

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol Teva 300 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg allopurinol.

Excipient(s) with known effect:

Each tablet contains lactose monohydrate, equivalent to 171 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round biconvex tablets, debossed "2K1 2K1" on one side and break line on the other side. 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 Teva is indicated in adults, children and adolescents:

Adults

- All forms of hyperuricaemia not controllable by diet including secondary hyperuricaemia of differing origin and in clinical complications of hyperuricaemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones
- The management of recurrent mixed calcium oxalate stones in concurrent hyperuricaemia, when fluid, dietary and similar measures have failed.

Children and adolescents

- Secondary hyperuricaemia of differing origin
- Uric acid nephropathy during treatment of leukaemia
- Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl transferase deficiency) and adenine phosphoribosyl transferase deficiency.

4.2 Posology and method of administration

Posology

For oral use.

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. 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 Dosage recommendations in renal disorders).

Paediatric population (up to the age of 15)

10 - 20 mg/kg bodyweight / day up to a maximum of 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. Refer to dosage advice under *Dosage recommendations in renal disorders* (also see section 4.4).

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.

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 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.

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.

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 sections 4.5 and 4.8).

Monitoring Advise: Dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Method of administration

Allopurinol may be taken orally once a day. To increase gastrointestinal tolerability, it should be taken after a meal. If the daily dosage exceeds 300 mg and gastrointestinal intolerance is evident, a divided dosage regimen may be appropriate.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided as there have been reports of fatal cases (see section 4.5).

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.

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).

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 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.

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.

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.

Hypersensitivity syndrome, SJS and TEN: 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 – Immune system disorders and Skin and subcutaneous tissue disorders).

Chronic renal impairment

Chronic renal impairment and concomitant use of diuretics, especially thiazide diuretics, may be an 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 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 $\mu\text{IU/ml}$) 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.

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 medicine 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: 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, a xanthine oxidase inhibitor, inhibition of xanthine oxidase will prolong their activity. Serum concentrations of 6-mercaptopurine or azathioprine may reach toxic levels with consequent life-threatening pancytopenia and myelosuppression when these medicinal products are given concurrently with allopurinol. Therefore, concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided. If it is determined that co-administration with 6-mercaptopurine or azathioprine is clinically needed, dosing should be reduced to one quarter (25%) of the usual dose of 6-mercaptopurine or azathioprine and frequent haematologic monitoring should be ensured (see section 4.4). Patients should be advised to report any signs or symptoms of bone marrow suppression (unexplained bruising or bleeding, sore throat, fever).

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 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. Dosage adjustment of chlorpropamide may be necessary during treatment with allopurinol.

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 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 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.

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.

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

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. Animal reproductive toxicity studies have shown conflicting results (see section 5.3).

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.

Breast-feeding

Allopurinol and its metabolite oxipurinol is excreted in the human breast milk.

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.

Allopurinol during breast-feeding 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 ($\geq 1/10$);

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).

The incidence of adverse reactions is higher in the presence of renal and/or hepatic disorder.

Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very rare	Furunculosis
Blood and lymphatic system disorders	Very rare	Agranulocytosis ¹ Thrombocytopenia ¹ Aplastic anaemia ¹ Leukopenia Leukocytosis Eosinophilia Pure red cell aplasia
Immune system disorders	Uncommon	Hypersensitivity reactions ²
	Very rare	Angioimmunoblastic Lymphadenopathy 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 Peripheral neuropathy Paraesthesia Somnolence Headache Taste perversion
	Not known	Aseptic meningitis
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	Epigastric pain Vomiting ⁴ Nausea ⁴ Diarrhoea
	Very rare	Recurrent haematemesis Steatorrhoea Stomatitis Changed bowel habit
Hepatobiliary disorders	Uncommon	Asymptomatic increases in liver function tests ⁵
	Rare	Hepatitis (including hepatic necrosis and granulomatous hepatitis) ⁵
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Steven-Johnson Syndrome / Toxic Epidermal Necrolysis ⁶
	Very rare	Angioedema ⁷ Fixed drug eruption Alopecia Discoloured hair
	Not known	Lichenoid drug 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 ⁸
Investigations	Common	Blood thyroid stimulating hormone increased ⁹

¹Very 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.

²Serious 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, acute cholangitis, xanthine stones 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.

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.

³Angioimmunoblastic lymphadenopathy has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

⁴In early clinical studies, nausea and vomiting were reported. To increase gastrointestinal tolerability, allopurinol should be taken after a meal.

⁵Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

⁶Skin 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). Allopurinol should be withdrawn *immediately* should such reactions occur. 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. 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. After recovery from mild reactions, allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, allopurinol should be *permanently* withdrawn as more severe hypersensitivity may occur (see 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*.

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

⁸Fever has been reported to occur with and without signs and symptoms of a more generalised allopurinol hypersensitivity reaction (see Immune system disorders).

⁹The 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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: M04A A01

Mechanism of action

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.

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 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 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 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 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 and Carcinogenicity

Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells *in vitro* at concentrations up to 100 µg/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.

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.

In animal experiments, long-term application of high doses of allopurinol resulted in formation of xanthin precipitates (urolithiasis), which led to morphological changes in uriniferous organs

There are no additional non-clinical data considered relevant to clinical safety beyond those included in other sections of this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Silica colloidal anhydrous
Maize Starch
Powdered cellulose
Sodium Starch Glycolate (Type A)
Sodium laurilsulfate
Povidone K30
Magnesium Stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Transparent PVC/PVdC/Aluminium blister:

This medicinal product does not require any special storage conditions.

HDPE Bottles:

Store in the original packaging.

Keep the bottle tightly closed in order to protect from light.

6.5 Nature and contents of container

Transparent PVC/PVdC/Aluminium blister. The pack sizes available are:

20, 28, 30, 50, 60, 90, 98, 100, 105 and 500 tablets and Hospital Pack of 50

HDPE Bottles. The pack sizes available are:

30 Tablets in 35 ml Bottle or 100 Tablets in 100 ml Bottle

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/099/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th September 2010

Date of last renewal: 30th August 2013

10 DATE OF REVISION OF THE TEXT

March 2025