1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

ZYLOPRIM (tablet)

ZYLOPRIM 300 (tablet)

COMPOSITION:

ZYLOPRIM

Each tablet of ZYLOPRIM contains 100 mg of allopurinol.

Excipients:

Lactose monohydrate, magnesium stearate, maize starch, povidone.

Contains sugar: Lactose monohydrate 50 mg

ZYLOPRIM 300

Each tablet of ZYLOPRIM 300 contains 300 mg of allopurinol.

Excipients:

Lactose monohydrate, magnesium stearate, maize starch, povidone.

Contains sugar: Lactose monohydrate 150 mg

CATEGORY AND CLASS

A3.3 Antigout preparations

PHARMACOLOGICAL ACTION:

Allopurinol is an anti-hyperuricaemic. 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.

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.

CONTRA-INDICATIONS:

Hypersensitivity to allopurinol. Severe hepatic or renal disorder. An acute gout attack.

DOSAGE AND DIRECTIONS FOR USE:

The dose should be titrated against the patient by monitoring serum urate/uric acid and/or urinary uric acid levels at appropriate intervals. Up to and including 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 tolerance.

Adults:

Daily oral dose 100 to 900 mg depending on severity of the condition or 2 to 10 mg/kg bodymass/day.

Children under 15 years:

Daily oral dose 100 to 400 mg or 10 to 20 mg/kg bodymass/day.

Dose precautions in renal disorder: Since allopurinol and its metabolites are excreted by the kidney, renal failure may lead to the retention of the medicine and 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: Allopurinol 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 to 400 mg ZYLOPRIM immediately after each dialysis.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The incidence of adverse effects is higher in the presence of renal and/or hepatic disorder and a dosage reduction should be considered in these cases. Skin reactions are the most common and may occur anytime during treatment. They may be pruritic, maculopapular, sometimes

scaly, sometimes purpuric and rarely exfoliative. As severe skin reactions may occur, ZYLOPRIM should be withdrawn **IMMEDIATELY** should such reactions occur. 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. Skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson and/or Lyell Syndrome occur rarely. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and very rarely, epilepsy. If such reactions do occur, ZYLOPRIM should be withdrawn **IMMEDIATELY AND PERMANENTLY**.

Nausea and vomiting have been reported. Recurrent haematemesis and steatorrhoea are extremely rare occurences. Angio-immunoblastic lymphadenopathy, following biopsy of a generalised lymphadenopathy, and granulomatous hepatitis rarely occur and appear to be reversible on withdrawal of ZYLOPRIM. Occasional reports have been received of thrombocytopaenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal function.

Other complaints which have been reported occasionally are: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesiae, neuropathy, visual disorders, cataract, macular changes, taste perversion, stomatitis, changed bowel habits, infertility, impotence, nocturnal emission, diabetes mellitus, hyperlipaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia, haematuria and gynaecomastia.

Special precautions:

Treatment of 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. **Renal disorder:** See under **DOSAGE AND DIRECTIONS FOR USE**.

Hepatic disorder:

ZYLOPRIM should be used with caution. **Acute gouty attacks:** 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 colchicine at prophylactic doses or an anti-inflammatory agent 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.

Pregnancy:

There is inadequate evidence of the safety of ZYLOPRIM in human pregnancy.

Lactation:

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

INTERACTIONS:

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 allopurinol 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 therepeutic activity of ZYLOPRIM, but the significance of this needs to be assessed in each case.

Chlorpropamide: In the presence of allopurinol, 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 allopurinol and the coumarins seen under experimental conditions has any clinical significance. However, all patients receiving anticoagulants must be carefully monitored.

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Massive absorption of ZYLOPRIM 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 medicines must be recognised. Adequate hydration to maintain maximum diuresis facilitates excretion of allopurinol and its metabolites. Haemodialysis may be resorted to if considered necessary.

IDENTIFICATION:

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

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

PRESENTATION:

ZYLOPRIM: 30, 150 or 300 tablets are packed in a clear polyvinyl chloride or polyvinyl chloride/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

ZYLOPRIM 300: 28 or 30 tablets are packed in a clear polyvinyl chloride or polyvinyl chloride/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:

ZYLOPRIM: C974 (Act 101/1965)

ZYLOPRIM 300: G/3.3/51

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive,

Woodmead, 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE:

Date of registration:

ZYLOPRIM: Old medicine

ZYLOPRIM 300: 25 September 1974

Date of most recent amendment to the professional information as approved by the authority: 30 November 1993

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