Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

ALLOPURINOL 100MG TABLETS
ALLOPURINOL 200MG TABLETS
ALLOPURINOL 300MG TABLETS

Procedure No: UK/H/1313/001-3/DC

UK Licence No: PL 00289/1093-5

TEVA UK LIMITED

LAY SUMMARY

On 10 June 2010, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovakia and the UK agreed to grant Marketing Authorisations to TEVA UK Limited for the medicinal products Allopurinol 100mg, 200mg and 300mg Tablets (PL 00289/1093-5; UK/H/1313/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 20 July 2010.

Allopurinol 100mg, 200mg and 300mg Tablets are Prescription-Only Medicines (POM) for the long-term, preventative treatment of gout and may be used in other conditions associated with an excess of uric acid in the body, including kidney stones and other types of kidney disease.

Allopurinol belongs to a group of medicines called enzyme inhibitors, which act to control the speed at which special chemical changes occur in the body.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Allopurinol 100mg, 200mg and 300mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Allopurinol 100mg, 200mg and 300mg Tablets
Type of Application	Generic, Article 10.1
Active Substances	Allopurinol
Form	Tablet
Strength	100, 200 and 300mg Tablets
MA Holder	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG
Reference Member State (RMS)	UK
CMS	UK/H/1313/001/DC & UK/H/1313/003/DC: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden and Slovakia UK/H/1313/002/DC: Austria, Bulgaria, Cyprus, Czech Republic, Germany, France, Ireland, Netherlands, Poland and Romania.
Procedure Number	UK/H/1313/001-3/DC
Timetable	Day 210 – 10 June 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Allopurinol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Allopurinol tablet contains 100mg of allopurinol.

Also contains lactose monohydrate, equivalent to 57 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, round biconvex tablets, debossed 4K1 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 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).

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.

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 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.

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, 25, 28, 30, 50, 60, 90, 98, 100 and 500 tablets 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 UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1093

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/07/2010

10 DATE OF REVISION OF THE TEXT

20/07/2010

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Allopurinol tablet contains 200mg of allopurinol.

Also contains lactose monohydrate, equivalent to 114 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
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
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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 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).

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.

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 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.

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 UK Limited
Brampton Road,
Hampden Park,
Eastbourne,

East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1094

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/07/2010

10 DATE OF REVISION OF THE TEXT
20/07/2010

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol 300 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Allopurinol tablet contains 300mg of allopurinol.

Also contains lactose monohydrate, equivalent to 171 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, round biconvex tablets, debossed 2K1 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 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).

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.

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.

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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**.**

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

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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.

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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.

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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.

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.

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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 .
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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.

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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, 90, 98, 100 and 500 tablets 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 UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG

UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1095

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/07/2010

10 DATE OF REVISION OF THE TEXT
20/07/2010

Module 3

ALLOPURINOL 100 mg, 200 mg AND 300 mg TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1 WHAT ALLOPURINOL IS AND WHAT IT IS USED FOR

- Allopurinol belongs to a group of medicines called enzyme inhibitors, which act to control the speed at which special chemical changes occur in the body.
- Allopurinol tablets are used for the long term, preventative treatment of gout and may be used in other conditions associated with an excess of uric acid in the body, including kidney stones and other types of kidney disease.

2 BEFORE YOU TAKE ALLOPURINOL

DO NOT take Allopurinol and talk to your doctor if you:
- are allergic (hypersensitive) to Allopurinol or any of the other ingredients of this medicine
- are currently having an attack of gout or have just had an attack of gout.

Take special care with Allopurinol
Talk to your doctor before you start to take this medicine if you:
- have problems with your liver and kidneys. Your doctor may give you a lower dose or ask you to take it less often than each day. They will also monitor you more closely
- have heart problems or high blood pressure
- are currently having an attack of gout.

If you are not sure if any of the following applies to you, talk to your doctor or pharmacist before taking allopurinol.

Taking other medicines
Tell your doctor before you start to take this medicine if you are taking:
- 6-mercaptopurine (used to treat blood cancer)
- azathioprine, cyclosporine (used to suppress the immune system).
  Please note, cyclosporine side effects may occur more frequently
- vidarabine (used in the treatment of herpes).
  Please note, vidarabine side effects can occur more frequently. Take special care if these occur
- salicylates (used to reduce pain, fever or inflammation e.g. Aspirin)
- probenecid (used to treat gout)
- chlorpropamide (used to treat diabetes).
  Chlorpropamide dose reduction may be necessary, particularly in patients with reduced kidney function
- warfarin, phenprocoumon, acenocoumarol (used to thin the blood).
  Your doctor will monitor your blood clotting values more frequently and if necessary, reduce the dose of these medicines
- phenytoin (used to treat epilepsy)
- theophylline (used to treat asthma and other breathing diseases).
  Your doctor will measure theophylline blood levels, particularly when treatment with Allopurinol begins, or following any dosage changes
- ampicillin or amoxicillin (used to treat bacterial infections).
  Patients should receive other antibiotics where possible, as allergic reactions are more likely to occur
- Medicines to treat aggressive tumours, such as
  - cyclophosphamide
  - doxorubicin
  - bleomycin
  - procarbazine
  - mechloroethamine

  Your doctor will monitor your blood counts frequently
- didanosine (used to treat HIV infection)
- captopril (used to treat high blood pressure).
  The risk of skin reactions can be raised, especially if your kidney function is chronically reduced.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
- If you are pregnant, planning to become pregnant or are breast-feeding, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
- Allopurinol Tablets can cause dizziness, drowsiness, and can affect your coordination. If you are affected, DO NOT drive, operate machinery or participate in dangerous activities.

Important information about some of the ingredients of Allopurinol
- This medicinal product contains **lactose**. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3 HOW TO TAKE ALLOPURINOL

Always use Allopurinol exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The tablets should be swallowed whole, preferably with a drink of water. You should take your tablets after a meal. You should drink plenty of fluids (2-3 litres a day) while you are taking this medicine. The usual dose is:

- **Adults (including the elderly)**
  Starting dose: 100 - 300 mg/day.
  When you start your treatment, your doctor may also prescribe an anti-inflammatory medicine or colchicine for a month or more, to prevent attacks of gouty arthritis.
  Your dose of allopurinol may be adjusted depending on the severity of the condition. The maintenance dose is:
  - mild conditions, 100 - 200 mg/day
  - moderately severe conditions, 300 - 600 mg/day
  - severe conditions, 700 - 900 mg/day.

  Your dose may also be altered by your doctor if you have reduced kidney and liver function, particularly if you are elderly.
  If the daily dose exceeds 300 mg/day and you are suffering from gastro-intestinal side effects such as nausea or vomiting (see section 4), your doctor may prescribe allopurinol in divided doses to reduce these effects.

If you have a serious kidney problem
- you may be asked to take less than 100 mg each day
- or you may be asked to take 100 mg at longer intervals than one day.

If you have dialysis two or three times a week, your doctor may prescribe a dose of 300 or 400 mg which is to be taken straight after your dialysis.

- **Children (under 15 years)**
  100 - 400 mg/day.
  Treatment may be started together with an anti-inflammatory medicine or colchicine, and the dose adjusted if you have reduced kidney and liver function, or divided to reduce gastro-intestinal side effects, as for Adults above.

If you take more Allopurinol than you should
If you (or someone else) swallow a lot of the tablets all together or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.
An overdose is likely to cause effects including nausea, vomiting, diarrhoea, or dizziness.
Please take this leaflet, any remaining tablets, and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Allopurinol
If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. DO NOT take a double dose to make up for a forgotten dose. Take the remaining doses at the correct time.

If you stop taking Allopurinol
You should continue to take these tablets for as long as your doctor tells you to. DO NOT stop taking your medicine without talking to your doctor first.

Ask your doctor or pharmacist if you have any further questions on the use of this product.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Allopurinol can cause side effects, although not everybody gets them.

Stop taking Allopurinol and contact your doctor immediately if you experience:
- an unexpected skin reaction (possibly in association with fever, swollen glands, joint pain, unusual blistering or bleeding, kidney problems or a sudden onset of fits).

Skin rashes are the most common side effect with allopurinol (affecting less than one person in 10 but more than one person in 100).

Allergic reactions (affects less than 1 in 10,000 people).
If you have an allergic reaction, stop taking allopurinol and see a doctor straight away. The signs may include:
- skin rash, flaking skin, boils or sore lips and mouth
- swelling of the face, hands, lips, tongue or throat
- difficulty swallowing or breathing
- very rarely signs may include sudden wheeziness, fluttering or tightness of the chest and collapse.

Do not take any more tablets unless your doctor tells you to do so.

If you experience any of the following while you are taking Allopurinol, stop taking your tablets and tell your doctor as soon as possible:
The following **uncommon** side effects have been reported (affecting less than one person in 100 but more than one person in 1,000):
- nausea , vomiting (very rarely, blood may be present) and diarrhoea
- symptoms of allergic reactions including itchy rash
- increase in results of liver function tests.

The following **rare** side effects have been reported (affecting less than one person in 1,000 but more than one person in 10,000):
- joint pain or painful swelling in the groin, armpits or neck
- jaundice (yellowing of the skin and whites of the eyes)
- may affect your liver or kidney function
- formation of stones in the urinary tract, symptoms may include blood in the urine and pain in the abdomen, flank, or groin.

The following **very rare** side effects have been reported (affecting less than one person in 10,000):
- high temperature
- blood in the urine
- a change in your normal bowel habit, or unusual foul-smelling bowel movements
- high fat levels in the blood
- a general feeling of being unwell
- weakness, numbness, unsteadiness on feet, inability to move muscles (paralysis) or loss of consciousness, pins and needles
- convulsions, fits or depression
- headache, dizziness, drowsiness or disturbance of vision
- chest pain, high blood pressure or a slow pulse
- retention of fluid leading to swelling (oedema) particularly of the ankles
- male infertility or inability to get or maintain an erection, or ejaculation during sleep ("wet dreams")
- enlargement of the breasts, in men as well as women
- a change in taste perception, inflammation in the mouth
- cataracts (clouding of the lens of the eye) and other problems with sight
- boils (small tender red lumps on the skin)
- hair loss or discolouration
- feeling thirsty, tired and losing weight (these may be symptoms of diabetes); your doctor may wish to measure the level of sugar in your blood to decide if this is happening
- muscle pain
- swollen glands, usually goes away once treatment with allopurinol ends.

You may occasionally feel sick, but this can usually be avoided by taking allopurinol after meals. Tell your doctor if this problem persists.

Occasionally, allopurinol may affect your blood or lymphatic system. These effects have usually occurred in people with liver or kidney problems. Tell your doctor as soon as you can if you notice that you are bruising more easily than usual, or if you develop a sore throat or other signs of an infection.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE ALLOPURINOL

Keep out of the reach and sight of children.
Do not use Allopurinol after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Allopurinol Tablets contain:
- The active substance is allopurinol.
  Each 100 mg tablet contains 100 mg of allopurinol.
  Each 200 mg tablet contains 200 mg of allopurinol.
  Each 300 mg tablet contains 300 mg of allopurinol.
- The other ingredients are lactose monohydrate, silica colloidal anhydrous, maize starch, powdered cellulose, sodium starch glycolate, sodium laurilsulfate, povidone K30 and magnesium stearate (E470b).

What Allopurinol Tablets look like and contents of the pack:
- Allopurinol 100 mg Tablets are white, round, biconvex tablets, debossed "4K1" on one side and plain on the other.
- Allopurinol 200 mg Tablets are white, round, biconvex tablets, debossed "3K1" on one side and plain on the other.
- Allopurinol 300 mg Tablets are white, round, biconvex tablets, debossed "2K1" on one side and plain on the other.

The product is available in transparent aluminium blisters in the following pack sizes:
Allopurinol 100 mg Tablets: 20, 25, 28, 30, 50, 60, 90, 98, 100 and 500 tablets and Hospital Pack of 50.
Allopurinol 200 mg Tablets: 20, 28, 30, 50, 60, 100 and Hospital Pack of 50.
Allopurinol 300 mg Tablets: 20, 28, 30, 50, 60, 90, 98, 100 and 500 tablets and Hospital Pack of 50.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG.

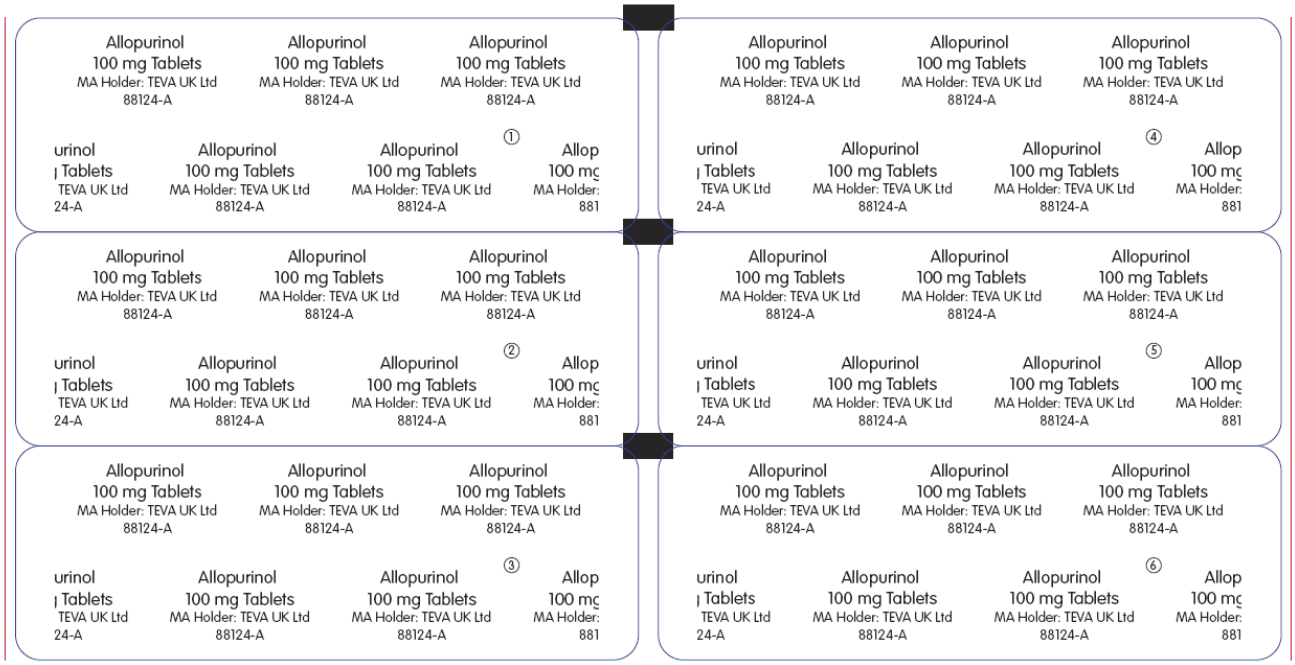
This leaflet was last revised in June 2010.

PL 00289/1093-1095

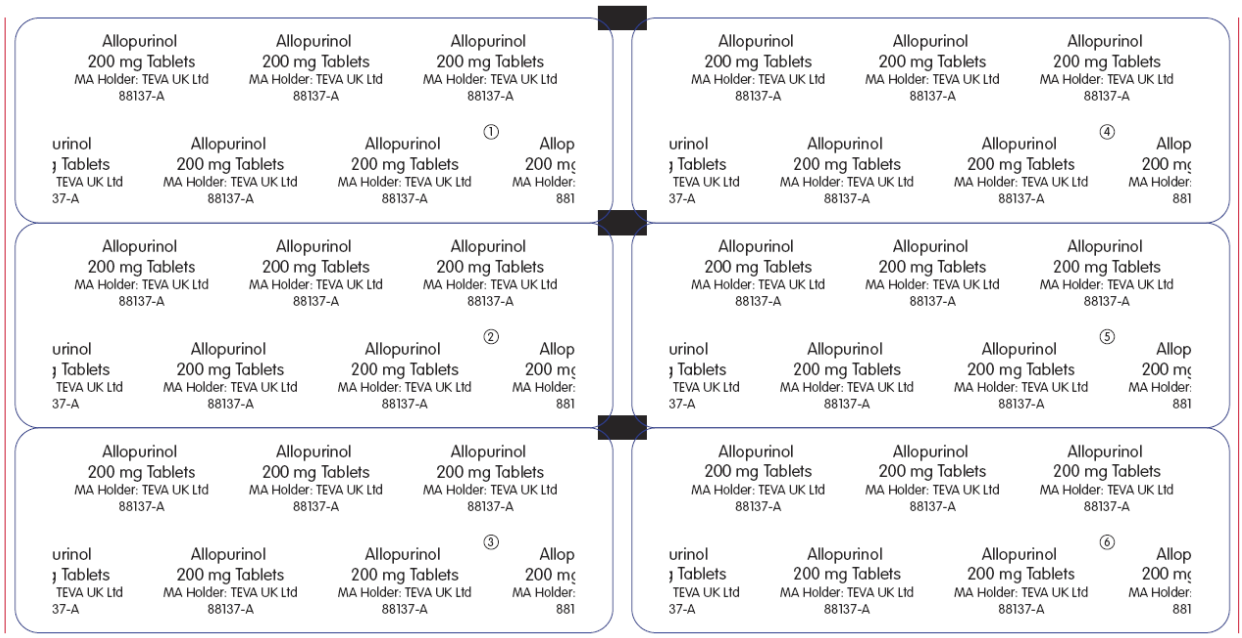
TEVA UK LIMITED

88150-A
160 x 323

Module 4
Labelling




Text and varnish free area for Overprinting/Embossing batch number and expiry date.
Original Artwork Scale = 1:1 (100%)
50mm
Each tablet contains 200 mg of allopurinol. Also contains lactose. See leaflet for further information.
DOSAGE:
Use as directed by the doctor.
Please read the enclosed package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
This medicinal product does not require any special storage conditions.
Allopurinol 200 mg Tablets
Please affix dispensary label here
Pharma code 227
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1094
88129-A
POM
5 017007 011781
Allopurinol
28 Tablets
200 mg
Allopurinol
200 mg Tablets
Oral Use
200 mg
28 Tablets
TEVA
Braille Reads in Marburg Medium:
Allopurinol
#200 mg tablets
Allopurinol 200 mg Tablets
200 mg
28 Tablets
47 x 16 x 134mm


Allopurinol 200 mg Tablets
MA Holder: TEVA UK Ltd
88137-A
①
②
③
④
⑤
⑥


Text and varnish free area for Overprinting/Embossing batch number and expiry date.
Original Artwork Scale = 1:1 (100%)
50mm
Each tablet contains 300 mg of allopurinol. Also contains lactose. See leaflet for further information.
DOSAGE:
Use as directed by the doctor.
Please read the enclosed package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
This medicinal product does not require any special storage conditions.
Allopurinol 300 mg Tablets
Please affix dispensary label here
Pharma code 241
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1095
88142-A
POM
® UK Reg'd T.M.
5 017007 011798
Allopurinol
300 mg Tablets
Oral Use
300 mg
28 Tablets
Braille Reads in Marburg Medium:
Allopurinol
#300 mg tablets
TEVA
Allopurinol 300 mg Tablets
28 Tablets
47 x 16 x 134mm


Allopurinol 300 mg Tablets MA Holder: TEVA UK Ltd 88144-A
①
②
③
④
⑤
⑥

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Allopurinol 100mg, 200mg and 300mg Tablets (PL 00289/1093-5; UK/H/1313/001-3/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as Reference Member State (RMS), and Austria, Bulgaria, Cyprus, Czech Republic, Germany, France, Ireland, Netherlands, Poland, Romania, (UK/H/1313/001-3) and Belgium, Denmark, Spain, Italy, Luxembourg, Norway, Portugal, Sweden and Slovakia (UK/H/1313/001 and 003 only) as Concerned Member States (CMS).

The products are prescription-only medicines for the treatment of:
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.

These are applications made according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Zyloric 100mg, 200mg and 300mg Tablets, which were originally granted licences in 1980 to The Wellcome Foundation Limited, UK (100mg and 300mg strengths) and in 1984 to Laboratoire Glaxosmithkline, France (200mg strength).

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.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 10 June 2010. After a subsequent national phase, the licences were granted in the UK on 20 July 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Allopurinol 100mg, 200mg and 300mg Tablets
Name(s) of the active substance(s) (INN)	Allopurinol
Pharmacotherapeutic classification (ATC code)	Preparations inhibiting uric acid production. (M04A A01)
Pharmaceutical form and strength(s)	100, 200 and 300mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1313/001-3/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/1313/001/DC & UK/H/1313/003/DC: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden and Slovakia UK/H/1313/002/DC: Austria, Bulgaria, Cyprus, Czech Republic, Germany, France, Ireland, Netherlands, Poland and Romania.
Marketing Authorisation Number(s)	PL 00289/1093-5
Name and address of the authorisation holder	TEVA UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Allopurinol

Chemical name: 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one Structure:

Molecular formula: $C_5H_4N_4O$

Molecular mass: 136.1

Appearance: Allopurinol is a white to almost white powder. It is very slightly soluble in water and in alcohol, and dissolves in a dilute solution of alkali hydroxide. Allopurinol has no chiral centres and has no stereo isomers. Allopurinol is known to exist as only one polymorphic form.

Allopurinol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance allopurinol are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, silica colloidal anhydrous, maize starch, powdered cellulose, sodium starch glycolate (Type A), sodium laurilsulfate, povidone K30 and magnesium stearate (E470b)

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious tablets, containing 100, 200 and 300mg allopurinol, that could be considered generic medicinal products of Zyloric Tablets.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
All strengths of finished product are packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters, in pack sizes of 20, 28, 30, 50 (including a hospital pack), 60 and 100. Additional pack sizes of 90, 98 and 500 tablets are available for the 100mg and 300mg strengths, and there is an additional pack size of 25 tablets for the 100mg alone.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 PRE-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of allopurinol are well-known, no new pre-clinical studies are required and none have been provided.

The applicant's pre-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a pre-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, single-dose, two–way, two-treatment, crossover, single-centre study to compare the pharmacokinetics of the test product Allopurinol 300mg Tablets versus the reference product Zyloric 300mg Tablets (Laboratoires Wellcome, France) in healthy adult male volunteers under fasted conditions.

All volunteers were dosed in a fasted state in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 96 hours post dose. The washout period between treatment periods was at least 10 days

The pharmacokinetic results for allopurinol and its active metabolite oxipurinol are presented below:

Table 1.Pharmacokinetic parameters allopurinol (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml
Test (mean)	4148.19	4306.47	1800
Standard dev.	2006.26	2065.59	727
Reference	3732.89	3907.91	1697
Standard dev.	1047.75	1070.68	678
***Ratio (90% CI)**	97.5-117.22%	97.3-115.7%	90.7-123.4%

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

**ln-transformed values*

Table 2:Pharmacokinetic parameters for the metabolite oxipurinol (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml
Test (mean)	183041.71	194324.74	5520
Standard dev.	29917.59	34696.17	740
Reference	184246.33	198830.27	5540
Standard dev.	35167.61	40820.00	737
***Ratio (90% CI)**	96.35-103.55%	94.6-101.9%	96.1-103.2%

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

**ln-transformed values*

The 90% confidence intervals for AUC and Cmax were within the predefined acceptance range for both allopurinol and its active metabolite oxipurinol. Bioequivalence was demonstrated for the parent compound (allopurinol) and the active metabolite (oxipurinol) for both products. Therefore, the proposed product is bioequivalent to the reference product.

As the 100, 200 and 300mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 300mg strength can be extrapolated to the 100mg and 200mg strengths.

Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy

No new efficacy data were submitted and none were required for these applications.

Safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products. The PIL is consistent with the SPC and in-line current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Allopurinol 100, 200 and 300mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant's Allopurinol 300mg Tablets and its respective reference product (Zyloric 300mg Tablets). As the 100mg and 200mg strengths of the product meet the biowaiver criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 300mg strength can be extrapolated to the other strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with allopurinol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome