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 with known effect
Each tablet contains 60 mg lactose (as monohydrate) and 1.2 mg sodium laurilsulfate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablets, debossed “4K1 4K1” on one side and with a breakline on both sides.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

Posology

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 given as 3 divided doses. 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*.

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

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. The following schedule may serve as guidance for dose adjustments at renal impairment:

Creatinine clearance	**Dosage**
>20 ml/min	normal dose
10-20 ml/min	100-200 mg per day
<10 ml/min	100 mg/day or longer dose intervals

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.

Method of administration

For oral administration.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Allopurinol is contraindicated 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.

4.4 Special warnings and precautions for use

Acute gouty attacks: Allopurinol treatment should not be started during or immediately after an acute attack of gout has completely subsided, as further attacks may be precipitated (see section 4.3).

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 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.

Allopurinol should not be prescribed to patients treated with azathioprine or 6-mercaptopurine unless the dose of these drugs is reduced to one-quarter of the previously prescribed dose (see section 4.5).

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. Reduced doses should be used in patients with hepatic or renal impairment. 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.

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.

Asymptomatic hyperuricaemia *per se* is not an indication for allopurinol therapy. Fluid and dietary modification with management 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.

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 the dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

In the treatment of renal gout and uric acid stones, the volume of urine produced should be at least 2 litres per day and the urinary pH should be kept in the range of 6.4 – 6.8.

- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of allopurinol.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. (Adoption to individual drug if such data are available)
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, allopurinol treatment should be discontinued.
- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS or TEN with the use of allopurinol, allopurinol must not be re-started in this patient at any time.

<u>Hypersensitivity syndrome, SJS and TEN</u>

Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and

Stevens-Johnson Syndrome (SJS)/ toxic epidermal necrolysis (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 (see section 4.8).

Chronic renal impairment
Patients with chronic renal impairment 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).

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 if 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 (see section 4.8).
SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

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.

Excipient(s)

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

6-mercaptopurine and azathioprine: At concomitant administration with allopurinol, the dose of 6-mercaptopurine or azathioprine should be reduced to 25% of the usual dose. Allopurinol is an inhibitor of xanthine oxidase and counteracts the metabolic inactivation of azathioprine and 6-mercaptopurine. Serum concentrations of these medicinal products can reach toxic levels unless dose reduction is undertaken.

Vidarabine (adenine arabinoside): 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.

Salicylates and uricosuric agents: 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.

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

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 increasing or starting allopurinol therapy.

Ampicillin/Amoxicillin: 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.

Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechloroethamine: 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.

Ciclosporin: 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.

Didanosine: In healthy volunteers and HIV patients receiving didanosine, plasma didanosine C_{max} 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.

Captopril: With concomitant administration of allopurinol and captopril, the risk of skin reactions can be raised, especially in cases of chronic renal failure.

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 Fertility, pregnancy and lactation

Pregnancy

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.

Breast-feeding

Allopurinol and its metabolite oxipurinol is excreted in the human breast milk. Concentrations of 1.4 mg/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.

Allopurinol during breastfeeding is not recommended.

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 (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥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 usually rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorders.

Infections and infestations
Very rare: Furunculosis

Blood and lymphatic system disorders
Very rare: Agranulocytosis, granulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, leukocytosis, eosinophilia, aplastic anemia and pure red cell aplasia

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.

Immune system disorders

Uncommon: Hypersensitivity reactions
Very rare: Angioimmunoblastic lymphadenopathy, anaphylactic reaction

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). If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn immediately and permanently.

When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal (see section 4.4).

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

Metabolism and nutrition disorders

Very rare: Diabetes mellitus, hyperlipidaemia

Psychiatric disorders

Very rare: Depression

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

Cardiac disorders

Very rare: Angina, bradycardia

Vascular disorders

Very rare: Hypertension

Gastrointestinal disorders

Uncommon: Vomiting, nausea, diarrhoea
Very rare: Recurrent haematemesis, steatorrhoea, stomatitis, change of bowel habit

In early clinical studies, nausea and vomiting were reported. To increase gastrointestinal tolerability, allopurinol should be taken after a meal.

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.

Skin and subcutaneous tissue disorders

Common: Rash
Very rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4); 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 or 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 low dose (e.g. 50 mg/day) which may be 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.

Musculoskeletal and connective tissue disorders
Very rare: muscle pain

Renal and urinary disorders
Rare: Urolithiasis
Very rare Haematuria, uraemia

Reproductive system and breast disorders
Very rare Male infertility, erectile dysfunction, gynaecomastia

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).

The following complaint has been reported occasionally: nocturnal emission.

Investigations
Common: blood thyroid stimulating hormone increased*

*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 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 20g 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: M04A A01.

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

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.

Elimination

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 Pharmocokinetics 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 nitraso 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 sulfate

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 25ºC. 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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0951

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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