Approved Professional Information for Medicines for Human Use:

[PRODUCT NAME]

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

[PRODUCT NAME] 100, 100 mg tablets

[PRODUCT NAME] 300, 300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each [PRODUCT NAME] 100 tablet contains 100 mg allopurinol.

Each [PRODUCT NAME] 300 tablet contains 300 mg allopurinol.

Contains sugar (lactose monohydrate).

Each [PRODUCT NAME] 100 tablet contains 52,03 mg lactose monohydrate.

Each [PRODUCT NAME] 300 tablet contains 153,60 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[PRODUCT NAME] 100 tablets are white to off-white coloured, round, biconvex uncoated tablets with ‘AL’ and ‘100’ separated by a breakline on one side and plain on the other side.

Tablet diameter: approximately 7,5 mm

[PRODUCT NAME] 300 tablets are peach coloured, round, biconvex uncoated tablets with ‘AL’ and 300 separated by a breakline on one side and plain on the other side.

Tablet diameter: approximately 11,0 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] is used to reduce urate concentrations in body fluids and/or urine to prevent or reverse the deposition of urate/uric acid.

[PRODUCT NAME] is indicated in adults:

- for the treatment of gout and hyperuricaemia associated with other conditions. It reduces the concentration of uric acid in plasma with gradual resolution of tophi and reduces the risk of the formation of uric acid calculi. It may be effective in patients with impaired renal function.
- in the treatment of hyperuricaemia associated with leukaemia or resulting from radiotherapy or the use of anti-neoplastic medicines such as mercaptopurine or during treatment with thiazides (e.g. hydrochlorothiazide).

4.2 Posology and method of administration

Posology

Adults

In gout, it is usual to commence with 100 mg daily and to increase this dose as required up to 200 mg to 400 mg daily in divided doses.

In severe conditions, daily doses of up to 900 mg may be necessary.

In hyperuricaemia associated with leukaemia a suggested initial dose is 200 mg three times daily commencing, if possible, 2 or 3 days before radiotherapy or the commencement of treatment with anti-neoplastic medicines, and adjusted as requested to a maintenance dose, usually of 300 mg to 400 mg daily.

Instructions for use

Fluid intake should be sufficient to maintain daily urinary volume above 2 litres.

[PRODUCT NAME] is well tolerated, especially after food. Patients on high doses (> 300 mg) may benefit from a divided dose regimen.

Special populations

Renal impairment

Since [PRODUCT NAME] and its metabolites are excreted by the kidney, impaired renal function may lead to retention of [PRODUCT NAME] 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). [PRODUCT NAME] 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 mg to 400 mg [PRODUCT NAME] immediately after each dialysis with none in the interim

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 [PRODUCT NAME] 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 [PRODUCT NAME] 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 section 4.2 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.

Paediatric population

For children the suggested initial dose is 8 mg per kg body mass daily.

Method of administration

For oral administration

4.3 Contraindications

- Hypersensitivity to the allopurinol or to any of the excipients listed in section 6.1.
- Pregnancy and breastfeeding (see section 4.6).
- Children, except those with malignancy.

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Allopurinol hypersensitivity reactions can manifest in many ways. Serious allergic reactions may occur including exfoliative rashes including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS), SJS and TEN.

Should a skin rash or other evidence of sensitivity occur, [PRODUCT NAME] should be withdrawn immediately (see section 4.8).

Other hypersensitivity responses may occur e.g. skin eruptions, fever, chills, leucopenia or leucocytosis and eosinophilia, arthralgia and vasculitis leading to renal and hepatic damage. These reactions may be severe, even fatal and may occur at any time during treatment. Patients with renal impairment or taking thiazide diuretics are at special risk. These reactions usually subside a few days after administration is stopped (see section 4.8).

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 hypersensitivitysyndrome and SJS/TEN. The reported frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20 % in Han Chinese population, 8-15 % in the Thai, about 12 % in the Korean population and 1-2 % in individuals of Japanese or European origin. Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patientsubgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the risk in thesepatients additionally In case that no HLA-B*5801 genotyping is available for patients with Han Chinese, Thai or Koreandescent the benefits should be thoroughly assessed and considered outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations. If the patient is a known carrier ofHLA-B*5801 (especially in those who are from Han Chinese, Thai or Korean descent), allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits are thought to exceed risks. Extra vigilance forsigns 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.

SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

Renal impairment

Patients with chronic renal impairment and concomitant diuretic use, in particular thiazides, 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).
In patients with impaired renal function, reduced doses should be used (see sections 5.2, and 4.2).

Hepatic impairment

[PRODUCT NAME] should be used with caution (see section 4.2).

Acute gout attacks

Treatment with [PRODUCT NAME] should not be started until an acute attack of gout has completely subsided as this can exacerbate the attack. When starting treatment with [PRODUCT NAME], mobilisation of urate deposition may result in exacerbation of attacks of acute gouty arthritis. It is hence advisable to give colchicine at prophylactic doses or an anti-inflammatory medicine for at least one month when starting therapy with [PRODUCT NAME]. This effect can also be minimised by using small initial doses (100 mg per day) of [PRODUCT NAME] and gradual increasing of the dose at intervals. If an acute attack of gout develops while the patient is receiving [PRODUCT NAME], therapy should be continued at the same dosage and the acute attack treated separately.

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 some cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution (increasing daily fluid intake).

Immunosuppressants

When [PRODUCT NAME] is used concurrently with azathioprine or mercaptopurine, the dosage of azathioprine or mercaptopurine must be reduced to one-fourth of the usual dose due to prolongation of activity of these medicines (see section 4.5).

Treatment of neoplasia:

Prior to instituting cytotoxic therapy, it is advisable to assess existing serum urate and urinary acid levels. Hyperuricaemia and/or hyperuricosuria should be corrected prior to starting treatment. Adequate hydration to maintain maximum diuresis throughout is important (see section 4.5).

Impaction of uric acid renal stones

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

Thyroid disorders

Increased TSH values (> 5,5 µIU/mL) were observed in patients on long-term treatment with allopurinol (5,8%) in a long-term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

Fluid intake and gastric irritation

Fluid intake should be sufficient to maintain daily urinary volume above 2 litres. Taking allopurinol after food minimises gastric irritation.

Excipient: lactose monohydrate

[PRODUCT NAME] contains lactose monohydrate:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take [PRODUCT NAME].

Excipient: sodium

[PRODUCT NAME] contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Aluminium hydroxide

If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

Azathioprine and 6-mercaptopurine

Azathioprine is metabolised to 6-mercaptopurine by xanthine oxidase. Inhibition of this enzyme by [PRODUCT NAME] results in prolongation of the activity of azathioprine and mercaptopurine and hence the dosage of azathioprine or mercaptopurine must be reduced to one-fourth of the usual dosage when these medicines are given concomitantly with [PRODUCT NAME] (see section 4.4 ~~WARNINGS AND SPECIAL PRECAUTIONS~~).

Cytostatics

Concurrent usage of cyclophosphamide and other anti-neoplastic medicines such as doxorubicin, bleomycin, procarbazine and mechlorethamine with [PRODUCT NAME], may cause an increase in the toxicity of these anti-neoplastic medicines.

With concurrent use blood dyscrasias occur more frequently than when these medicine treatments are administered alone. Blood count monitoring should therefore be performed at regular intervals (see section 4.4).

Xanthines

Allopurinol may reduce the clearance of theophylline and other xanthines and their dosage might have to be reduced to avoid toxicity.

Theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Chlorpropamide

Administration of [PRODUCT NAME] concomitantly with chlorpropamide may lead to prolonged hypoglycaemic action since there may be competition in the renal tubule for the excretion of chlorpropamide. Poor renal function may exacerbate this further.

Salicylates and uricosuric agents

Oxypurinol, the major active metabolite of allopurinol, is excreted by the kidney in a very similar way to urate. Medicines with uricosuric activity such as probenecid or large doses of salicylates may accelerate the excretion of oxypurinol. This may lead to partial loss of therapeutic activity of [PRODUCT NAME], but the significance of this needs to be assessed in each case.

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.

Angiotensin-converting-enzyme (ACE) inhibitors

An increase in hypersensitivity reactions, and possibly other side effects, may occur in patients taking [PRODUCT NAME] with an ACE inhibitor. Care is advised during concomitant use of an ACE inhibitor with [PRODUCT NAME], particularly in patients with renal impairment.

Coumarin anticoagulants

There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol, therefore, all patients receiving anticoagulants concomitantly with [PRODUCT NAME] should be carefully monitored.

Amoxicillin and ampicillin

There may be an increased incidence of skin rashes in patients receiving amoxicillin or ampicillin concomitantly with [PRODUCT NAME]. In patients receiving therapy with [PRODUCT NAME], it is recommended that an alternative to amoxicillin or ampicillin is utilised.

Vidarabine (adenine arabinoside)

As evidence suggests that the plasma half-life of vidarabine (adenine arabinoside) is increased in the presence allopurinol, additional vigilance for increased toxic effects is recommended during concomitant use of [PRODUCT NAME] and vidarabine.

Didanosine

Concomitant use of didanosine and [PRODUCT NAME] is not recommended due to possible increases in C_{max} and AUC values of didanosine during concomitant therapy. If co-administration cannot be avoided, a dose reduction of didanosine may be required and close monitoring of the patient is advised.

Ciclosporin

Plasma concentrations of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered during co-administration of ciclosporin and [PRODUCT NAME].

Phenytoin

[PRODUCT NAME] may inhibit the hepatic oxidation of phenytoin but the clinical significance has not been determined.

4.6 Fertility, pregnancy and lactation

Pregnancy

[PRODUCT NAME] in pregnancy is contraindicated (see section 4.3).

Breastfeeding

Allopurinol and oxypurinol have been detected in human breast milk. Use of [PRODUCT NAME] in lactating mothers is contraindicated (see section 4.3).

Fertility

No data available

4.7 Effects on ability to drive and use machines

Adverse effects such as headaches, drowsiness and vertigo have been reported in patients receiving allopurinol.

Patients should exercise caution before driving and using machinery until they are certain that [PRODUCT NAME] does not adversely affect performance.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with allopurinol.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Furunculosis	
Blood and lymphatic system disorders		Leucopenia, leucocytosis, eosinophilia, thrombocytopenia, aplastic anaemia, agranulocytosis	
Immune system disorders		Hypersensitivity reactions, angioimmunoblastic lymphadenopathy, anaphylactic reaction	
Metabolism and nutrition disorders		Diabetes mellitus, hyperlipidaemia, taste perversion	
Psychiatric disorders		Depression	
Nervous system disorders		Peripheral neuritis, drowsiness, headache, paraesthesia, ataxia, somnolence, neuropathy, paralysis, coma, epilepsy	Aseptic meningitis

Eye disorders		Cataract formation, visual impairment, maculopathy	
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Bradycardia, angina	
Vascular disorders		Vasculitis leading to renal and hepatic damage, hypertension, oedema	
Gastrointestinal disorders		Nausea, vomiting, abdominal pain, gastric irritation, diarrhoea, haematemesis, steatorrhea, stomatitis, change of bowel habit, taste disturbances	
Hepatobiliary disorders		Hepatitis (including hepatic necrosis and granulomatous hepatitis), abnormal liver function tests, hepatic damage, hepatotoxicity	
Skin and subcutaneous tissue disorders	Skin eruptions/rash	Exfoliative rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, discoloured hair, angioedema	
Musculoskeletal and connective tissue disorders		Arthralgia	

Renal and urinary disorders		Haematuria, uraemia, azotaemia	
Reproductive system and breast disorders		Male infertility, impotence, gynaecomastia, erectile dysfunction	
General disorders and administration site conditions		Fever, chills, malaise, oedema	
Investigations		Blood thyroid stimulating hormone increased	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

The most likely reaction to allopurinol overdose would be gastrointestinal intolerance. Nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20 g of allopurinol.

Treatment

Administer sufficient fluids to maintain maximum diuresis since this in turn facilitates excretion of allopurinol and its metabolites.

Treatment is symptomatic and supportive.

If considered necessary, haemodialysis may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 3.3 Antigout preparations

Pharmacotherapeutic group: Preparations inhibiting uric acid production, ATC Code: M04AA01

Mechanism of action

Allopurinol is a xanthine oxidase inhibitor. Allopurinol is also a substrate for xanthine oxidase and the product of this reaction is the metabolite oxypurinol, which is also an inhibitor of xanthine oxidase.

Allopurinol and its main metabolite, oxypurinol inhibit the enzyme xanthine oxidase, preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. As a result of inhibition of this enzyme responsible for the terminal steps in uric acid biosynthesis, plasma and urine uric acid concentrations are reduced.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, allopurinol is well absorbed with peak plasma concentrations reached within 60 to 90 minutes. Oral bioavailability is up to 90 %.

Distribution

Allopurinol and its active metabolite, oxypurinol are distributed in total tissue water, with the exception of the brain, where their tissue concentrations are one-third of those in other tissues. The apparent volume of distribution is approximately 1,6 litre/kg.

Neither compound is bound to plasma proteins.

It is likely that allopurinol and oxypurinol will be present in the highest concentrations in the liver and intestinal mucosa as these are areas where xanthine oxidase activity is high.

Biotransformation

Allopurinol has a plasma half-life of about 1 to 2 hours and most of its pharmacological activity is due to its metabolite, oxypurinol which has estimated plasma half-life of 18–30 hours (prolonged further in renal impairment). This provides effective inhibition of xanthine oxidase maintained over a 24-hour period with a single daily dose of [PRODUCT NAME]. In patients with normal renal function, oxypurinol will accumulate until a steady-state plasma oxypurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day, will generally have plasma oxypurinol concentrations of 5-10 mg/litre. Both allopurinol and oxypurinol are conjugated to form their respective ribonucleosides.

Elimination

Faecal elimination accounts for approximately 20 % of the ingested dose of allopurinol and 10–30 % is excreted unchanged in the urine. The remainder undergoes metabolism.

Oxypurinol is eliminated unchanged in the urine, but has a long elimination half-life as it is slowly excreted via glomerular filtration and undergoes tubular reabsorption.

Renal impairment

The clearance of allopurinol and oxypurinol is greatly reduced in patients with poor renal function resulting in higher plasma levels with chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20 mL/min, showed plasma oxypurinol concentrations of approximately 30 mg/L 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 [PRODUCT NAME] according to creatinine clearance is therefore required in patients with renal impairment (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,

maize starch,

povidone,

sodium starch glycollate,

dried maize starch,

micronized stearic acid.

[PRODUCT NAME] 300 tablets also contain a colourant:

sunset yellow FCF aluminium lake (E110).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in the original packaging until required for use.

Keep blister strips in carton until required for use.

Store at or below 25 °C.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Tablets are packed in clear PVDC coated PVC/Aluminium foil blister strips of 7 or 10, which are further packed in printed cartons, in pack sizes of 28, 30 or 100 tablets. Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

Allopurinol 100 Austell: 49/3.3/0016

Allopurinol 300 Austell: 49/3.3/0017

Allopurinol 100 Camox: 49/3.3/0018

Allopurinol 300 Camox: 49/3.3/0019

Lessuric 100: 49/3.3/0020

Lessuric 300: 49/3.3/0021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 October 2015

10. DATE OF REVISION OF THE TEXT

28 April 2023