

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Allopurinol Tablets BP 300mg

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Allopurinol 300mg

Excipient(s) with known effect

Lactose

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

White, round tablet with “300 AP” separated by a breakline on reverse

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Allopurinol is indicated to reduce excessive urate levels, where deposition of urate/uric acid has occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis). Allopurinol is also indicated where excessive urate levels are a predictable clinical risk (e.g. cancer chemotherapy).

Excess body urate is frequently idiopathic but may also be found in association with other conditions e.g. neoplastic disease and its treatment; certain enzyme deficiency disorders which lead to overproduction of urate (e.g. Lesch-Nyhan syndrome, glucose-6-phosphate deficiency including glycogen storage disease); chronic renal impairment; diuretic therapy and psoriasis.

Allopurinol is indicated for the management of recurrent mixed calcium oxalate renal stones in patients with raised serum or urinary uric acid, where fluid, dietary and similar measures have failed.

Allopurinol is also indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with adenine phosphoribosyltransferase deficiency.

#### 4.2 Posology and method of administration

##### Posology

##### *Adults*

Allopurinol should be introduced at low dosage e.g. 100mg/day to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor (see section 4.2 Renal impairment).

Initial dosage should be 100 mg/day which may be taken as a single dose. Thereafter, titrate dose according to serum uric acid levels (maximum daily dose 900mg). Doses above 300mg should be administered in divided doses.

The maintenance dose depends upon individual response.

Usual maintenance doses:

Mild conditions: 100mg to 200mg daily

Moderately severe conditions: 200mg to 600mg daily

Severe conditions: 700 to 900mg

#### *Paediatric population*

Children under 15 years: 10 – 20mg/kg body weight/day, maximum 400mg daily.

Use in children is mainly indicated in malignant conditions especially leukaemia and certain enzyme disorders (eg Lesch-Nyhan syndrome).

#### *Elderly*

No specific data are available. The lowest dose that achieves the desired clinical response should be used, and due attention paid to co-existing conditions, such as renal impairment.

#### *Renal impairment*

Allopurinol and its metabolites are excreted via the kidney so renal function impairment may lead to retention of the drug and its metabolites with consequent prolongation of plasma half-lives. In severe renal insufficiency, it may be advisable to use less than 100mg per day or to use single doses of 100mg at longer intervals than one day. The amount and frequency of dosage may require reduction as indicated by monitoring serum uric acid levels. Schedule for guidance in adults:

If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2mg/litre).

#### *Renal dialysis*

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

#### *Hepatic impairment*

Reduced doses should be used in patients with impaired hepatic function. 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 before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalisation of urine to increase solubility of urinary urate/uric acid. Dosage of allopurinol should be at 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.

#### *Use with uricosurics*

Allopurinol does not interfere with the action of uricosurics so they may be given concurrently. When changing from uricosuric therapy to allopurinol, one to three weeks overlap is recommended to ensure continuous hypouricaemic effect.

#### Method of administration

For oral use, take after food.

### **4.3 Contraindications**

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### Hypersensitivity syndrome, SJS and 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 to 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 (see section 4.8).

#### Hepatic or renal impairment

Reduced doses should be used in patients with hepatic or renal impairment (see section 4.2). 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

Treatment with allopurinol should not be started until an acute attack of gout has subsided, as further attacks may be precipitate.

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 µIU/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.

#### Lactose

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

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

#### 6-mercaptopurine and azathioprine

Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action 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 the enhanced toxic effects.

#### Salicylates and uricosuric agents

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

#### Chlorpropamide

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

#### 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.

#### Phenytoin and carbamazepine

Allopurinol may inhibit hepatic oxidation of phenytoin but the clinical significance has not been demonstrated. Plasma carbamazepine concentrations can be gradually increased and the dose of carbamazepine may need to be reduced.

#### 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 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, mechloethamine

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 mechloethamine (chlormethine hydrochloride) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

#### 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.

#### Didanosine

In healthy volunteers and HIV patients receiving didanosine, plasma didanosine  $C_{max}$  and AUC values were approximately doubled with concomitant allopurinol treatment (300mg 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 oxypurinol 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.

#### Capecitabine

Concomitant use of allopurinol and capecitabine (prodrug of fluorouracil) should be avoided because allopurinol may decrease the activity of capecitabine.

#### 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.

## 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 (see section 5.3).

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 the human breast milk. Allopurinol during breast-feeding is not recommended.

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

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  | $\geq 1/1,000$ 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) |                                |

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.

| <b>Table 1: Tabulated Summary of Adverse Reactions</b> |                  |   |
|--|------------------|---|
| <b>System Organ Class</b>                              | <b>Frequency</b> | <b>Adverse Reaction</b>   |
| Infections and infestations                            | Very rare        | Furuncle  |
| Blood and lymphatic system disorders                   | Very rare        | Agranulocytosis <sup>1</sup><br>Aplastic anaemia <sup>1</sup><br>Thrombocytopenia <sup>1</sup>              |
|  | Not known        | Haemolytic anaemia  |
| Immune system disorders                                | Uncommon         | Hypersensitivity <sup>2</sup>   |
|  | Very rare        | Angioimmunoblastic T-cell lymphoma <sup>3</sup>   |
| Metabolism and nutrition disorders                     | Very rare        | Diabetes mellitus<br>Hyperlipidaemia  |
| Psychiatric disorders                                  | Very rare        | Depression  |
| Nervous system disorders                               | Very rare        | Coma<br>Paralysis<br>Ataxia<br>Neuropathy peripheral<br>Paraesthesia<br>Somnolence<br>Headache<br>Dysgeusia |
| Eye disorders  | Very rare        | Cataract<br>Visual impairment<br>Maculopathy  |
| Ear and labyrinth disorders                            | Very rare        | Vertigo   |
| Cardiac disorders                                      | Very rare        | Angina pectoris<br>Bradycardia  |
| Vascular disorders                                     | Very rare        | Hypertension  |
| Gastrointestinal disorders                             | Uncommon         | Vomiting <sup>4</sup><br>Nausea <sup>4</sup>  |
|  | Very rare        | Haematemesis<br>Steatorrhoea<br>Stomatitis<br>Changed of bowel habit  |
| Hepatobiliary disorders                                | Uncommon         | Liver function test abnormal <sup>5</sup>   |
|  | Rare             | Hepatitis (including hepatic necrosis and granulomatous hepatitis) <sup>5</sup>                             |
| Skin and subcutaneous tissue disorders                 | Common           | Rash  |
|  | Rare             | Stevens-Johnson syndrome/toxic epidermal necrolysis <sup>6</sup>  |
|  | Very rare        | Angioedema <sup>7</sup><br>Drug eruption<br>Alopecia<br>Hair colour changes                                 |
| Renal and urinary disorders                            | Very rare        | Haematuria<br>Azotaemia   |
| Reproductive system and breast disorders               | Very rare        | Infertility male<br>Erectile dysfunction<br>Gynaecomastia   |
| General disorders and administration site              | Very rare        | Oedema<br>Malaise   |



|                |           |  |
|----------------|-----------|--|
| conditions     |           | Asthenia<br>Pyrexia <sup>8</sup>                         |
|                | Not known | Chills   |
| Investigations | Common    | Blood thyroid stimulating hormone increased <sup>9</sup> |

<sup>1</sup> 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.

<sup>2</sup> A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia hepato-splenomegaly, abnormal liver function tests, and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium and colon). 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.

Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. 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.

<sup>3</sup> Angioimmunoblastic T-cell lymphoma has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of Allopurinol.

<sup>4</sup> 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.

<sup>5</sup> Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

<sup>6</sup> 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, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). The highest risk for SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment. The best results in managing such reactions come from early diagnosis and immediate discontinuation of any suspect drug. 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. 50 mg/day) and gradually increased. The HLA-B\*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the rash recurs, allopurinol should be permanently withdrawn as more severe hypersensitivity may occur (see section 4.8 Immune system disorders). If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT re-introduce

allopurinol due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.

<sup>7</sup> Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.

<sup>8</sup> Fever has been reported to occur with and without signs and symptoms of a more generalised Allopurinol hypersensitivity reaction (see section 4.8 Immune system disorders).

<sup>9</sup>The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies did not report any impact on free T4 levels or had TSH levels indicative of subclinical hypothyroidism.

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

### **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 effect 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 and its main metabolite oxipurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalysing 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 plasma 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 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 0.5 to 1.5 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 20 ml/min, showed plasma oxipurinol concentrations of approximately 30 mg/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 section 5.2 Pharmacokinetics in patients with renal impairment).

### **5.3 Preclinical safety data**

#### **A. 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.

#### **B. Carcinogenicity**

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

#### **C. 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**

Lactose  
Maize starch  
Povidone  
Stearic acid  
Sodium starch glycollate

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

4 years – blister packs  
3 years – polypropylene containers

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

Store in a dry place not above room temperature (25°C)

Keep this medicine out of the sight and reach of children.

**6.5 Nature and contents of container**

Polypropylene tablet container and cap (Securitainer)

Pack sizes: 21, 100, 250, 500 and 1000 tablets

Aluminium/PVC blister strips enclosed in outer carton

Packs sizes: 28 and 56 tablets

**6.6 Special precautions for disposal**

Not relevant

**7. MARKETING AUTHORISATION HOLDER**

Strides Pharma UK Ltd

Unit 4 Metro Centre

Tolpits Lane

Watford

Hertfordshire

WD18 9SS

**8. MARKETING AUTHORISATION NUMBER(S)**

PL 13606/0007

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

23 December 1996 / 7 May 2002

**10. DATE OF REVISION OF THE TEXT**

08/01/2018