Clean Amended Professional Information for Medicines for Human Use:

URIPOLT 100 & 300 mg Tablets

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

URIPOLT 100 mg tablets

URIPOLT 300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

URIPOLT 100 contains 100 mg of allopurinol.

Contains sugar (lactose monohydrate): 37,26 mg per tablet.

URIPOLT E 300 contains 300 mg of allopurinol.

Contains sugar (lactose monohydrate): 111,80 mg per tablet.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets.

URIPOLT 100 tablets are white to off white, scored, flat cylindrical tablets debossed with ‘I’ and ‘56’ on either side of the break line on one side and plain on the other side.

URIPOLT 300 tablets are white to off white, scored, flat cylindrical tablets debossed with ‘I’ and ‘57’ on either side of the break line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

URIPOLT 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.

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. Up to and including 300 mg URIPOLT may be taken once a day. Larger doses should be administered as divided doses of not more than 300 mg. It is recommended that URIPOLT 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 body mass/day.

Special populations

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 allopurinol 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 URIPOLT immediately after each dialysis.

Paediatric population

Children under 15 years:

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to allopurinol or to any of the other excipients of URIPOLT (see section 6.1).
- Severe hepatic or renal disorder.
- An acute gout attack.

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN. These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. 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 has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20 % in Han Chinese population, 8-15 % in the Thai, about 12 % in the Korean population and 1-2 % in individuals of Japanese or European origin. Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the risk in these patients additionally. In case that no HLA-B*5801 genotyping is available for patients with Han Chinese, Thai or Korean descent the benefits should be thoroughly assessed and considered to outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations. If the patient is a known carrier of HLA-B*5801 (especially in those who are from Han Chinese, Thai or Korean descent), allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

Treatment of neoplasia

Before instituting cytotoxic therapy, it is advisable to assess existing serum urate and urinary acid levels. Hyperuricaemia and/or hyperuricosuria should be corrected prior to starting treatment. Adequate hydration to maintain maximum diuresis throughout is important. Renal disorder (see section 4.2).

Hepatic and renal impairment

Reduced doses should be used in patients with hepatic or renal impairment. URIPOLT should be used with caution in patients with hypertension and cardiac insufficiency treated with diuretics and ACE inhibitors.

Patients with chronic renal impairment and concomitant diuretic use in particular thiazides may be at risk of developing hypersensitivity reactions. including SJS/TEN associated with allopurinol. Extra vigilance for the signs of hypersensitivity syndrome or SJS/TEN is required, and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms (see section 4.8).

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, reinforcing the need for particular care in this group of patients.

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. URIPOLT 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 URIPOLT.

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

Asymptomatic hyperuricaemia

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

Acute gouty attacks

URIPOLT 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 URIPOLT, as with uricosuric medicines, an acute attack of gouty arthritis may be precipitated. Therefore, it is advisable to give prophylaxis with a suitable anti-inflammatory medicine or colchicine for at least one month. The literature should be consulted for details of appropriate dosage, precautions and warnings. If acute attacks develop in patients receiving allopurinol, 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 could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Impaction of uric acid renal stones

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

Thyroid disorders

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

Lactose

URIPOLT contains lactose. Patients with the rare hereditary conditions of galactose intolerance total lactase deficiency or, glucose-galactose malabsorption should not take URIPOLT. Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

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 medicines is given by mouth concomitantly with URIPOLT, only one-quarter of the usual dosage of these medicines 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 therapeutic activity of URIPOLT, 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 URIPOLT 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.

Vidarabine (Adenine arabinoside)

Evidence suggests that the plasma half-life of adenine arabinoside is increased in the presence of allopurinol. 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 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 allopurinol therapy.

Ampicillin/Amoxicillin

An increase in 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 an alternative to ampicillin or amoxicillin is used where available.

Cytostatics

With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone.

Blood count monitoring should therefore be performed at regular intervals.

Ciclosporin

The plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. 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 allopurinol treatment (300 mg daily) without affecting terminal half-life. Co-administration of these 2 medicines is generally not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.

Diuretics

An interaction between allopurinol and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported.

An increased risk of hypersensitivity has been reported when allopurinol is given with diuretics, in particular thiazides, especially in renal impairment.

Angiotensin-converting-enzyme (ACE) inhibitors

An increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors especially in renal impairment.

Aluminium hydroxide

If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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

Fertility

URIPOLT can cause infertility in male patients.

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

4.8 Undesirable effects

a. Summary of the safety profile

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, URIPOLT should be withdrawn IMMEDIATELY should such reactions occur.

b. Tabulated summary of adverse reactions

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Infections and infestations	Less frequent	Furuncle

Blood and lymphatic system disorders	Less frequent	Leucopenia, leucocytosis, eosinophilla, haemolytic anaemia, agranulocytosis, aplastic anaemia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction, angio-immunoblastic T-cell lymphoma, vasculitis, angio-immunoblastic lymphadenopathy
Metabolism and nutrition disorders	Less frequent	Diabetes mellitus, hyperlipidaemia
Psychiatric disorders	Less frequent	Depression, drowsiness
Nervous system disorders	Less frequent	Coma, paralysis, ataxia, peripheral neuropathy, paraesthesia, somnolence, headache, dysgeusia, paralysis
	Frequency unknown	Aseptic meningitis

Eye disorders	Less frequent	Cataract, visual impairment, maculopathy
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Angina pectoris, bradycardia
Vascular disorders	Less frequent	Hypertension
Gastrointestinal disorders	Less frequent	Vomiting, nausea, haematemesis, steatorrhoea, stomatitis, change of bowel habit, taste perversion
Hepato-biliary disorders	Less frequent	Abnormal liver function test, hepatitis (including hepatic necrosis and granulomatous hepatitis), hepatotoxicity, hepatic damage
Skin and subcutaneous tissue disorders	Frequent	Rash

	Less frequent	Angioedema, drug eruption, Stevens-Johnson syndrome/toxic epidermal necrolysis, alopecia, hair colour changes
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia
Renal and urinary disorders	Less frequent	Uraemia, interstitial nephritis, azotaemia, haematuria, renal damage
Reproductive system and breast disorders	Less frequent	Infertility male, erectile dysfunction, gynaecomastia, impotence
	Frequency unknown	Nocturnal emission
General disorders and administration site conditions	Less frequent	Oedema, malaise, asthenia, pyrexia, chills

Investigations	Frequent	Increased blood thyroid stimulating hormone

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Massive absorption of URIPOLT 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A3.3 Antigout preparations

Pharmacotherapeutic group: Preparations inhibiting uric acid production.

ATC code: M04AA01.

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.

5.2 Pharmacokinetic properties

Absorption

Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Allopurinol has been detected in the blood 30-60 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 URIPOLT but fall rapidly and are barely detectable after 6 hours. Peak plasma levels of oxipurinol generally occur after 3-5 hours after oral administration of URIPOLT 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. 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.

Biotransformation

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

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 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 URIPOLT. 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 5-10 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.

Pharmacokinetics in patients with renal impairment

Allopurinol and oxipurinol clearance are 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 URIPOLT is therefore required in patients with renal impairment.

Pharmacokinetics in elderly patients

The kinetics of the medicine are not likely to be altered other than due to deterioration in renal function (see section 5.2 Pharmacokinetics in patients with renal impairment).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch

Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package to protect from moisture and light.

6.5 Nature and contents of container

URIPOLT 100 and URIPOLT 300 are packed in clear PVC/Aluminium blister strips. The blisters are packed in cartons which are finally packed inside shippers.

Pack size: Blister strips are packed in 2 x 14’s or 4 x 14’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ascendis Pharma (Pty) Ltd

31 Georgian Crescent East

Bryanston

2191

South Africa

8. REGISTRATION NUMBER

URIPOLT 100 – 56/3.3/0893

URIPOLT 300 – 56/3.3/0894

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 September 2024

10. DATE OF REVISION OF THE TEXT