SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Allopurinol Tablets BP 300mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Allopurinol 300mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

White, round tablet with "300 AP" separated by a breakline on reverse

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allopurinol is indicated to reduce excessive urate levels, where deposition of urate/uric acid has occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis). Allopurinol is also indicated where excessive urate levels are a predictable clinical risk (e.g. cancer chemotherapy).

Excess body urate is frequently idiopathic but may also be found in association with other conditions e.g. neoplastic disease and its treatment; certain enzyme deficiency disorders which lead to overproduction of urate (e.g. Lesch-Nyhan syndrome, glucose-6-phosphate deficiency including glycogen storage disease); chronic renal impairment; diuretic therapy and psoriasis.

Allopurinol is indicated for the management of recurrent mixed calcium oxalate renal stones in patients with raised serum or urinary uric acid, where fluid, dietary and similar measures have failed.

Allopurinol is also indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones associated with adenine phosphoribosyltransferase deficiency.

4.2 Posology and method of administration

For oral use, take after food

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.

Adults: Initial dosage should be 100 mg/day which may be taken as a single dose. Thereafter, titrate dose according to serum uric acid levels (maximum daily dose 900mg). Doses above 300mg should be administered in divided doses.

The maintenance dose depends upon individual response.
Usual maintenance doses:
Mild conditions: 100mg to 200mg daily
Moderately severe conditions: 200mg to 600mg daily
Severe conditions: 700 to 900mg

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

Elderly: No specific data are available. The lowest dose that achieves the desired clinical response should be used, and due attention paid to co-existing conditions, such as renal impairment.

Dosage in renal impairment: Allopurinol and its metabolites are excreted via the kidney so renal function impairment may lead to retention of the drug and its metabolites with consequent prolongation of plasma half-lives. In severe renal insufficiency, it may be advisable to use less than 100mg per day or to use single doses of 100mg at longer intervals than one day. The amount and frequency of dosage may require reduction as indicated by monitoring serum uric acid levels. Schedule for guidance in adults:

If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2mg/litre).

Dosage in renal dialysis: Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two or three times a week, an alternative schedule of 300-400mg allopurinol after each dialysis, with non in the interim, should be considered.

Dosage in hepatic impairment: Reduced doses should be used in patients with impaired hepatic function. Periodic liver function tests are recommended during the early stages of therapy.

Neoplastic disease: To prevent acute uric acid nephropathy in neoplastic conditions, allopurinol treatment should precede treatment with cytotoxic drugs.

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 alkalisation of urine to increase solubility of urinary urate/uric acid. Dosage of allopurinol should be at lower end of the recommended dosage schedule.

Use with uricosurics: Allopurinol does not interfere with the action of uricosurics so they may be given concurrently. When changing from uricosuric therapy to allopurinol, one to three weeks overlap is recommended to ensure continuous hypouricaemic effect.

4.3 Contraindications

Hypersensitivity to allopurinol or any of the excipients.

4.4 Special warnings and precautions for use

Allopurinol is not indicated for the treatment of asymptomatic hyperuricaemia.

Hypersensitivity syndrome, SJS and TEN

Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN. These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

HLA-B*5801 allele

The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

Acute gout attacks: Treatment with allopurinol should not be started until an acute attack of gout has subsided.

Exacerbation of acute gouty attacks may occur in the early stages of hypouricaemic therapy. 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 an acute attack develops after allopurinol has been initiated, allopurinol therapy should be continued, and the attack treated with an appropriate 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 rise in the xanthine concentration in the urine due to allopurinol may lead to deposition of xanthine in the urinary tract. Fluid intake should be sufficient to ensure optimal urine dilution.

Hepatic and/or renal impairment: A reduction in the dosage should be considered in the presence of hepatic or renal impairment (see section 4.2). Care is advised in

elderly patients and those receiving treatment for hypertension or cardiac insufficiency, (e.g. with ACE Inhibitors or diuretics), as they may have some concomitant renal impairment. Such patients may be at increased risk of adverse reactions (see 4.5, 4.8).

Impaction of uric acid renal stones: Adequate therapy with allopurinol will lead to dissolution of large uric acid renal pelvic stones, consequently, there is a risk that impaction in the ureter may occur.

Excipients: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Interaction with other medicinal products and other forms of interaction

Azathioprine, 6-mercaptopurine:
If administered 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.

Didanosine:
Concomitant administration is not recommended as it may result in significant increases to the AUC and Cmax values for didanosine. Patients treated with didanosine who require allopurinol administration should be switched to an alternative treatment regimen.

Capecitabine/5-Fluorouracil
Interactions with allopurinol and 5-fluorouracil have been observed; with possible decreased efficacy of the cytotoxic agent. Concomitant use of allopurinol with 5-fluorouracil or capecitabine should be avoided.

Ciclosporin:
The plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol.

ACE Inhibitors:
Concurrent use of allopurinol and ACE inhibitors may lead to an increased risk of haematological reactions such as leucopenia, especially if there is pre-existing renal failure.

Ampicillin/Amoxicillin:
Combined use of ampicillin or amoxicillin and allopurinol, has been reported to be associated with an increased incidence of rash, relative to that observed with single drug use. Concurrent use should be avoided where possible.

Coumarin anticoagulants:
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased by allopurinol

Theophylline:
Allopurinol has been reported to increase serum levels of theophylline in some patients, therefore it is advisable to monitor patients when introducing, or increasing the dose of allopurinol.

Phenytoin:
Allopurinol may inhibit hepatic oxidation of phenytoin, resulting in increased phenytoin serum levels and possible toxicity.

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 compete for excretion in the renal tubule.

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.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of allopurinol in pregnant women. Studies of oral allopurinol in animals have not shown reproductive toxicity, however, a single study of intraperitoneal use was associated with reproductive toxicity (see section 5.3).

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

Lactation
Allopurinol and oxipurinol are excreted in human breast milk. Concentrations of 1.4mg/litre allopurinol and 53.7 mg/litre oxipurinol were detected in breast milk from a woman taking allopurinol 300 mg/day. 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

Adverse reactions such as somnolence, vertigo and ataxia have been reported in patients receiving allopurinol, therefore, patients should exercise caution before driving, using machinery or participating in dangerous activities until they know that their performance is not adversely affected.

4.8 Undesirable effects

Currently accepted clinical data required to determine the frequency of undesirable effects are lacking for allopurinol. Adverse reactions are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic impairment.

Infections and infestations
Skin infections (furunculosis, folliculitis)

Blood and lymphatic system disorders
Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, eosinophilia, lymphadenopathy, including reversible angioimmunoblastic lymphadenopathy (see Immune system disorders).

There have also been reports of haemolytic anaemia and pure red cell aplasia.

Immune system disorders
A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn immediately and permanently.

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

Metabolism and nutrition disorders
Diabetes mellitus, hyperlipidaemia

Psychiatric disorders
Depression

Nervous System
Coma, paralysis, ataxia, convulsions, neuropathy, paraesthesiae, somnolence, headache, taste disturbances

Eye disorders
Cataract, visual disturbances, macular changes

Ear and labyrinth disorders
Vertigo

Cardiac disorders
Angina, bradycardia

Vascular disorders
Hypertension, vasculitis

Gastrointestinal disorders
Nausea and/or vomiting, which may be avoided by taking allopurinol after meals. Recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit

Hepatobiliary disorders
Asymptomatic increases in liver function tests, hepatitis (including hepatic necrosis and granulomatous hepatitis). Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

Skin and subcutaneous tissue disorders
Skin rash is the most commonly reported adverse reaction, and may be pruritic, maculopapular, sometimes scaly or purpuric, rarely exfoliative. Allopurinol should be withdrawn immediately. After recovery from mild reactions allopurinol may be introduced at a low 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, fixed drug eruption, alopecia, discoloured hair

The HLA-B*5801 allele has been identified as a genetic risk factor for allopurinol associated SJS/TEN in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Japanese and European descent. Up to 20-30% of some Han Chinese, African and Indian populations carry the HLA-B*5801 allele whereas only 1-2% of Northern European, US European and Japanese patients are estimated to be HLA-B*5801 carriers. However, the use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established.

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*.

Musculoskeletal and connective tissue disorders
In the early stages of treatment with allopurinol an acute attack of gouty arthritis may be precipitated. Arthralgia

Renal and urinary disorders
Renal impairment (see Immune system disorders). Haematuria, uraemia

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

General disorders
Malaise, oedema, asthenia, pyrexia

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The literature describes ingestion of 22.5g of allopurinol by a 15-year-old girl. The girl received gastric lavage within 3 hours of ingestion and 50g of activated charcoal; no signs of toxicity developed. A patient who ingested 20g of allopurinol experienced nausea, vomiting, diarrhoea and dizziness; the patient recovered following supportive care.

Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity which should have no untoward effects unless 6-mercaptopurine and/or azathioprine is being taken concomitantly. In this case the risk of increased activity of these drugs must be recognised.

Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. Haemodialysis may be used if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Allopurinol is an analogue of hypoxanthine. Both allopurinol and its primary metabolite alloxanthine, reduce the formation of uric acid from purine precursors (hypoxanthine and xanthine) by inhibition of the enzyme xanthine oxidase.

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. 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 Pharmacokinetics in patients with renal impairment).

5.3 Preclinical safety data

A. Mutagenicity
Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100 micrograms/ml and in vivo at doses up to 600 mg/day for mean period of 40 months.
Allopurinol does not produce nitraso compounds in vitro or affect lymphocyte transformation in vitro.
Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

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

C. 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

Lactose
Maize starch
Povidone
Stearic acid
Sodium starch glycollate

6.2 Incompatibilities

None known

6.3 Shelf life

4 years – blister packs
3 years – polypropylene containers

6.4 Special precautions for storage

Store in a dry place not above room temperature (25°C)

6.5 Nature and contents of container

Polypropylene tablet container and cap (Securitainer)
Pack sizes: 21, 100, 250, 500 and 1000 tablets

Aluminium/PVC blister strips enclosed in outer carton
Packs sizes: 28 and 56 tablets

6.6 Special precautions for disposal

Not relevant

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 December 1996 / 7 May 2002

10. DATE OF REVISION OF THE TEXT

26/10/2017