1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZYLOPRIM* 100 mg tablets

ZYLOPRIM* 300 300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of ZYLOPRIM contains 100 mg allopurinol.

Contains sugar: Lactose monohydrate 50 mg

For full list of excipients, see section 6.1.

Each tablet of ZYLOPRIM 300 contain 300 mg allopurinol.

Contains sugar: Lactose monohydrate 150 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Zyloprim Tablets: A round, white biconvex, bisected tablet, debossed with Z1 on one side.

Zyloprim 300 Tablets: A round, white biconvex, bisected tablet, debossed with Z3 on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

ZYLOPRIM is indicated in:

- the management of the main clinical manifestations of urate deposition which are: gouty arthritis, skin tophi, idiopathic gout, uric acid lithiasis and acute uric acid nephropathy.
- the management of patients with neoplastic and myeloproliferative disease with high cell turnover rates which cause elevations of serum and urinary levels. These include leukaemia, lymphomas, or other malignancies, especially when cytotoxic therapy has been initiated.
- the management of patients with recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria when fluid, dietary and similar measures have failed.
- certain enzyme disorders which lead to over production of urate, for example;
  - hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome;
  - glucose-6-phosphatase including glycogen storage diseases.

4.2. Posology and method of administration

Posology

The dose should be titrated against the patient by monitoring serum urate/uric acid and/or urinary uric acid levels at appropriate intervals. Doses of up to 300 mg ZYLOPRIM may be taken once a day. Larger doses should be administered as divided doses of not more than 300 mg. It is recommended that ZYLOPRIM

be taken after meals for better gastrointestinal tolerance.

Adults

Daily oral dose should be introduced at a low dosage of 100 mg/day to reduce the risk of adverse reaction such as nausea, vomiting and diarrhoea and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor. (see sections 4.2 and 4.4). The usual maintenance dose is 300 mg/day. However, doses up to 900 mg/day have been used.

Special populations

Elderly

In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used (see sections 4.2 and 4.4).

Renal impairment

Dose precautions in renal disorder

Since ZYLOPRIM and its metabolites are excreted by the kidney, renal failure may lead to the retention of the medicine and /or its metabolites with consequent prolongation of plasma half-lives. To reduce attendant risks, the amount and frequency of the dosage may require reduction. The following schedule is provided for guidance in adults: If creatinine clearance exceeds 20 ml/minute - give standard dose. If creatinine clearance is between 10 and 20 ml/minute - give 100 to 200 mg/day. If creatinine clearance is less than 10 ml/minute - give 100 mg/day or at longer intervals. If plasma monitoring facilities are available, plasma oxypurinol levels should be maintained below 100 micromol/litre (15,2 micrograms/mL).

Dose precautions in renal dialysis

ZYLOPRIM and its metabolites are removed by renal dialysis and dosages should be adjusted accordingly. Consideration should be given to an alternative dosage schedule of 300 ZYLOPRIM immediately after each dialysis.

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 ZYLOPRIM 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 ZYLOPRIM 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 sections 4.5 and 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

Children under 15 years

Daily oral dose 100 to 400 mg or 10 to 20 mg/kg bodymass/day. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyham syndrome.

Method of administration

For oral administration.

4.3. Contraindications

ZYLOPRIM is contraindicated in:

- Patients with hypersensitivity to allopurinol or to any of the excipients in ZYLOPRIM (see sections 2 and 6.1)).
- Severe hepatic or renal disorder (see section 4.2).
- An acute gout attack (see section 4.4).

4.4. Special warnings and precautions for use

Hypersensitivity syndrome, SJS and TEN

ZYLOPRIM 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-Johnsons syndrome (SJS), and toxic epidermal necrolysis (TEN)) and hypersensitivity syndrome (also known as Drug Rash with Eosinophilia and Systemic Symptoms, DRESS) (see section 4.8). After recovery from mild reactions ZYLOPRIM

may, if desired, be reintroduced at a small dose (e.g. 50 mg per day) and gradually

increased. If the rash recurs, ZYLOPRIM should be PERMANENTLY withdrawn.

*HLAB-B*5801 allele*

The HLA-B*58:01 allele has been identified as a genetic risk factor for ZYLOPRIM 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 to 30 % of people of Han Chinese, African and Indian ancestry carry the HLAB-B*58:01 allele whereas only 1 to 2 % of Northern European, US European and Japanese are estimated to be HLA-B*58:01 carriers.

Screening for HLA-B*58:01 should be considered before starting treatment with ZYLOPRIM in patient subgroups where the prevalence is known to be high. If the individuals test positive, ZYLOPRIM should not be started unless there are no other reasonable therapeutic options and the benefits of use outweigh the potential associated risks. Patients who are found to be negative for HLA-B*58:01 still have a risk of SJS/TEN . The clinical diagnosis of SJS/TEN, and other hypersensitivity reactions remain the bases of the decision making. If such reactions occur at anytime during treatment, ZYLOPRIM should be withdrawn immediately and permanently.

Corticosteroids

may be beneficial in overcoming hypersensitivity skin reactions. (see section 4.8).

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 ZYLOPRIM should be

used with care in this group.

Chronic renal impairment

Chronic renal insufficiency and concomitant diuretic use, in particular thiazides, has been associated with an increased risk of ZYLOPRIM induced SJS/TEN, and other serious hypersensitivity reactions.

Hyperuricaemia

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

Acute gouty attacks

ZYLOPRIM treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated by ZYLOPRIM. Mobilisation of urate deposition may result in exacerbation of attacks of acute gouty arthritis. Hence, when starting treatment with ZYLOPRIM, it is advisable to give an anti-inflammatory medicine for at least one month. This effect can be avoided by using a small initial dose (100 mg per day) of ZYLOPRIM, gradually increasing the dose at intervals. If acute attacks develop in patients receiving ZYLOPRIM, 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 may rise sufficiently to allow deposition of ZYLOPRIM or its metabolites in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Neoplasia

Before instituting cytotoxic therapy it is advisable to assess existing serum urate and urinary acid levels. When hyperuricaemia and/or hyperuricosuria are present, they should be corrected prior to starting treatment. Adequate hydration to maintain maximum diuresis throughout is important.

Lactose warning

ZYLOPRIM tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicines and other forms of interaction

6-Mercaptopurine and azathioprine

6-Mercaptopurine and azathioprine are inactivated by the action of xanthine oxidase. Hence inhibition of xanthine oxidase may prolong the action of these medicines. Therefore, when either of these substances is given by mouth concomitantly with ZYLOPRIM, only one-quarter of the usual dosage of these substances should be given.

Salicylates and uricosuric medicines

Oxypurinol, the major metabolite of ZYLOPRIM and itself therapeutically active, is excreted by the kidney in a very similar way to urate. Hence medicines causing

uricosuria (e.g. probenecid, large doses of salicylate) may also accelerate the excretion of oxypurinol. This may lead to partial loss of therapeutic activity of ZYLOPRIM, but the significance of this needs to be assessed in each case.

Chlorpropamide

In the presence of ZYLOPRIM, there may be competition in the renal tubule for excretion of chlorpropamide. When renal function is poor, the recognised risk of prolonged hypoglycaemic activity of chlorpropamide may be increased if ZYLOPRIM is given concomitantly.

Coumarin anticoagulants

There is no evidence that interaction between ZYLOPRIM and the coumarins seen under experimental conditions has any clinical significance. However, all patients receiving anticoagulants must be carefully monitored.

Phenytoin

ZYLOPRIM may inhibit hepatic oxidation of phenytoin but the clinical significance has not been demonstrated.

Vidarabine (Adenine arabinoside)

Evidence suggests that the plasma half-life of adenine arabinoside is increased in the presence of ZYLOPRIM. When the two medicines are used concomitantly, extra vigilance is necessary, to recognise enhanced toxic effects.

Theophylline

Inhibition of the metabolism of theophylline has been observed. 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 doses of ZYLOPRIM therapy.

Ampicillin/Amoxicillin

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

Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechloroethamine

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic medicines has been reported in patients with neoplastic disease (other than leukaemia) in the presence of ZYLOPRIM.

Ciclosporin

Plasma concentration of ciclosporin may be increased during concomitant treatment with ZYLOPRIM. The possibility of enhanced ciclosporin toxicity should be considered if the 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 ZYLOPRIM treatment (300 mg daily) without affecting terminal half life. Therefore, dose reductions of didanosine may be required when used concomitantly with ZYLOPRIM.

Diuretics

An interaction between ZYLOPRIM and furosemide that results in increased serum urate and plasma oxypurinol concentrations can occur. There is an increased risk of hypersensitivity when ZYLOPRIM is given with diuretics, in particular thiazides, especially in renal impairment.

Angiotensin-converting-enzyme (ACE) inhibitors

An increased risk of hypersensitivity can occur when ZYLOPRIM is given with ACE inhibitors especially in renal impairment.

4.6. Fertility, pregnancy and lactation

The safety of ZYLOPRIM in pregnancy and lactation has not been established.

Breastfeeding

ZYLOPRIM should not be given to breastfeeding mothers since it is excreted in breast milk.

Fertility

There are insufficient fertility data available to indicate whether ZYLOPRIM, has any effect on fertility.

4.7. Effects on ability to drive and use machines

ZYLOPRIM has moderate influence on the ability to drive and use machines since adverse reactions such as somnolence, vertigo and ataxia have been reported in patients taking ZYLOPRIM (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic medicines.

The frequency categories assigned to the adverse reactions below are estimates: for most reactions, suitable data for calculating incidence are not available.

Adverse reactions identified through post-marketing surveillance were considered to be less frequent.

a) Tabulated list of adverse reactions for ZYLOPRIM

System organ class	Frequent	Less Frequent
Infections and Infestations		Furuncle
Blood and the lymphatic system disorders		Agranulocytosis, aplastic anaemia, thrombocytopenia
Immune system disorders		Hypersensitivity, angioimmunoblastic, T-cell lymphoma
Metabolism and nutrition disorders		Diabetes mellitus, hyperlipidaemia
Psychiatric disorders		Depression
Nervous system disorders		Coma, paralysis, ataxia, peripheral neuropathy, paraesthesia, somnolence, headache, dysgeusia
Eye disorders		Cataract, impairment, maculopathy
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Angina pectoris, bradycardia
Vascular disorders		Hypertension
Gastrointestinal disorders		Vomiting, nausea, diarrhoea, haematemesis, steatorrhoea, stomatitis, change of bowel habit
Hepato-biliary disorders		Abnormal liver function test, hepatitis (including hepatic necrosis and granulomatous hepatitis)
Skin and subcutaneous tissue disorders	Rash, pruritic, maculopapular,	Stevens-Johnson syndrome/toxic epidermal necrolysis,

	sometimes scaly	angioedema, medicine eruption, alopecia, hair colour changes
Renal and urinary disorders		Haematuria, azotaemia
Reproductive system and breast disorders		Male infertility, erectile dysfunction, gynaecomastia
General disorders and administrative site conditions		Oedema, malaise, asthenia, pyrexia

b) *Description of selected adverse reactions*

Blood and the lymphatic system disorders

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

Immune system disorders

Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia and/or eosinophilia (DRESS), and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), may occur (see Skin and subcutaneous tissue disorders). Associated vasculitis and tissue response may be manifested in various ways including hepato-splenomegaly, hepatitis, vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), renal impairment and seizures. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). Acute anaphylactic shock can occur. If such reactions do occur ZYLOPRIM 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.

Angioimmunoblastic T-cell lymphoma has been described following biopsy of a generalised lymphadenopathy. It may not be reversible on withdrawal of ZYLOPRIM.

Skin and subcutaneous tissue disorders

Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, scaly, purpuric and 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. ZYLOPRIM should be withdrawn immediately should such reactions occur. After recovery from mild reactions, ZYLOPRIM may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, ZYLOPRIM 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 ZYLOPRIM 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, ZYLOPRIM should be withdrawn immediately and permanently.

4.9. Overdose

Symptoms

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Treatment

Adequate hydration to maintain maximum diuresis facilitates excretion of ZYLOPRIM and its metabolites. Haemodialysis may be resorted to if considered necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Allopurinol inhibits xanthine oxidase (XO), the enzyme which catalyses the following reactions: hypoxanthine XO > xanthine > XO urate (uric acid).

Allopurinol decreases body urate by reducing formation and hence the amount entering the miscible pool. Allopurinol inhibits the conversion of hypoxanthine and xanthine to urate, thus leading to a proportional redistribution of oxypurines (i.e. relative increase of hypoxanthine and xanthine). It also decreases the overall oxypurine formation since re-entry of hypoxanthine and xanthine into the purine anabolic pathway reduces de novo purine synthesis by feedback inhibition. In the presence of excess body urate, the reduction of the miscible pool permits mobilization and excretion of urate deposited throughout the body, such as in the skin, joints, bones and kidney.

5.2. Pharmacokinetic properties

Absorption

Allopurinol is rapidly absorbed from the upper gastrointestinal tract. Estimates of bioavailability vary from 67 % to 90 %. Peak plasma levels of allopurinol generally occur approximately 1,5 h after oral administration of 300 mg allopurinol, but fall rapidly and are barely detectable after 6 h. Peak plasma levels of oxipurinol, the

principal metabolite, generally occur after 3 to 5 h 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.

Biotransformation

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

It has been shown that reutilisation of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by allopurinol and oxipurinol. This reutilization does not disrupt normal nucleic acid anabolism, however, because feedback inhibition is an integral part of purine biosynthesis. As a result of xanthine oxidase inhibition, the serum concentration of hypoxanthine plus xanthine in patients receiving allopurinol for treatment of hyperuricemia is usually in the range of 0,3 to 0,4 mg/dL compared to a normal level of approximately 0,15 mg/dL. A maximum of 0,9 mg/dL of these oxypurines has been reported when the serum urate was lowered to less than 2 mg/dL by high doses of ZYLOPRIM. These values are far below the saturation levels at which point their precipitation would be expected to occur (above 7 mg/dL).

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 medicine excreted in the urine.

Allopurinol has a plasma half-life of about 0,5 to 1,5 h.

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 h in man. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5 to 10 mg/litre.

Special Population

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.

Elderly patients

The kinetics of ZYLOPRIM have not been studied in the elderly, but are not expected to be altered other than due to deterioration in renal function (see section 5.2).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ZYLOPRIM Tablets: Lactose monohydrate, magnesium stearate, maize starch, povidone.

ZYLOPRIM 300 Tablets: Lactose monohydrate, magnesium stearate, 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 in a dry place.

Protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

ZYLOPRIM Tablets: Clear plastic/silver aluminium blister packs of 30, 150, 300, packed into cartons.

ZYLOPRIM 300 Tablets: Clear plastic/silver aluminium blister packs of 28, 30, packed into cartons.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

ZYLOPRIM Tablets: C974 (Act 101/1965)

ZYLOPRIM 300 Tablets: G/3.3/51

9. DATE OF FIRST AUTHORISATION

30 November 1993

10. DATE OF REVISION OF TEXT

15 February 2022

ZA_ZYLOTAB_2202_00