic therapy which result in a high cell turnover rate.

Allopurinol is indicated for the prevention and treatment of calcium oxalate/phosphate renal stones in the presence of high uric acid levels of the blood and/or urine.

4.2 Posology and method of administration:

Posology

Allopurinol may increase the frequency of acute attacks during the first few months of therapy; it is therefore recommended that low doses be given initially and slowly increased, and that anti-inflammatory agents or colchicine should be given concomitantly during this period as prophylactic cover. The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Adults

Initiating therapy: In patients with good renal function, doses of 100 mg should be given and increased by 50 mg to 100 mg at weekly intervals until target serum urate is reached (less than 0.36 mmol/L). 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.

If changing therapy from a uricosuric agent alone, the dose should be reduced gradually while allopurinol is introduced.

In severe cases of chronic gout, allopurinol can be used together with a uricosuric agent unless the latter is contraindicated (see section 4.3)

Paediatric population

Children

The average daily dose is 10-20 mg/kg body weight up to a maximum of 400 mg per day. Use in children is rarely indicated except in malignant conditions and certain enzyme disorders.

Elderly population

The lowest dose, which produces satisfactory urate reduction, should be used. Special attention to dosage is necessary if there is overt renal dysfunction (see section 4.2 and section 4.4).

Renal impairment

The excretion of allopurinol and its metabolites is prolonged so dosage reductions are recommended. Doses of 100 to 200 mg daily should be used if creatinine clearance is between 10 – 20 mL/min. and not more than 100 mg per day should be used if clearance is less. These doses may be halved or reduced even further when initiating therapy and then slowly increased depending on response. Allopurinol and its metabolites may be removed by renal dialysis.

Hepatic impairment

Dosage reductions are necessary if the hepatic function is compromised. Liver function tests and complete blood counts should be performed before, and periodically during allopurinol therapy.

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Malignancy or cancer therapy hyperuricaemia

Therapy should be initiated 2 to 3 days prior to cytotoxic therapy after which maintenance doses are given according to response. Adequate hydration is essential throughout.

Method of Administration

Allopurinol may be taken once daily after a meal. It is normally well tolerated, especially after food. Should the total daily dose exceed 300 mg and/or gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

4.3 Contraindications:

Allopurinol should not be administered to individuals known to be hypersensitive to allopurinol or to any of the components of the formulation, listed in section 6.1.

4.4 Special warnings and precautions for use:

Hypersensitivity syndrome, SJS and TEN

Allopurinol should be discontinued immediately at the first sign of a rash or other sign of immediate allergic reactions. The risk of skin reactions appears to be highest in the first 2 months of treatment and in patients taking higher doses. However, reactions may also be delayed. Skin reactions can include erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or a diffuse maculopapular or exfoliative dermatitis, fatal cases have been reported. Skin reactions may also occur as part of a generalised hypersensitivity reaction. A DRESS syndrome (drug rash with eosinophilia and systemic symptoms) characterised by exfoliative dermatitis with eosinophilia complicated by symptoms such as hepatitis and interstitial nephritis has been described in association with allopurinol treatment. Patients have been successfully treated by immediate withdrawal of allopurinol and use of corticosteroids.

Chronic renal impairment

Patients with chronic renal impairment and concomitant diuretic use, in particular thiazides, may be at increased risk of developing hypersensitivity reactions including SJS/TEN associated with allopurinol. Extra vigilance for the signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms (see section 4.8).

Acute gouty attacks

To avoid precipitating an acute attack of gout, allopurinol should be introduced slowly and the patient should usually be given initial prophylactic cover (see section 4.2). Allopurinol should not be started during an acute attack as it may prolong the attack. However, allopurinol is continued when acute attacks occur in patients already on treatment.

Xanthine deposition

In conditions where the rate of urate formation is greatly increased, the concentration of xanthine in the urine could result in the formation of xanthine stones in the urinary tract. To avoid xanthine stones being deposited, it is advisable to maintain a high fluid intake and a neutral or alkaline urinary pH, especially if initial uric acid concentrations are high and the patient is symptomatic.

Impaction of uric acid renal stones

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

Asymptomatic hyperuricaemia

Allopurinol is not recommended for the treatment of asymptomatic hyperuricaemia

4.5 Interaction with other medicinal products and other forms of interaction:

Warfarin/Coumarin Anticoagulants:

Patients may need careful monitoring, as there have been reports of an increased response to oral anticoagulants.

Azathioprine and mercaptopurine:

Allopurinol inhibits the oxidative metabolism of azathioprine and mercaptopurine by xanthine oxidase. When mercaptopurine or azathioprine is given concurrently with allopurinol, only one quarter of the usual dose of mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity and increase the possibility of toxic effect e.g., an azathioprine dose of 100 mg should be reduced to 25 mg. All patients receiving this combination must be carefully monitored. The risk of overdosage is also increased when allopurinol is being given concomitantly with mercaptopurine or azathioprine, (see section 4.9).

Amoxicillin / Ampicillin:

Allopurinol or hyperuricaemia may potentiate aminopenicillin allergenicity and the combination should be avoided if possible.

Uricosuric Agents and Salicylates:

Medicines with uricosuric activity may accelerate the excretion of oxypurinol the active metabolite of allopurinol. This may decrease the therapeutic activity of allopurinol, but the significance should be assessed in each case.

Didanosine:

Plasma didanosine C_{max} and AUC levels were approximately doubled with concomitant allopurinol treatment without affecting the terminal half-life. Therefore coadministration is not recommended. If concomitant use is unavoidable a dose reduction of didanosine may be required and patients should be closely monitored.

Diuretics:

Thiazide diuretics may increase the risk of serious allopurinol toxicity, including hypersensitivity reactions and the combination should be monitored, especially if renal function is compromised.

Theophylline and Other Xanthines:

High dose allopurinol (600 - 900 mg) can reduce the clearance of theophylline and other xanthines and may cause theophylline toxicity unless the dosage of the latter is reduced.

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Chlorpropamide:

Caution is indicated as allopurinol may enhance the hypoglycaemic effect of chlorpropamide by competing for renal tubular secretion.

Vidarabine (Adenine Arabinoside):

Extra vigilance is necessary when vidarabine and allopurinol are used concomitantly as the plasma half-life of vidarabine may be increased resulting in enhanced toxic effects.

Phenytoin:

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

Angiotensin Converting Enzyme Inhibitors:

Isolated reports indicate that concurrent administration of captopril and allopurinol may predispose to hypersensitivity reactions e.g. Stevens-Johnson syndrome. Patients on the combination should be monitored and if a reaction occurs, use of the medications discontinued.

Cyclophosphamide and other Cytotoxic Agents:

Concurrent cyclophosphamide or other cytotoxic therapy and allopurinol therapy may increase the incidence of bone marrow depression as compared with cyclophosphamide alone. The mechanism for this interaction is not known. However, in a well-controlled study patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechlorethamine allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

Cyclosporin:

Plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporin toxicity should be considered if the medicines are co-administered.

4.6 Pregnancy and lactation:

Pregnancy

Although animal studies have not indicated any incidence of teratogenicity, the effect of allopurinol on the human foetus is unknown and it should be used in pregnancy only if clearly indicated.

Breast-feeding

Allopurinol and oxypurinol are distributed into breast milk. Allopurinol should thus be used with caution in view of the potential for adverse effects, especially hypersensitivity reactions.

4.7 Effects on ability to drive and use machines:

Drowsiness may occur. Patients should be warned not to engage in activities where alertness is mandatory until their response to allopurinol is known.

4.8 Undesirable Effects:

The most common adverse effect of allopurinol is a pruritic, maculopapular rash (10%) which may occur more frequently in patients with renal failure.

Skin and Subcutaneous Tissue Disorders

Rash, alopecia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis. Skin reactions may be delayed and rarely have been followed by severe hypersensitivity reactions which may be fatal. It is therefore recommended that allopurinol be withdrawn immediately if a rash or other signs of allergy occur.

Immune System Disorders

Hypersensitivity reactions, angioimmunoblastic lymphadenopathy, DRESS.

Serious hypersensitivity reactions, including skin reactions and characterised by fever, chills, leucopenia or leucocytosis, eosinophilia, arthralgia, pruritus, have occurred occasionally. A generalised hypersensitivity vasculitis can lead to renal and hepatic damage and very rarely seizures. These above reactions may be severe and lifethreatening and may occur more frequently in patients with renal impairment and/or taking thiazide diuretics. Allopurinol should be withdrawn immediately and permanently (see section 4.4).

Eye Disorders

Some patients develop cataracts but a causal relationship to allopurinol is still uncertain.

General Disorders and Administration Site Conditions

Asthenia, oedema, fever (can occur with or without symptoms of a generalised hypersensitivity reaction)

Nervous System Disorders

Headache, vertigo, ataxia, peripheral neuritis, drowsiness, confusion, coma, paraesthesia, taste perversion.

Blood and Lymphatic System Disorders

Agranulocytosis, aplastic anaemia, thrombocytopenia

Metabolism and Nutrition Disorders

Diabetes mellitus, hyperlipidaemia

Psychiatric Disorders

Depression

Cardiac Disorders

Angina, bradycardia

Gastrointestinal Disorders

Nausea, vomiting, diarrhoea, abdominal pain, gastritis and dyspepsia. Patients can be advised to take allopurinol after food.

Hepatobiliary Disorders

Alterations in liver function tests hepatomegaly, hepatitis and jaundice Hepatic dysfunction has occasionally been reported with or without signs of hypersensitivity.

Renal and Urinary Disorders

Interstitial nephritis, xanthine stone deposition, impaction of partly dissolved renal uric acid stones in the ureter.

Adequate hydration is important especially in patients with significant hyperuricaemia and tophaceous deposits. Alkalinization of the urine will further reduce crystalluria. On initiating therapy, patients may experience an increase in acute gouty attacks (see Dosage and Administration).

Reproductive System and Breast Disorders

Impotence, male infertility, gynaecomastia

4.9 OVERDOSE:

Symptoms:

Nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20 g of allopurinol. Ingestion of larger doses has been reported without adverse effects.

Treatment

The patient should be monitored and receive general supportive measures. Concomitant medication, especially with mercaptopurine or azathioprine may affect the symptoms noted. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary haemodialysis may be used.

5 Pharmacological Properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antigout preparations inhibiting uric acid production

ATC Code: M04 AA01

Allopurinol is used to decrease uric acid concentrations in plasma and/or urine when hyperuricaemia is clinically significant. Allopurinol and its active metabolite oxypurinol inhibit xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid. Inhibition of this enzyme accounts for the major pharmacological effects of allopurinol. In addition, allopurinol increases re-utilization of hypoxanthine and xanthine for nucleotide and nucleic acid synthesis via an action involving the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRTase). The resultant increase in nucleotide concentration leads to feedback inhibition of de novo purine synthesis. Allopurinol thereby decreases uric acid concentrations in both serum and urine.

Accompanying the decreases in uric acid produced by allopurinol is an increase in serum and urine concentrations of hypoxanthine and xanthine. Plasma concentrations of these oxypurines are only slightly increased and renal clearance is rapid and greater than that of uric acid. In the absence of allopurinol, normal urinary output of oxypurines is almost solely in the form of uric acid. After administration of allopurinol, it is composed of hypoxanthine, xanthine and uric acid. Since each has its independent solubility, the concentration of uric acid in plasma is reduced without exposing the urinary tract to an excessive load of uric acid, thus decreasing the risk of crystalluria. By lowering the uric acid concentration in the plasma below its limits of

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solubility, allopurinol facilitates dissolution of tophi. Although the levels of hypoxanthine and xanthine are increased, the risk of their deposition is less than that of uric acid as they are more soluble and are rapidly cleared by the kidney (see section 4.4).

5.2 Pharmacokinetic properties:

Absorption:

Up to 90% of an oral dose of allopurinol is absorbed in the gastrointestinal tract. After allopurinol tablet administration, peak plasma levels occur generally at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively.

Distribution:

Allopurinol and oxypurinol are not bound to plasma proteins and distribute in the total tissue water.

Biotransformation:

The allopurinol is rapidly metabolised to the active metabolite oxypurinol (alloxanthine). Both allopurinol and oxypurinol are conjugated to form their respective ribonucleosides (Allopurinol-riboside and oxypurinol-7-riboside).

Elimination:

Allopurinol has a plasma half-life of 1 to 3 hours. It is converted in the liver primarily to the active metabolite oxypurinol, which has a plasma half-life of 12 to 30 hours in people with normal renal function; this is prolonged in the presence of renal dysfunction. Excretion is mainly through the kidneys with up to 10% being excreted unchanged in the urine. 70% is excreted in the urine as oxypurinol but this occurs more slowly since it also undergoes tubular reabsorption. The remainder of the dose is excreted in the faeces as unchanged drug.

Serum urate concentrations usually begin to decline slowly within 48 to 72 hours reaching a plateau after 1 to 3 weeks of therapy. However, in patients with tophaceous gout or those who are under-secretors of uric acid, a decline in serum urate levels may be delayed for the first few months.

5.3 Preclinical safety data:

Mutagenicity

Cytogenic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100 g/mL and in vivo at doses up to 60mg/day for a mean period of 40 months. Allopurinol does not produce nitroso compounds or affect lymphocyte transformation in vitro. Evidence suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

Carcinogenicity

No evidence of carcinogenicity has been found in mice treated with allopurinol for up to 2 years.

Teratogenicity

While one study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, in a similar study in rats at 120 mg/kg on day 12 of

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gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol (up to 100 mg/kg/day in mice, up to 200 mg/kg/day in rats and up to 150 mg/kg/day in rabbits) during days 8 to 16 of gestation produced no teratogenic effects.

An in vitro study using foetal mouse salivary glands in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

6 Pharmaceutical Particulars

6.1 List of Excipients.

Sr. No.	Ingredients	Specifications
1.	Maize Starch	BP
2.	Dibasic Calcium Phosphate	BP
3.	Microcrystalline Cellulose	BP
4.	PVPK 30	BP
5.	Methylene Chloride	BP
6.	Purified Talc	BP
7.	Magnesium Stearate	BP
8.	Sodium Starch Glycolate	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store in cool & dry place

6.5 Nature and contents of container

Blister pack of 10 Tablets.