PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

ALLOPURINOL 100 UNICORN (100 mg allopurinol) tablets

ALLOPURINOL 300 UNICORN (300 mg allopurinol) tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

ALLOPURINOL 100 UNICORN: each tablet contains 100 mg allopurinol.

ALLOPURINOL 300 UNICORN: each tablet contains 300 mg allopurinol.

ALLOPURINOL UNICORN contains sugar (lactose monohydrate 50,70 mg per 100 mg tablet and 149,60 mg per 300 mg tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

ALLOPURINOL 100 UNICORN: white to off-white, approximately 7,5 mm round, biconvex, uncoated tablets with ‘AL’ & ‘100” separated by breakline on one side & plain on other side. The tablet can be divided into equal doses.

ALLOPURINOL 300 UNICORN: Peach coloured, approximately 11 mm round, biconvex, uncoated tablets with ‘AL’ & ‘300’ separated by breakline on one side and plain on other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ALLOPURINOL UNICORN 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.
- treatment of hyperuricaemia associated with leukaemia or resulting from radiotherapy or the use of anti-neoplastic medicines such as mercaptopurine or during treatment with diuretics of the thiazide or similar type.

4.2 Posology and method of administration

Posology

Gout

An initial dose of 50 mg twice daily, increasing the dose as required up to 200 – 400 mg daily in divided doses. In severe conditions, a dosage of 600 mg may be required.

Hyperuricaemia associated with leukemia

The initial dose is 200 mg three times a day. Therapy should start 2 – 3 days before radiotherapy or at the initiating of anti-neoplastic therapy. The dose should be adjusted to a maintenance dose of usually 300 – 400 mg per day.

Paediatric population

The initial daily dose is 8 mg/kg body mass.

Impaired renal function:

Dosage must be reduced in proportion to the reduction in glomerular filtration.

Method of administration

Oral.

Fluid intake should be sufficient to maintain daily urinary volume above 2 litres.

4.3 Contraindications:

Hypersensitivity to allopurinol or to any of the ingredients in **ALLOPURINOL UNICORN** (see **section 6.1**).

Treatment for an acute attack of gout.

Children, except those with malignancy.

Lactating mothers (see **section 4.6**).

4.4 Special warnings and precautions for use

Hypersensitivity reactions, SJS ad TEN:

ALLOPURINOL UNICORN should be withdrawn immediately when a skin rash or other evidence of hypersensitivity occurs, as this could result in more serious hypersensitivity reactions (including maculopapular exanthema, hypersensitivity syndrome (also known as Drug rash with Eosinophilia and Systematic symptoms (DRESS)), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) (see **section 4.8**) Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

HLA-B*5801 allele:

The HLA-B*5801 allele increases the risk of developing allopurinol related hypersensitivity syndrome. The incidence of the HLA-B*5801 allele differs amongst ethnic populations:

Patients known to be carriers of HLA-B*5801 allele (e.g. Asian descendants)

should not be given **ALLOPURINOL UNICORN**. These patients should be closely monitored for the signs of hypersensitivity syndrome or SJS/TEN and advised to stop treatment immediately at the first appearance of symptoms.

Chronic renal impairment:

Extra monitoring is required for the signs of hypersensitivity syndrome or SJS/TEN in patients with chronic renal impairment. Patients should be informed of the need to stop treatment immediately and permanently at first appearance of symptoms.

Extra vigilance should be taken for patients with chronic renal impairment concomitantly using diuretics (such as thiazides) or ACE inhibitors with **ALLOPURINOL UNICORN** (see **section 4.8**), as this may increase the risk of developing hypersensitivity reactions including SJS/TEN associated with allopurinol.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of life-threatening cutaneous reactions SJS or TEN is within first weeks of treatment, which will require the treatment of allopurinol to be discontinued. Drug rash with Eosinophilia and Systematic symptoms (DRESS) (characterised by fever, eosinophilia, atypical circulating lymphocites, lymphadenopathy and hepatitis) has also been reported with the use of allopurinol tablets. Early diagnosis and withdrawal is associated with a better prognosis.

Hepatic or renal impairment:

A reduction in dosage should be considered in patients with severe renal or hepatic disorders.

Thyroid disorders:

Increased TSH values (> 5,5 µIU/mL) were observed in patients on long-term treatment with allopurinol. Caution is advised for patients with alteration of thyroid function.

Asymptomatic hyperuricaemia:

ALLOPURINOL UNICORN should not be used in asymptomatic hyperuricaemia. To correct this condition, it is required to adjust the diet and fluid intake, together with management of the underlying cause.

Acute gouty attack:

ALLOPURINOL UNICORN should not be used for treatment of an acute attack of gout, as further attacks may rise. In the early stages of treatment with **ALLOPURINOL UNICORN**, an attack of gouty arthritis may be triggered. 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 **ALLOPURINOL UNICORN**, treatment should continue at the same dosage whilst the acute attack is being treated with a suitable anti-inflammatory medicine.

Xanthine deposition:

A possibility of xanthine stone formation exists in children with Lesch-Nyhan syndrome and can be minimised by adequate hydration alkalinisation of the urine and increasing daily fluid intake to achieve optimal urine dilution.

Impaction of uric acid renal stones:

Adequate therapy with **ALLOPURINOL UNICORN** will lead to dissolution of large uric renal pelvic stones, with remote possibility of impaction in the ureter.

Information of excipients of ALLOPURINOL UNICORN*:*

ALLOPURINOL UNICORN contains lactose. Patients with rare hereditary conditions of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take **ALLOPURINOL UNICORN.**

ALLOPURINOL UNICORN contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

- *6-mercaptopurine and azathioprine:*

  The metabolism of 6-mercaptopurine and azathioprine is inhibited by allopurinol. Concomitant use with **ALLOPURINOL UNICORN** prolongs these medicines activity. Thus to avoid potential life-threatening toxicity, the doses should be markedly reduced to one quarter of usual dose when either of the medicines are given with **ALLOPURINOL UNICORN**.

- *Ciclosporin:*

  ALLOPURINOL UNICORN may cause an increase in plasma concentrations of ciclosporin enhancing ciclosporin toxicity. Caution is advised when considering concomitant administration of these two medicines.

- *Vidarabine (Adenine arabinoside):*

  Caution is required when using **ALLOPURINOL UNICORN** with vidarabine as the concomitant use may enhance toxic effects, due to an increased half-life of vidarabine. There is no unequivocal evidence that **ALLOPURINOL UNICORN** potentiates the activity of other cytotoxic medicines.

- *Didanosine:*

  Concurrent use of **ALLOPURINOL UNICORN** with HIV medicine didanosine is not recommended as allopurinol approximately doubles the plasma didanosine

Cmax and AUC values. If concomitant use cannot be avoided, a dose reduction of didanosine with close monitoring of patients is required.

- *Antigout medicines:*

  Oxipurinol, the therapeutically active metabolite of allopurinol, is excreted by kidneys in a similar way as urate. Medicines with uricosuric activity such as probenecid, benzbromarone or large doses of salicylate may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of **ALLOPURINOL UNICORN**, but the significance needs to be assessed in each case.

- *Anticoagulants:*

  Cautioned should be borne in mind when concomitantly using oral anticoagulants such as warfarin with **ALLOPURINOL UNICORN**

- *Chlorpropamide:*

  ALLOPURINOL UNICORN should not be given concomitantly with chlorpropamide since there may be competition in the renal tubule for the excretion of chlorpropamide. When renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity due to chlorpropamide.

- *Diuretics*

  Concomitant use of **ALLOPURINOL UNICORN** with diuretics such as thiazides, especially in renal impairment increases the risk of hypersensitivity reactions. An interaction between **ALLOPURINOL UNICORN** and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported.

- *Angiotensin-converting-enzyme (ACE) inhibitors*:

  Concomitant use of **ALLOPURINOL UNICORN** with ACE inhibitors may lead to an increase risk of haematological reactions such as leucopenia, especially if there is pre-existing renal failure.

- *Antacids:*

  Concurrent use of **ALLOPURINOL UNICORN** and aluminium hydroxide containing medicines may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

- *Phenytoin:*

  ALLOPURINOL UNICORN may inhibit hepatic oxidation of phenytoin.

- *Xanthines:*

  Theophylline levels should be monitored in patients starting or increasing **ALLOPURINOL UNICORN** therapy, as allopurinol may reduce the clearance of theophylline through the biotransformation process due to the inhibition of xanthine oxidase. Dosage should be reduced to avoid toxicity.

- *Antibacterials:*

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

- *Cytostatic medicines:*

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. Blood count monitoring should be performed at regular intervals as concurrent administration of **ALLOPURINOL UNICORN** and cytotoxic medicines (e.g cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), may cause blood dyscrasias to occur more frequently compared to when these medicines are administered alone.

- *Aspirin and salicylates:*

  Aspirin and salicylates increase uric acid concentrations thus can decrease efficacy of **ALLOPURINOL UNICORN**. Concomitant use with **ALLOPURINOL UNICORN** should be avoided in hyperuricaemia and gout therapy.

4.6 Fertility, pregnancy and lactation

Caution is advised with the use of **ALLOPURINOL UNICORN** during pregnancy. Allopurinol and its metabolite oxipurinol are detected in breast milk. Therefore administration of **ALLOPURINOL UNICORN** during lactation is contraindicated (see **section 4.3**).

4.7 Effects on ability to drive and use machines

ALLOPURINOL UNICORN can cause side effects such as somnolence, vertigo or ataxia; which will impair the patient's ability to drive and operate machinery. Caution should be advised if/when performing these tasks.

4.8 Undesirable effects

Infections and infestations

Less frequent Furunculosis

Blood and lymphatic system disorders

Less frequent Agranulocytosis, aplastic anaemia, thrombocytopenia*

Frequency unknown Eosinophilia, haemolytic anaemia, leucopenia

**Thrombocytopenia, agranulocytosis and aplastic anaemia have been very rarely reported, especially in subjects with impaired renal and/or hepatic function, emphasising the requirement for care in this group of subjects.*

Immune system disorders

Less frequent Anaphylaxis, angioedema, angioimmunoblastic T-cell lymphoma*, hypersensitivity reactions**

Frequency unknown arthralgia

Angioimmunoblastic T-cell lymphoma has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdra*wal of ***ALLOPURINOL UNICORN*.

***A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia hepatosplenomegaly, abnormal liver function tests, and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, it may be at any time during treatment, **ALLOPURINOL UNICORN** should be withdrawn immediately and permanently.*

Re-challenge should not be undertaken in subjects with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be helpful in treating hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal

and/or hepatic disorder has usually been present especially when the outcome has been fatal.

Metabolism and nutrition disorders

Less frequent Diabetes mellitus, hyperlipidaemia

Frequency unknown Exacerbation of gouty attacks

Psychiatric disorders

Less frequent Depression

Nervous system disorders

Less frequent Ataxia, coma, headache, neuropathy including peripheral nephritis, paraesthesia, paralysis, somnolence, taste perversion

Frequency unknown Dizziness, drowsiness

Eye disorders

Less frequent Cataract, macular changes, visual disorders

Ear and labyrinth disorders

Less frequent Vertigo

Cardiac disorders

Less frequent Angina pectoris, bradycardia

Vascular disorders

Less frequent Hypertension

Frequency unknown Vasculitis

Gastrointestinal disorders

Less frequent Changed bowel habits, haematemesis, steatorrhoea, stomatitis, nausea, vomiting

Frequency unknown Abdominal pain, diarrhoea, gastric irritation

Hepatobiliary disorders

Less frequent Asymptomatic increase in liver functions, hepatitis (including hepatic necrosis and granulomatous hepatitis)

Skin and subcutaneous tissue disorders

Frequent rash

Less frequent Alopecia, discoloured hair, fixed-drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Frequency unknown skin reaction associated with eosinophilia, exfoliative rash

Renal and urinary disorders

Less frequent Azotaemia, haematuria, uraemia

Frequency unknown Nephrolithiasis

Reproductive system and breast disorders

Less frequent Gynaecomastia, impotence, infertility (male), erectile dysfunction

Frequency unknown Nocturnal emissions

General disorders and administrative site conditions

Less frequent Asthenia, general malaise, oedema, pyrexia

Investigations

Frequent Blood thyroid stimulating hormone increased

4.9 Overdose

Massive absorption of **ALLOPURINOL UNICORN** may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless medicines such as adenine arabinoside, azathioprine or 6-mercaptopurine is being take concurrently. In this case, the risk of increased activity of these medicines must be recognised.

Symptoms of overdose:

Abdominal pain, diarrhoea, dizziness, headache, nausea, vomiting and somnolence. Rarely there may be hepatitis and renal insufficiency.

Treatment of overdose:

Treatment is symptomatic and supportive.

Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/ kg for children) if the patients presents within 1 hour of ingestion of more than 50 mg/kg. If more than 50 mg/kg has been ingested check urea and electrolytes (U&Es) or liver function test (LFTs).

Adequate hydration to maintain adequate diuresis facilitates excretion of active allopurinol and its metabolites. Other measures as indicated by patient's clinical condition.

Haemodialysis is unlikely to be required. Haemodialysis may be considered in patients with severe renal or hepatic impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Pharmacological Class: A 3.3 Antigout preparations

Allopurinol is a xanthine-oxidase inhibitor, the enzyme responsible for the terminal steps in uric acid production. Allopurinol and its main metabolite oxipurinol lower the level of uric acid in plasma and urine by inhibiting xanthine oxidase, the enzyme responsible for 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 absorbed from the upper gastrointestinal (GI) tract. Allopurinol is detected in the blood 30 – 60 minutes following oral administration. It is converted in the body to its metabolite oxipurinol (alloxanthine) Peak plasma levels of allopurinol generally occur approximately 1,5 hours following oral administration of allopurinol tablets, but fall and are barely detectable after 6 hours. Peak plasma levels of oxipurinol generally occur after 3 to 5 hours following oral administration, and are much more sustained.

Distribution:

Allopurinol and oxipurinol are not bound to plasma proteins therefore variations in protein binding are not thought to significantly alter clearance.

Metabolism:

Biotransformation:

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

Elimination:

The 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, with approximately 20 % excreted in the faeces.

Both allopurinol and oxipurinol are excreted mainly in the urine. The half-life of oxipurinol (a less potent inhibitor of xanthine oxidase than allopurinol) is 18 – 30 hours. Therefore effective inhibition of xanthine oxidase is maintained over 24 hour period with single daily dose of allopurinol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. These patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5 – 10 mg/litre. Allopurinol and oxipurinol are not bound to serum proteins has a long elimination half-life because it undergoes tubular reabsorption.

Patients with 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 – 20 ml/min, demonstrated 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 normal renal function. A reduction in the dose of allopurinol is therefore required in patients with renal impairment.

Elderly patients:

The pharmacokinetics of allopurinol are not likely to be altered other than due to deterioration in renal functions (see "**section 5.2**: *Patients with real impairment*").

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Maize starch, povidone, sodium starch glycollate, stearic acid, sunset yellow

Contains sugar: lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Do not remove from the outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

ALLOPURINOL UNICORN tablets are packed in clear PVDC coated

PVC/Aluminium blister strips of 10 tablets, 3 blister strips are further packed in an outer carton. Pack size: 30s.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town, 8001

South Africa

8 REGISTRATION NUMBER(S)

ALLOPURINOL 100 UNICORN: 54/3.3/0583

ALLOPURINOL 300 UNICORN: 54/3.3/0584

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 10 August 2022

10 DATE OF REVISION OF THE TEXT

27 August 2024