Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol Teva 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Allopurinol tablet contains 200 mg of allopurinol.

Excipient(s):
Each 200 mg tablet contains lactose monohydrate, equivalent to 114 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White, round biconvex tablets, debossed 3K1 on one side, plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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 phosophoribosyl transferase deficiency.

4.2 Posology and method of administration

For oral use.

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.

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*).

Children (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 Special warnings and precautions for use).

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 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects).

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

4.3 Contraindications

Hypersensitivity to allopurinol or to any of the excipients.

4.4 Special warnings and precautions for use

Acute gouty attacks: Allopurinol treatment should not be started until an acute attack of gout has completelysubsided, as further attacks may be precipitated.
In the early stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritismay be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent orcolchicine for at least one month. The literature should be consulted for details of appropriate dosage andprecautions 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 sensitivity occurs. Reduced doses should be used in patients with hepatic or renal impairment. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia 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 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, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose 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: 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): 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.

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.

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 cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechloroethamine (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 (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.

4.6 Fertility, pregnancy and lactation

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.

Reports indicate that allopurinol and oxipurinol are excreted in 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. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from allopurinol therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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).

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

Infections and infestations
Very rare: furunculosis.

Blood and lymphatic system disorders
Very rare: agranulocytosis, granulocytosis, aplastic anaemia, thrombocytopenia, leukopenia, leukocytosis, eosinophilia 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.
Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis occur rarely (see Skin and subcutaneous tissue disorders).

Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment, 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. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.
Angioimmunoblastic lymphadenopathy has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepatosplenomegaly, 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.

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, changed 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: angioedema, fixed drug eruption, alopecia, discoloured hair .
Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Allopurinol should be withdrawn *immediately* should such reactions occur.
After recovery from mild reactions, Allopurinol may, if desired, be re-introduced at a small dose (e.g. 50mg/day) and gradually increased.
If the rash recurs, Allopurinol should be *permanently* withdrawn as more severe hypersensitivity may occur (see *Immune system disorders*).
Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.

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*).

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

Pharmacokinetic group: Preparations inhibiting uric acid production.
ATC Code: M04A A01

Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxipurinol lower the level of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. In addition to the inhibition of purine catabolism in some but not all hyperuricaemic patients, de novo purine biosynthesis is depressed via feedback inhibition of hypoxanthine-guanine phosphoribosyltransferase. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7 riboside.

5.2 Pharmacokinetic properties

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

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

Approximately 20% of the ingested allopurinol is excreted in the faeces in 48 − 72 hours. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1 to 2 hours.

Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxipurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of Allopurinol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5-10 mg/litre.

Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

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

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

5.3 Preclinical safety data

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

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

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

20, 28, 30, 50, 60, 100 and Hospital Pack of 50

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/99/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th September 2010

10 DATE OF REVISION OF THE TEXT

January 2013