

## **Summary of Product Characteristics for Pharmaceutical Products**

### **1. Name of the medicinal product:**

Allogout 100 mg tablets

Allogout 300 mg tablets

### **2. Qualitative and quantitative composition**

Allogout – 100:

Each tablet contains 100 mg Allopurinol USP.

Excipient with known effect:

Mannitol

For a full list of excipients, see section 6.1.

Allogout – 300:

Each tablet contains Allopurinol 300mg

Excipients with known effect:

Mannitol

For the full list of excipients, see section 6.1

### **3. Pharmaceutical form**

Uncoated Tablets.

### **4. Clinical particulars**

#### **4.1 Therapeutic indications**

Allopurinol is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, 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; certain enzyme disorders which lead to overproduction of urate, for example: hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome; glucose-6-phosphatase including glycogen storage disease; phosphoribosylpyrophosphate synthetase, phosphoribosylpyrophosphate amidotransferase; adenine phosphoribosyltransferase. Allopurinol is indicated for management of

2,8-dihydroxyadenine (2, 8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase.

Allopurinol 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.

## **4.2 Posology and method of administration**

Posology

Adults:

Allopurinol 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. 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 bodyweight/day should be used.

Paediatric population:

Children under 15 years: 10 to 20 mg/kg bodyweight/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. Allopurinol 300mg should not be given to children

Older people:

In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used. Particular attention should be paid to advice in patients with renal impairment

### **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 per day or to use single doses of 100 mg at longer intervals than one day. If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2 mg/litre).

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

### **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, e.g. neoplasia, Lesch-Nyhan syndrome**

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with Allopurinol Ipca 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 Allopurinol Ipca 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 section 4.2 *Renal impairment* should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also section 4.5 and section 4.8.

**Monitoring Advice**

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

**Method of administration**

Allopurinol 300mg USP 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.

**4.3 Contraindications**

Allopurinol should not be administered to individuals known to be hypersensitive to the active substance or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

Hypersensitivity syndrome, Steven Johnsons Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN. These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. HLA-B\*5801 allele The HLA-B\*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B\*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, 8-15% in the Thai, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin. Screening for HLA-B\*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the

risk in these patients additionally in case that no HLA-B\*5801 genotyping is available for patients with Han Chinese, Thai or Korean descent the benefits should be thoroughly assessed and considered outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations. If the patient is a known carrier of HLA-B\*5801 (especially in those who are from Han Chinese, Thai or Korean descent, allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

SJS/TEN can still occur in patients who are found to be negative for HLA-B\*5801 irrespective of their ethnic origin. 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. Hepatic or renal impairment.

Reduced doses should be used in patients with hepatic or renal impairment. 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. Asymptomatic hyperuricaemia: Asymptomatic hyperuricaemia 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. 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 for at least one month. The literature should be consulted for details of appropriate dosage and precautions and warnings. If acute 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. 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. 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.

Thyroid disorders: Increased TSH values ( $>5.5$   $\mu\text{IU/mL}$ ) were observed in patients on long-term treatment with allopurinol (5.8%) in a long-term

open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

**Cytostatics** With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone. Blood count monitoring should therefore be performed at regular intervals.

**Aluminium hydroxide:**

If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines. **Coumarin anticoagulants:** There have been rare reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol, therefore, all patients receiving anticoagulants must be carefully monitored.

**Azathioprine and 6-mercaptopurine:**

Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. 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.

**Vidarabine (Adenine arabinoside):**

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 recognise enhanced toxic effects.

**Salicylates and uricosuric agents:**

Oxipurinol, the major active metabolite of allopurinol, is excreted by the kidney in a similar way to urate. Hence drugs with uricosuric activity such as probenecid or large doses of salicylates may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of allopurinol.

**Chlorpropamide:**

If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity, because allopurinol and chlorpropamide may compete for excretion in the renal tubule.

**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. The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. 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 with

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.

**Ciclosporin:**

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

**Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechlorethamine:** Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (other than leukaemia), in the presence of allopurinol. However, in a well-controlled study of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechlorethamine (chlormethine hydrochloride) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

**Didanosine:**

In healthy volunteers and HIV patients receiving didanosine, plasma didanosine C<sub>max</sub> and AUC values were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting terminal half-life. Co-administration of these 2 drugs is generally not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.

**Diuretics:**

An interaction between allopurinol and furosemide that results in increased serum urate and plasma oxipurinol concentrations has been reported. An increased risk of hypersensitivity has been reported when allopurinol is given with diuretics, in particular thiazides, especially in renal impairment.

**Angiotensin-converting-enzyme (ACE) inhibitors:**

An increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors especially in renal impairment

## **4.6 Pregnancy and Lactation**

**Pregnancy:** 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. Use in pregnancy only when there is no safer alternative and when the disease itself carries risk for the mother or unborn child. **Breast-feeding:** Allopurinol and its metabolite oxipurinol is excreted in human breast milk. Allopurinol during breastfeeding is not recommended.

Concentrations of 1.4mg/litre allopurinol and 53.7 mg/litre 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 the breast-fed baby

#### 4.7 Effects on ability to drive and use machines

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 until they are reasonably certain that allopurinol does not adversely affect performance.

#### 4.8 Undesirable effects

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.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ ),

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ),

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ),

Very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Some of the symptoms reported as undesirable effects may be associated symptoms of migraine.

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very rare	Furuncle
Blood and lymphatic system disorders	Very rare	Agranulocytosis Aplastic anaemia Thrombocytopenia
Immune system disorders	Uncommon	Hypersensitivity
	Very rare	Angioimmunoblastic T-cell lymphoma 3, Anaphylactic reaction
Metabolism and nutrition disorders	Very rare	Diabetes mellitus Hyperlipidaemia
Psychiatric disorders	Very rare	Depression

Nervous system disorders	Very rare	Coma Paralysis Ataxia Neuropathy peripheral Paraesthesia Somnolence Headache Dysgeusia
	Not known	Aseptic meningitis

Reporting of suspected adverse reactions. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

## 4.9 Overdose

Ingestion of up to 22.5 g allopurinol without adverse effect has been reported. Symptoms and signs including nausea, vomiting, diarrhoea 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 6-mercaptopurine and/or azathioprine. 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: Preparations inhibiting uric acid production, ATC code: M04AA01 Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxipurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. In addition to the inhibition of purine catabolism in some but not all hyperuricaemic patients, de novo purine biosynthesis is depressed via feedback inhibition of hypoxanthine-guanine phosphoribosyltransferase. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7 riboside.

### 5.2 Pharmacokinetic properties



**Absorption:** Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected allopurinol in the blood 30-60 minutes after dosing. Estimates of bioavailability vary from 67% to 90%. Peak plasma levels of allopurinol generally occur approximately 1.5 hours after oral administration of Allopurinol but fall rapidly and are barely detectable after 6 hours. Peak levels of oxipurinol generally occur after 3-5 hours after oral administration of Allopurinol and are much more sustained.

**Distribution:** Allopurinol is negligibly bound by plasma proteins and therefore variations in protein binding are not thought to significantly alter clearance. The apparent volume of distribution of allopurinol is approximately 1.6 litre/kg which suggests relatively extensive uptake by tissues. Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxipurinol will be present in the highest concentrations in the liver and intestinal mucosa where xanthine oxidase activity is high.

**Biotransformation** The main metabolite of Allopurinol tablets is oxipurinol. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7-riboside.

**Elimination:** Approximately 20% of the ingested allopurinol is excreted in the faeces. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1 to 2 hours. Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxipurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore, effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of Allopurinol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5-10 mg/litre. Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

**Pharmacokinetics in patients with renal impairment.** Allopurinol and oxipurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20ml/min, showed plasma oxipurinol concentrations of approximately 30mg/litre after prolonged treatment with 300 mg allopurinol per day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function. A reduction in the dose of Allopurinol is therefore required in patients with renal impairment.

**Pharmacokinetics in elderly patients.** The kinetics of the drug are not likely to be altered other than due to deterioration in renal function (see Pharmacokinetics in patients with renal impairment).

### 5.3 Preclinical safety data

#### *Mutagenicity*

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 a mean period of 40 months.

Allopurinol does not produce nitroso compounds *in vitro* or affect lymphocyte transformation *in vitro*.

Evidence from biochemical and other cytological investigations strongly 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 and rats treated with allopurinol for up to 2 years.

#### *Teratogenicity*

One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, however in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in mice up to 100 mg/kg/day, rats up to 200 mg/kg/day and rabbits up to 150 mg/kg/day 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.	Name of the Ingredients	Specification
1.	Crosscarmellose sodium	BP
2.	Crosspovidone	BP
3.	MCC PH102	BP
4.	Povidone K-30	BP
5.	Mannitol	BP
6.	Purified Water	IHS
7.	Magnesium Stearate	BP
8.	Sodium Starch Glycolate	BP

<b>9.</b>	Sodium Lauryl Sulphate	BP
<b>10.</b>	Purified Talc	BP

## **6.2 Incompatibilities**

None reported

## **6.3 Shelf-Life**

36 months

## **6.4 Special Precautions for storage**

Store below 30°C.  
Protect from light and moisture.  
Keep medicine out of reach of children

## **6.5 Nature and Content of container**

Blister pack of 10 tablets

## **6.6 Special precautions for disposal and other handling**

Not applicable.

## **7. Marketing Authorization Holder**

*Please provide details for the Marketing Authorization Holder*

## **8. Marketing Authorization Number**

*Please provide details for the Marketing Authorization Number*

## **9. Date of first authorization/renewal of the authorization**

CTD9964

## **10. Date of revision of the text**

09/05/2025