SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol 300mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains allopurinol 300mg

Excipient with known effect: Also contains Lactose monohydrate 70.80 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White, round, biconvex, uncoated tablets marked with '300' on one face and 'BL' on the other

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Allopurinol is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy). The main clinical conditions where urate/uric acid deposition may occur are: idiopathic gout; uric acid lithiasis; acute uric acid nephropathy; neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously, or after cytotoxic therapy; certain enzyme disorders which lead to overproduction of urate, for example: hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome; glucose-6-phosphatase including glycogen storage disease; phosphoribosylpyrophosphate synthetase, phosphoribosylpyrophosphate amidotransferase; adenine phosphoribosyltransferase.

Allopurinol is indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase.

Allopurinol is indicated for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary and similar measures have failed.

4.2 Posology and method of administration

Posology

Adults: Allopurinol should be introduced at low dosage e.g. 100 mg/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 Patients with renal impairment*). The following dosage schedules are suggested:

100 to 200 mg daily in mild conditions,
300 to 600 mg daily in moderately severe conditions,
700 to 900 mg daily in severe conditions.

If dosage on a mg/kg bodyweight basis is required, 2 to 10 mg/kg bodyweight/day should be used.

Paediatric population

Children under 15 years: 10 to 20 mg/kg bodyweight/day up to maximum of 400 mg daily. Use in children is mainly indicated, except in malignant conditions (especially leukaemia), and certain enzyme disorders (eg Lesch-Nyhan syndrome).

Use in the elderly: In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used. Particular attention should be paid to advice in *Patients with renal impairment* and section 4.4.

Patients with renal impairment:
Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the drug and/or its metabolites with consequent prolongation of plasma half-lives. In severe renal insufficiency, it may be advisable to use less than 100 mg per day or to use single doses of 100 mg at longer intervals than one day. If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2 mg/litre). Allopurinol

and it metabolites are removed by renal dialysis. If frequent dialysis is required, an alternative schedule of 300-400mg after each dialysis, with none in the interim, should be considered.

Patients with 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 starting 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. Dosage of allopurinol should be at the lower end of the recommended dosage schedule.
If urate nephropathy or other pathology has compromised renal function, the advice given in *Patients with renal impairment* should be followed.
These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also section 4.5 and section 4.8.

Monitoring Advice
The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Method of Administration

Allopurinol may be taken orally once a day after a meal. It is well tolerated, especially after food. Should the daily dosage exceed 300 mg and gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, SJS and TEN
Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) (see section 4.8). These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn

immediately. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

Chronic renal impairment

Patients with chronic renal impairment and concomitant diuretic use, in particular thiazide, may be at increased risk of developing hypersensitivity reactions including SJS/TEN associated with allopurinol. Extra vigilance for the signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms (see section 4.8).

HLA-B*5801 allele

The HLA-B*58:01 allele has been identified as a genetic risk factor for allopurinol associated SJS/TEN (and possibly other serious hypersensitivity reactions) in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Thai, Korean, Japanese and European descent. Up to 20-30% of people of Han Chinese, about 12 % in the Korean population African and Indian ancestry carry the HLA-B*58:01 allele whereas only 1-2% of Northern European, US European and Japanese are estimated to be HLA-B*58:01 carriers. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.
Screening for HLA-B*58:01 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks.Patients who are found to be negative for HLA-B*58:01 still have a low risk of SJS/TEN. The clinical diagnosis of SJS/TEN, and other hypersensitivity reactions, remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. (See Adverse Reactions – Immune system disorders and Skin and subcutaneous tissue disorders).

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Allopurinol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Allopurinol treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a

better prognosis. If the patient has developed SJS or TEN with the use of Allopurinol tablets, Allopurinol tablets must not be re-started in this patient at any time.

Hepatic or renal impairment

Reduced doses should be used in patients with hepatic or renal impairment (see Section 4.2). Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia per se is generally not considered an indication for use of allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.

Acute gouty attacks:

Allopurinol treatment should not be started until an acute attack of gout has been 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 attack is treated with a suitable anti-inflammatory agent.

Xanthine deposition:

In conditions where the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Impaction of uric acid renal stones:

Adequate therapy with allopurinol will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

Lactose intolerance:
Allopurinol tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

6-mercaptopurine and azathioprine: Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with Allopurinol, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.

Vidarabine (Adenine Arabinoside): Evidence suggests that the plasma half-life of vidarabine is increased in the presence of allopurinol. When the two products are used concomitantly extra vigilance is necessary, to recognise 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 hypoglycaemia activity because allopurinol and chlorpropamide may compete for excretion in the renal tubule.

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.

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.

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.

Ciclosporin: Reports suggest that the plasma concentration of ciclosporin (risk of nephrotoxicity) may be increased during concomitant treatment withallopurinol. The possibility of enhanced ciclosporin toxicity should be considered if the drugs are co-administered.

Phenytoin: Allopurinol may inhibit hepatic oxidation of phenytoin but the clinical significance has not been demonstrated.

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.

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.

Antacids: Allopurinol may fail to reduce the blood-uric-acid concentrations when given at the same time as aluminium hydroxide. Intake of antacids and allopurinol should be separated by 3 hours.

ACE inhibitors:

An increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors especially in renal impairment.

Diuretics
An interaction between allopurinol and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported.

An increased risk of hypersensitivity has been reported when allopurinol is given with diuretics, in particular thiazides, especially in renal impairment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of safety of allopurinol in human pregnancy, although it has been in wide use for many years without apparent ill consequence.

Use in pregnancy only when there is no safer alternative and when the disease itself carries risk for the mother or unborn child.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

Since adverse reactions such as somnolence, vertigo, nausea and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that allopurinol does not adversely affect performance.

4.8 Undesirable effects

These are usually rare and mostly of a minor nature; the incidence is higher in the presence of renal and/or hepatic disorders.

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 (≥10%)

Common ≥1/100 and <1/10 (≥1% and <10%)

Uncommon ≥1/1000 and <1/100 (≥0.1% and <1%)

Rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%)

Very rare <1/10,000 (<0.01%)

Table 1. Undesirable effects

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very Rare	Furuncle
Blood and lymphatic system disorders	Very Rare	Agranulocytosis[1] Aplastic anaemia[1] Thrombocytopenia[1]
Immune system disorders	Uncommon Very Rare	Hypersensitivity[2] Angioimmunoblastic T-cell lymphoma[3]
Metabolism and nutrition disorders	Very Rare	Diabetes mellitus Hyperlipidaemia
Psychiatric disorders	Very Rare	Depression
Nervous system disorders	Very Rare	Coma Paralysis

		Ataxia Neuropathy peripheral Paraesthesia Somnolence Headache Dysguesia
Eye disorders	Very rare	Cataract Visual impairment Maculopathy
Ear and labyrinth disorders	Very rare	Vertigo
Cardiac disorders	Very rare	Angina pectoris Bradycardia
Vascular disorders	Very Rare	Hypertension
Gastrointestinal disorders	Uncommon Very Rare	Vomiting[4] Nausea[4] Haematemesis Steatorrhoea Stomatitis Change of bowel habit
Hepatobiliary disorders	Uncommon Rare	Liver function test abnormal[5] Hepatitis (including hepatic necrosis and granulomatous hepatitis[5]
Skin and subcutaneous tissue disorders	Common Rare	Rash Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome/toxic epidermal Necrolysis[6] (see section 4.4) Angioedema[7]

	Very Rare	Drug eruption Alopecia Hair colour changes
Renal and urinary disorders	Very rare	Haematuria Azotaemia
Reproductive system and breast disorders	Very rare	Infertility male Erectile dysfunction Gynaecomastia
General disorders and administration site conditions	Very rare	Oedema Malaise Asthenia Pyrexia[8]

1. 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.

2., A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia and/or eosinophilia, and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), occur rarely (see Skin and subcutaneous tissue disorders) in various combinations. Associated vasculitis and tissue response may be manifested in various ways including hepato-splenomegaly, hepatitis, abnormal liver function tests, vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), renal impairment and, very rarely, seizures. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon).Very rarely acute anaphylactic shock has been reported. If such reactions do occur, it may be at any time during treatment. Allopurinol should be withdrawn *immediately and permanently*. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

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

4. In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking Allopurinol after meals.

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

6 Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as Stevens-Johnson syndrome and toxic

epidermal necrolysis (SJS/TEN). The highest risk for SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment. The best results in managing such reactions come from early diagnosis and immediate discontinuation of any suspect drug. Allopurinol should be withdrawn immediately should such reactions occur. After recovery from mild reactions, Allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, Allopurinol should be permanently withdrawn as more severe hypersensitivity may occur (see Immune system disorders). If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT re-introduce allopurinol due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.

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

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

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms

Ingestion of up to 22.5 g allopurinol without adverse effect has been reported. Symptoms and signs including nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20g allopurinol.

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, adenine arabinoside, and/or azathioprine is being taken concurrently. In this case, the risk of increased activity of these drugs must be recognised.

Management

Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. Other measures as indicated by the patient's clinical condition. Haemodialysis is unlikely to be required. Haemodialysis may be considered in patients with severe renal or hepatic impairment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations inhibiting uric acid production

ATC CODE: M04AA01

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

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

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

Biotransformation
The main metabolite of allopurinol is oxipurinol. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7-riboside.

Elimination
Approximately 20% of the ingested allopurinol is excreted in the faeces. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged

drug excreted in the urine. Allopurinol has a plasma half-life of about 0.5 to 1.5 hours.

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

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

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

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

5.3 Preclinical safety data

Mutagenicity
Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells *in vitro* at
concentrations up to 100 micrograms/ml and *in vivo* at doses up to 600 mg/day for a mean period of 40 months.

Allopurinol does not produce nitroso compounds *in vitro* or affect lymphocyte transformation *in vitro.*

Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

Carcinogenicity

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

Teratogenicity
One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, however in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in mice up to 100 mg/kg/day, rats up to 200 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of gestation produced no teratogenic effects.

An *in vitro* study using foetal mouse salivary glands in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Allopurinol 300mg tablets:

Lactose

Maize starch

Povidone

Magnesium stearate

Sodium starch glycolate.

6.2 Incompatibilities

None known.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Securitainers: Store in a cool, dry place and protect from light.
Blister packs: Do not store above 25°C. Keep the blister in the outer carton to protect from light and moisture.

6.5 Nature and contents of container

Allopurinol 300mg tablets:

Blister strips comprising 250µm PVC film and 20µm Aluminium foil packed into an outer carton.

Pack sizes: 28, 30, 56, 60, 100

Securitainer with polyethylene closures.

Pack sizes: 28, 30, 56, 60 and 100.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0140

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/10/2016