SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ADCO ALLOPURINOL 300 (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ADCO ALLOPURINOL 300 tablet contains 300 mg allopurinol.
Contains sugar: each tablet contains 180 mg lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
White, bisected, biconvex tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO ALLOPURINOL 300 is indicated 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.

ADCO ALLOPURINOL 300 is also used in the treatment of hyperuricaemia associated with leukaemia or resulting from radiotherapy or the use of anti-neoplastic agents such as mercaptopurine or during treatment with diuretics of the thiazide or similar type.

4.2 Posology and method of administration

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 ADCO ALLOPURINOL 300 may be taken once a day.
It is recommended that ADCO ALLOPURINOL 300 be taken after meals for better tolerance.
In severe conditions, doses of up to 600 mg may be necessary.

Paediatric population

For children the suggested initial dose is 8 mg per kg body mass daily.
Fluid intake should be sufficient to maintain daily urinary volume above 2 litres.

Renal impairment

Dosage must be reduced in patients with renal impairment in proportion to the reduction in glomerular filtration (see section 4.4).

Method of administration
For oral use.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
ADCO ALLOPURINOL 300 is contra-indicated in the following patients:

- Those who have exhibited serious adverse effects from the medication
- Pregnant mothers
- Lactating mothers, and
- Children, except those with malignancy.

ADCO ALLOPURINOL 300 should not be used in acute gout.

4.4 Special warnings and precautions for use
Reactions may include hypersensitivity responses of the skin and blood (see section 4.8).
ADCO ALLOPURINOL 300 should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions (including Stevens-Johnson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).
Acute gout may be precipitated. ADCO ALLOPURINOL 300 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 ADCO ALLOPURINOL 300, 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 a month.
If acute attacks develop in patients receiving ADCO ALLOPURINOL 300, treatment should continue at the same dosage while the acute attack is treated with a suitable anti-inflammatory medicine.

A possibility of xanthine stone formation exists in children with Lesch-Nyhan syndrome and can be minimised by alkalinisation of the urine and increasing daily fluid intake.
Angioedema has been reported to occur with and without signs and symptoms of a more generalized hypersensitivity reaction.
Fever has been reported to occur with and without signs and symptoms of a more generalized ADCO ALLOPURINOL 300 hypersensitivity reaction (see section 4.8).
Adequate therapy with ADCO ALLOPURINOL 300 will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

Hepatic and renal impairment
Reduced doses should be used in patients with hepatic or renal impairment. ADCO ALLOPURINOL 300 should be used with caution in patients with hypertension and cardiac insufficiency treated with diuretics and ACE inhibitors.
Hepatic dysfunction has been reported without overt evidence of more generalized hypersensitivity.
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.

Asymptomatic hyperuricaemia is generally not considered an indication for use of ADCO ALLOPURINOL 300. Fluid and dietary modification with management of the underlying cause may correct the condition.

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. ADCO ALLOPURINOL 300 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 ADCO ALLOPURINOL 300.

Nausea and vomiting can be avoided by taking ADCO ALLOPURINOL 300 after meals.

Contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction
The inactivation of mercaptopurine is inhibited by allopurinol and the dosage of mercaptopurine must be reduced when the medicines are given concomitantly.
Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with ADCO ALLOPURINOL 300, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.
Allopurinol should not be administered concomitantly with chlorpropamide since there may be competition in the renal tubule for the excretion of chlorpropamide. When renal function is poor this may lead to a prolonged chlorpropamide hypoglycaemic action.

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.
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 ADCO ALLOPURINOL 300, but the significance of this needs to be assessed in each individual case.
There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with ADCO ALLOPURINOL 300. Therefore, all patients receiving anticoagulants must be carefully monitored.

ADCO ALLOPURINOL 300 may inhibit hepatic oxidation of phenytoin, but the clinical significance has not been demonstrated.

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 ADCO ALLOPURINOL 300 therapy.

An increase in frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with ADCO ALLOPURINOL 300, 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 ADCO ALLOPURINOL 300, an alternative to ampicillin or amoxicillin is used where available.

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 ADCO ALLOPURINOL 300. However, in a well-controlled study of patients treated with cyclophosphamide, doxorubicin and/or bleomycin, allopurinol, as contained in ADCO ALLOPURINOL 300, did not appear to increase the toxic reaction of these cytotoxic medicines.

Plasma concentration of ciclosporin may be increased during concomitant treatment with ADCO ALLOPURINOL 300. Enhanced ciclosporin toxicity should be considered if these medicines are co-administered.
In healthy volunteers and HIV patients receiving didanosine, plasma didanosine Cmax and AUC values were approximately doubled with concomitant allopurinol, as contained in ADCO ALLOPURINOL 300, 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

ADCO ALLOPURINOL 300 is contraindicated in pregnancy (see section 4.3).

Breastfeeding

ADCO ALLOPURINOL 300 is contraindicated in lactation (see section 4.3).

Fertility

Not 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 ADCO ALLOPURINOL 300, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADCO ALLOPURINOL 300 does not adversely affect performance.

4.8 Undesirable effects

a) Summary of safety profile

Severe adverse reactions include skin eruptions, fever, chills, malaise, muscle ache, transient leukopenia or leukocytosis and eosinophilia; arthralgia, vasculitis, peripheral neuritis, bone-marrow depression and cataract.
If these reactions occur treatment should be discontinued.

Headache, drowsiness, alopecia, nausea, vomiting, abdominal pain, vertigo, diarrhoea and gastric irritation are noted but do not require that therapy be stopped.

b) Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTIONS
Infections and infestations	Less frequent	Furunculosis
Blood and lymphatic system disorders	Less frequent	Transient leukopenia or leukocytosis and eosinophilia. Bone-marrow depression. Haemolytic anaemia, agranulocytosis, aplastic anaemia, thrombocytopenia
Immune system disorders	Less frequent	Arthralgia, vasculitis, hypersensitivity reactions (including skin reactions associated with exfoliation, lymphadenopathy, eosinophilia, Stevens-Johnson syndrome and toxic epidermal necrolysis), angioimmunoblastic lymphadenopathy
Metabolism and nutrition disorders	Less frequent	Diabetes mellitus, hyperlipidaemia
Psychiatric disorders	Less frequent	Drowsiness, depression
Nervous system disorders	Less frequent	Peripheral neuritis, headache, seizures, paraesthesia, coma, paralysis, ataxia, somnolence
Eye disorders	Less frequent	Cataract, visual disturbances, macular changes
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Angina, bradycardia
Vascular disorders	Less frequent	Hypertension
Gastrointestinal disorders	Less frequent	Nausea, vomiting, abdominal pain, diarrhoea and gastric irritation,

		taste disturbances, recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit
Hepatobiliary disorders	Less frequent	Hepatic damage, hepatotoxicity, altered liver function, hepatitis (including hepatic necrosis and granulomatous hepatitis)
Skin and subcutaneous tissue disorders	Frequent	Skin eruptions (rash)
	Less frequent	Alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, skin eruptions, exfoliative rash, angioedema, discoloured hair
Musculoskeletal and connective tissue disorders	Less frequent	Muscle ache, arthralgia
Renal and urinary disorders	Less frequent	Renal damage, haematuria, uraemia
Reproductive system and breast disorders	Less frequent	Gynaecomastia, male infertility, erectile dysfunction
General disorders and administration site conditions	Less frequent	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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRAs website.

4.9 Overdose
Symptoms
The most likely reaction would be gastro-intestinal intolerance.
Ingestion of up to 22,5 g allopurinol, as contained in ADCO ALLOPURINOL 300, 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
Administer sufficient fluids to maintain maximum diuresis since this in turn facilitates excretion of allopurinol and its metabolites.
Treatment is symptomatic and supportive.
Recovery followed general supportive measures. Massive absorption of ADCO ALLOPURINOL 300 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. If considered necessary haemodialysis may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 3.3 Antigout preparation

Pharmacotherapeutic group: Antigout preparations inhibiting uric acid production ATC code: M04 AA01

Mechanism of action

Allopurinol inhibits xanthine oxidase, the enzyme responsible for the terminal steps in uric acid biosynthesis.

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).

5.3 Preclinical safety data

No information available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Croscarmellose sodium
Povidone K25

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months for the product packed in PVC/Aluminium foil blister and 48 months for the polypropylene securitainer and high density polyethylene containers.

6.4 Special precautions for storage

Store at or below 30 °C.
Protect from light and moisture.

6.5 Nature and contents of container

30 and 250 tablets packed in white polypropylene securitainers with LDPE (low density polyethylene) closures.
30 and 250 tablets packed in white HDPE (high density polyethylene) containers with HDPE closures.
30 and 1000 tablets packed in clear PVC film/ printed aluminium foil blister packs in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road
Erand Gardens Midrand, 1685.
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
29/3.3/0229

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25 October 1995

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