

## 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** 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** 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 may be taken once a day.

It is recommended that ADCO-ALLOPURINOL 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).

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### 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 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 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ADCO-ALLOPURINOL should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions (including Stevens-Johnson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 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, 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, 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 hypersensitivity reaction (see section 4.8)

Adequate therapy with ADCO-ALLOPURINOL 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 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.

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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. 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 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.

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

### **Contains sugar**

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, 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, but the significance of this needs to be assessed in each individual case.

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There have been reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with ADCO-ALLOPURINOL. Therefore, all patients receiving anticoagulants must be carefully monitored.

ADCO-ALLOPURINOL 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 therapy.

An increase in frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with ADCO-ALLOPURINOL, 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, 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. However, in a well-controlled study of patients treated with cyclophosphamide, doxorubicin and/or bleomycin, allopurinol, as contained in ADCO-ALLOPURINOL, did not appear to increase the toxic reaction of these cytotoxic medicines.

Plasma concentration of ciclosporin may be increased during concomitant treatment with PURICOS. Enhanced ciclosporin toxicity should be considered if these medicines are co-administered.

In healthy volunteers and HIV patients receiving didanosine, plasma didanosine C<sub>max</sub> and AUC values were approximately doubled with concomitant allopurinol, as contained in ADCO-ALLOPURINOL, 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 is contraindicated in pregnancy (see section 4.3).

#### Breast-feeding

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

#### Fertility

Not data available.

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### 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, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADCO-ALLOPURINOL 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

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<b>Eye disorders</b>	Less frequent	Cataract, visual disturbances, macular changes
<b>Ear and labyrinth disorders</b>	Less frequent	Vertigo
<b>Cardiac disorders</b>	Less frequent	Angina, bradycardia
<b>Vascular disorders</b>	Less frequent	Hypertension
<b>Gastrointestinal disorders</b>	Less frequent	Nausea, vomiting, abdominal pain, diarrhoea and gastric irritation, taste disturbances, recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit
<b>Hepatobiliary disorders</b>	Less frequent	Hepatic damage, hepatotoxicity, altered liver function, hepatitis (including hepatic necrosis and granulomatous hepatitis)
<b>Skin and subcutaneous tissue disorders</b>	Frequent	skin eruptions (Rash)
	Less frequent	Alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, skin eruptions, exfoliative rash, angioedema, discoloured hair
<b>Musculoskeletal and connective tissue disorders</b>	Less frequent	Muscle ache, arthralgia
<b>Renal and urinary disorders</b>	Less frequent	Renal damage, Haematuria, uraemia
<b>Reproductive system and breast disorders</b>	Less frequent	Gynaecomastia, male infertility, erectile dysfunction
<b>General disorders and administration site conditions</b>	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 asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

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### 4.9 Overdose

#### Symptoms

The most likely reaction would be gastro-intestinal intolerance.

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

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 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 CLASSIFICATION:

### 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.

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### 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

Magnesium stearate

Maize starch

Polysorbate 80

Sodium starch glycollate

Talc

Croscarmellose sodium

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Lactose  
Maize starch  
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

#### **ADCO-ALLOPURINOL 300:**

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.

### 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 NUMBERS

**Adco-Allopurinol 300:** 29/3.3/0229

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 March 1993

## 10. DATE OF REVISION OF THE TEXT

22 February 2024