

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Allopurinol 100 mg Tablets

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 100 mg Allopurinol.

Excipients: lactose monohydrate

Each tablet Allopurinol 100 mg contains 60 mg lactose monohydrate

For a full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Tablet

White, biconvex tablets, debossed: 4K1, plain on reverse.

### **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. skin tophi, gouty arthritis, and 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: uric acid lithiasis; idiopathic gout; 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 also indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase. Allopurinol is also 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**

For oral administration.

Dosage should be modified by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Dose frequency:

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

Adults:

2 - 10 mg/kg bodyweight/day or 100 - 200 mg daily in mild conditions, 300 - 600 mg daily in moderately severe conditions, or 700 - 900 mg daily in severe conditions. The initial dose should be in the range of 100 to 300 mg per day which may be taken as a single dose preferably after food.

Children under 15 years:

10 - 20 mg/kg bodyweight/day, or 100 to 400 mg daily. Use in children is rarely indicated except in malignant conditions, especially in leukaemia and certain enzyme disorders, for example Lesch-Nyhan syndrome.

Elderly:

No specific dosage recommendations, the lowest dosage which produces satisfactory urate reduction should be used. Also refer to dosage advice under *Dosage recommendations in renal disorders* and section 4.4 *Special warnings and precautions for use*.

Treatment of high urate turnover conditions e.g. neoplasia, Lesch-Nyhan syndrome:

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with allopurinol before commencing 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. The dose of allopurinol should be in the lower range.

If urate nephropathy or other pathology has compromised renal function, advice provided in *Dosage recommendations in renal disorder* should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also sections 4.5 *Interaction with other medicinal products and other forms of interaction* and 4.8 *Undesirable effects*.

Dosage recommendations in renal disorders:

Allopurinol and its metabolites are excreted by the kidney, therefore impairment of renal function may lead to retention of the drug and/or its metabolites. The plasma half lives may as a consequence be prolonged. Serious consideration should be given in the presence of impaired renal function, to initiating treatment with a maximum dose of 100 mg/day and increasing it only if the serum and/or urinary rate response is unsatisfactory. 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.

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.

Alternative schedules based on creatinine clearances are unsatisfactory, because of inaccuracy of low clearance values.

If plasma oxipurinol concentration monitoring is available, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/Litre (15.2 microgram/ml).

Dose recommendations in renal dialysis:

Allopurinol and its metabolites are removed by renal dialysis. If frequent dialysis is required an alternative schedule of 300 - 400 mg allopurinol after each dialysis with none in the interim should be considered.

### 4.3 Contraindications

Allopurinol is contraindicated where there is known intolerance, where there is hypersensitivity to any of the excipients and in cases of acute gout. However, prophylactic therapy may be started when the acute attack has completely subsided, provided that anti-inflammatory therapy is also taken.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.4 Special warnings and precautions for use

Treatment should not be started during or immediately after an acute attack of gout (see section 4.3 *Contraindications*).

As with other uricosuric agents, in the early stages of treatment with allopurinol, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to employ prophylactic therapy with a suitable anti-inflammatory agent or colchicine (0.5 mg three times a day) for at least a month.

The dosage of allopurinol should be reduced in patients with renal or hepatic diseases.

Particular care should be taken in the elderly where renal function may be reduced thus leading to a retention of the drug and its metabolites with the consequent prolongation of action.

Allopurinol should be withdrawn immediately when a skin rash or other evidence of hypersensitivity occurs. It should be withdrawn immediately and permanently at the first sign of intolerance.

Patients under treatment for cardiac insufficiency or hypertension, for example with ACE inhibitors or diuretics, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia *per se* is not an indication for allopurinol therapy. Fluid and dietary modification with modification of the underlying cause may correct the condition. If other clinical conditions suggest a need for allopurinol, it must be introduced at a low dosage (50 to 100 mg/day) to reduce the risk of adverse reactions. The dose should only be increased if the serum urate response is unsatisfactory.

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

The therapeutically active major metabolite of allopurinol, oxipurinol, is excreted by the kidney in a similar way to urate. Therefore drugs with uricosuric activity e.g. probenecid, or large doses of salicylate, may accelerate oxipurinol excretion. This may have the effect of decreasing the therapeutic activity of allopurinol, however the significance needs to be assessed in every case.

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.

When 6-mercaptopurine or azathioprine is given by mouth concurrently with allopurinol, only one quarter of the usual dose of those drugs should be given because inhibition of xanthine oxidase will prolong their activity. If allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity.

There is evidence to suggest that the plasma half-life of vidarabine (adenine arabinoside) is increased in the presence of allopurinol. Extra vigilance is required during concomitant use of the two products to recognise enhanced toxic effects.

Allopurinol may inhibit the hepatic oxidation of phenytoin, however the clinical significance of this has not been established.

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 increasing or starting allopurinol therapy.

An increase in the frequency of skin rash has been reported among patients receiving amoxicillin or ampicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the association has not been established. However, it is recommended that in patients receiving allopurinol an alternative to amoxicillin or ampicillin is used where available.

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 doxorubicin, bleomycin, cyclophosphamide, procarbazine and/or mechloroethamine (mustine hydrochloride) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

There have been reports suggesting 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 to be co-administered.

#### **4.6 Pregnancy and lactation**

There is insufficient evidence of the safety of allopurinol in human pregnancy, although it has been widely used for many years without apparent ill consequence.

Allopurinol should be used in pregnancy only where there is no safer alternative and when the disease itself carries risks for the mother or child.

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 rats up to 200 mg/kg/day, mice up to 100 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of the gestation period produced no teratogenic effects.

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

Reports indicate that allopurinol is excreted in human breast milk. 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 vertigo, somnolence 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 sure that allopurinol does not adversely affect performance.

#### 4.8 **Undesirable effects**

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The frequency categories assigned to the adverse drug reactions below are estimates: for most reactions, suitable data for calculating incidence are not available. Adverse drug reactions identified through post-marketing surveillance were considered to be rare or very rare. The following convention has been used for the classification of frequency:

Very common ( $\geq 1/10$ );

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

Uncommon ( $\geq 1/1000$  to  $\leq 1/100$ );

Rare ( $\geq 1/10,000$  to  $\leq 1/1000$ );

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

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.

##### **Cardiac disorders**

Very rare: angina, bradycardia.

##### **Blood and lymphatic system disorders**

Very rare: agranulocytosis, aplastic anaemia, thrombocytopenia

Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

##### **Nervous system disorders**

Very rare: coma, paralysis, ataxia, neuropathy, paraesthesiae, somnolence, headache, taste perversion.

##### **Eye disorders**

Very rare: cataract, visual disorder, macular changes.

##### **Ear and labyrinth disorders**

Very rare: vertigo.

##### **Gastrointestinal disorders**

Uncommon: vomiting, nausea.

Very rare: recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit.

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.

#### **Renal and urinary disorders**

Very rare: haematuria, uraemia.

#### **Skin and subcutaneous tissue disorders**

Common: rash.

Very rare: angioedema, fixed drug eruption, alopecia, discoloured hair .

Skin reactions 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 re-introduced at a small dose (e.g. 50mg/day) and gradually increased. If the rash recurs, Allopurinol should be *permanently* withdrawn as more severe hypersensitivity may occur (see *Immune system disorders*).

Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.

#### **Metabolism and nutrition disorders**

Very rare: diabetes mellitus, hyperlipidaemia.

#### **Infections and infestations**

Very rare: furunculosis.

#### **Vascular disorders**

Very rare: hypertension.

#### **General disorders and administration site conditions**

Very rare: oedema, general malaise, asthenia, fever.

Fever has been reported to occur with and without signs and symptoms of a more generalised Allopurinol hypersensitivity reaction (see *Immune system disorders*).

#### **Immune system disorders**

Uncommon: hypersensitivity reactions.

Very rare: angioimmunoblastic lymphadenopathy.

Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis occur rarely (see Skin and subcutaneous tissue disorders). Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment and very rarely, seizures. Very rarely acute anaphylactic shock has been reported. 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.

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

### **Hepatobiliary disorders**

Uncommon: asymptomatic increases in liver function tests.

Rare: hepatitis (including hepatic necrosis and granulomatous hepatitis).

Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

### **Reproductive system and breast disorders**

Very rare: male infertility, erectile dysfunction, gynaecomastia.

### **Psychiatric disorders**

Very rare: depression.

## **4.9 Overdose**

There have been reports of accidental or deliberate ingestion of up to 5 g, (or very rarely 20 g), of allopurinol. Symptoms or signs have included nausea, vomiting, diarrhoea and dizziness. Recovery followed general supportive measures. Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity. This should have no untoward effect unless 6-mercaptopurine and/or azothiaprime is being taken concomitantly. Adequate hydration to maintain optimum diuresis will facilitate excretion of allopurinol and its metabolites. If it is considered necessary, haemodialysis may be used.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

ATC Code: M04A A01 Preparations inhibiting uric acid production.

Allopurinol and its primary metabolite, oxipurinol is an inhibitor of the enzyme xanthine oxidase. In man, uric acid is formed primarily by the oxidation of hypoxanthine and xanthine, a reaction which is catalysed by xanthine oxidase.

At low concentrations, allopurinol is a substrate for and competitive inhibitor of the enzyme. At high concentration it is a non-competitive inhibitor.

Allopurinol thus reduces the plasma concentration and urinary excretion of uric acid and increases the plasma concentration and renal excretion of the more soluble oxypurine precursors.

### **5.2 Pharmacokinetic properties**

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.

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.

Approximately 20% of the ingested allopurinol is excreted in the faeces in 48 - 72 hours. 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 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.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose Monohydrate  
Colloidal Anhydrous Silica  
Maize Starch  
Powdered cellulose  
Sodium Starch Glycolate (Type A)  
Sodium Lauryl Sulphate  
Povidone (E1201)  
Magnesium Stearate (E572)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months.

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package.

### **6.5 Nature and contents of container**

Transparent PVC/PVdC/Al blister strips in packs of 7, 10, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

Not applicable.

## **7 MARKETING AUTHORISATION HOLDER**

TEVA UK Limited  
Brampton Road

Hampden Park  
Eastbourne  
East Sussex  
BN22 9AG.  
Trading address:  
Leeds LS27 OJG  
England.

**8      MARKETING AUTHORISATION NUMBER(S)**

PL 00289/0951

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

16/10/2008

**10     DATE OF REVISION OF THE TEXT**

16/10/2008

**11     DOSIMETRY (IF APPLICABLE)**

**12     INSTRUCTIONS FOR PREPARATION OF  
RADIOPHARMACEUTICALS (IF APPLICABLE)**