1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PURICOS-100 tablets

PURICOS 300 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PURICOS-100:

Each tablet of PURICOS-100 contains 100 mg allopurinol.

Contains sugar: Lactose monohydrate 100 mg

PURICOS 300:

Each tablet contains 300 mg allopurinol.

Contains sugar: Lactose monohydrate 180 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

PURICOS-100: A white, round, shallow, biconvex tablet, bisected on one side, with a diameter ranging between 9,0 mm to 10,0 mm.

PURICOS 300: A white, round, shallow, biconvex tablet, bisected on one side, with a diameter ranging between 10,6 mm to 11,7 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

PURICOS 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

Adults

In gout, it is usual to commence with 50 mg twice 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.

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

Special populations

Renal impairment

Since PURICOS and its metabolites are excreted by the kidney, impaired renal function may lead to retention PURICOS 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).

PURICOS 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 PURICOS 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.

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

PURICOS is contraindicated in:

- Hypersensitivity to allopurinol or to any of the other ingredients of PURICOS (see section 2).
- Pregnancy and breastfeeding (see section 4.6).
- Children, except those with malignancy.

4.4. Special warnings and precautions for use

Hypersensitivity

PURICOS should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) (see sections 4.3 and 4.8).

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 (SJS) and toxic epidermal necrolysis (TEN).

PURICOS should be withdrawn immediately should such reactions occur. After recovery from mild reactions, PURICOS may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, PURICOS should be permanently withdrawn as more severe hypersensitivity may occur (see section 4.8).

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.

Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.
Fever has been reported to occur with and without signs and symptoms of a more generalised PURICOS hypersensitivity reaction (see section 4.8).

*HLA-B*5801 allele*
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 % to 30 % of some Han Chinese, African and Indian populations carry the HLA-B*5801 allele whereas only 1 % to 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 PURICOS has not been established.

Hepatic and renal impairment
Reduced doses should be used in patients with hepatic or renal impairment. PURICOS should be used with caution in patients with hypertension and cardiac insufficiency treated with diuretics and ACE inhibitors.

Adverse reactions in association with PURICOS 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 disorder.

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

Asymptomatic hyperuricaemia

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

Acute gout attacks:

PURICOS 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 PURICOS, an acute attack of gout arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory medicine or colchicine for at least one month.

If acute attacks develop in patients receiving PURICOS, treatment should continue at the same dosage while the acute attack is treated with a suitable anti-inflammatory medicine.

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

Thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function have been reported rarely, reinforcing the need for particular care in this group of patients.

Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment and very rarely, seizures. Acute anaphylactic shock has been reported. If such reactions do occur, it may be at any time during treatment. PURICOS 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 following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of PURICOS.

Nausea and vomiting can be avoided by taking PURICOS after meals.

Excipients

PURICOS contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take PURICOS.

4.5. Interaction with other medicines 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 PURICOS, 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 these two products are used concomitantly caution is necessary, to recognise enhanced toxic effects.

Salicylates and uricosuric medicines: oxipurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, medicines with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of PURICOS, but the significance of this needs to be assessed in each individual case.

Chlorpropamide: If PURICOS 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 reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with PURICOS. Therefore, all patients receiving anticoagulants must be carefully monitored.

Phenytoin: PURICOS 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 PURICOS therapy.

Ampicillin / amoxicillin: An increase in frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with PURICOS, compared to patients who are not receiving both medicines. The cause of the reported association has not been established. However, it is recommended that in patients receiving PURICOS, an alternative to ampicillin or amoxicillin is used where available.

Cyclophosphamide, doxorubicin, bleomycin: Enhanced bone marrow suppression by

cyclophosphamide and other cytotoxic medicines has been reported among patients with neoplastic disease (other than leukaemia), in the presence of allopurinol, as contained in PURICOS. However, in a well-controlled study of patients treated with cyclophosphamide, doxorubicin and/or bleomycin, allopurinol, as contained in PURICOS, did not appear to increase the toxic reaction of these cytotoxic medicines.

Ciclosporin: Plasma concentration of ciclosporin may be increased during concomitant treatment with PURICOS. Enhanced ciclosporin toxicity should be considered if these medicines 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, as contained in PURICOS, treatment (300 mg daily) without affecting terminal half-life. Co-administration of these two medicines is not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.

4.6. Fertility, pregnancy and lactation

Pregnancy

PURICOS is contraindicated in pregnancy (see section 4.3).

Breastfeeding

PURICOS is contraindicated in lactation (see section 4.3).

Fertility

No data available.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

a) *Tabulated list of adverse reactions*

System organ class	Frequent	Less frequent
Infections and infestations		Furunculosis
Blood and the lymphatic system disorders		Leucopenia leucocytosis eosinophilia haemolytic anaemia agranulocytosis aplastic anaemia thrombocytopenia
Immune system disorders		Hypersensitivity reactions (including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia, eosinophilia, Stevens-Johnson syndrome and toxic epidermal necrolysis), vasculitis, angioimmunoblastic lymphadenopathy
Metabolism and nutrition disorders		Diabetes mellitus, hyperlipidaemia
Psychiatric disorders		Drowsiness, depression
Nervous system disorders		Headache, peripheral neuritis, seizures, paraesthesia, coma, paralysis, ataxia, somnolence
Eye disorders		Cataract, visual disturbances, macular changes
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Angina, bradycardia
Vascular disorders		Hypertension
Gastrointestinal disorders		Nausea, vomiting, abdominal pain, diarrhoea, gastric irritation, taste disturbances, recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit

Hepato-biliary disorders		Hepatic damage, hepatotoxicity, altered liver function, hepatitis (including hepatic necrosis and granulomatous hepatitis)
Skin and subcutaneous tissue disorders	Rash	Stevens-Johnson syndrome, toxic epidermal necrolysis, skin eruptions, exfoliative rash, alopecia, angioedema, discoloured hair
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders		Renal damage, haematuria, uraemia
Reproductive system and breast disorders		Gynaecomastia, male infertility, erectile dysfunction
General disorders and administrative site conditions		Fever, chills, malaise, oedema, asthenia.

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 providers 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

Symptoms

Ingestion of up to 22,5 g allopurinol, as contained in PURICOS, 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.

Treatment

Treatment is symptomatic and supportive.

Recovery followed general supportive measures. Massive absorption of PURICOS 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, as contained in PURICOS, and its metabolites. If considered necessary haemodialysis may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Antigout preparations inhibiting uric acid production

ATC code: M04 AA01

Mechanism of action

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 catalysing 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 well absorbed from the upper gastrointestinal tract (duodenum and upper jejunum). Studies have detected allopurinol in the blood 30 to 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 to 5 hours after oral administration of allopurinol and are much more sustained.

Distribution

Allopurinol is poorly 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.

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 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 to 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.

Special populations

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 (see section 4.2).

Elderly:

The pharmacokinetics of the allopurinol are not likely to be altered other than due to deterioration in renal function (see Renal impairment).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

PURICOS-100: Lactose monohydrate, magnesium stearate, maize starch, pregelatinised starch, polysorbate, purified talc, sodium starch glycollate.

PURICOS 300: Croscarmellose sodium, lactose monohydrate, maize starch, povidone.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep container tightly closed.

Keep in original packaging until required for use.

6.5. Nature and contents of container

PURICOS-100: 100 tablets are packed in a clear polyvinylchloride film sealed with an aluminium foil backing. One or more blister strips are packed into an outer cardboard carton together with a leaflet.

PURICOS-100: 500 tablets are packed in a white polypropylene container and sealed with a white low density polyethylene cap with a tamper evident seal, together with a white foam insert or rayon, together with a leaflet.

PURICOS-100: 30 tablets are packed in a metallised polyester patient ready lay flat pack and sealed with a clear low density polyethylene zip. The lay flat is overwrapped with a clear polyethylene bag.

PURICOS 300: 30 tablets are packed in a clear polyvinylchloride film sealed with an aluminium foil backing. One or more blister strips are packed into an outer cardboard carton together with a leaflet.

PURICOS 300: 250 tablets are packed in a white polypropylene container and sealed with a white low density polyethylene cap with a tamper evident seal, together with a white foam insert or rayon, together with a leaflet.

PURICOS 300: 28 or 30 tablets are packed in a metallised polyester patient ready lay flat pack and sealed with a clear low density polyethylene zip.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

PURICOS-100: K/3.3/305

PURICOS 300: L/3.3/257

9. DATE OF FIRST AUTHORISATION

PURICOS-100: 06 March 1979

PURICOS 300: 15 October 1979

10. DATE OF REVISION OF TEXT

12 August 2020

ZA_PURITAB_2008_00