

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

COSURIC/Allopurinol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg Allopurinol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White round tablet engraved 'COSURIC 100'

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cosuric is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy). The main clinical conditions where urate/uric acid deposition may occur are: idiopathic gout; uric acid lithiasis; acute uric acid nephropathy; neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously, or after cytotoxic therapy; certain enzyme disorders which lead to overproduction of urate, for example: hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome; glucose-6-phosphatase including glycogen storage disease; phosphoribosyl-pyrophosphate synthetase, phosphoribosylpyrophosphate amidotransferase; adenine phosphoribosyltransferase.

Cosuric is indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase.

Cosuric is indicated for the management of 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

Allopurinol should be introduced at low dosage, e.g. 100 mg/day, to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor.

Adults

Cosuric should be introduced at low dosage e.g. 100 mg daily to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor (see 'Patients with renal impairment'). The following dosage schedules are suggested;

- in mild conditions; 100-200 mg daily
- in moderately severe conditions; 300-600 mg daily
- in severe conditions; 700-900 mg daily

If dosage on a mg/kg bodyweight basis is required, 2 to 10 mg/kg bodyweight/day should be used.

Paediatric population

Children under 15 years: The daily dose is 10-20 mg per kilogram bodyweight. The maximum dose is 400 mg daily.

Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Older people

The dose should be maintained at the lowest necessary to maintain satisfactory serum and urinary urate levels. Particular attention should be paid to advice in 'Patients with renal impairment' and section 4.4.

Commencing therapy: When commencing treatment with COSURIC, as with all uricosuric agents, an acute attack of gout may be precipitated. It is recommended that a prophylactic dose of an anti-inflammatory agent or colchicine is given for at least one month after hyperuricaemia is corrected. Aspirin and salicylates are not recommended for prophylactic use.

Use with uricosurics: COSURIC may be given concurrently with uricosuric agents. However, when changing to COSURIC from uricosuric therapy it is advisable to overlap treatment for one to three weeks thus ensuring a continuous hypouricaemic effect.

In neoplastic conditions to avoid acute uric acid nephropathy COSURIC should precede any treatment with cytotoxic drugs.

Patients with renal impairment

Since allopurinol and its metabolites are excreted via the kidney, impaired renal function may lead to retention of the drug and/or its metabolites will occur with consequent prolongation of plasma half-lives. Prolongation of action of COSURIC

may require reduction as indicated by regular monitoring of serum uric acid levels. For guidance, the following scheme provided relates to adults:

- if renal creatinine is greater than 20 ml/per minute use a standard dose.
- in severe renal insufficiency, when creatinine clearance is less than 10 ml/per minute use less than 100 mg daily or to use single doses of 100 mg at regular intervals longer than one day.

If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2 mg/litre).

In renal dialysis: Renal dialysis removes allopurinol and its metabolites. When dialysis is required two to three times a week then consideration should be given to an alternative dosage schedule of 300 mg – 400 mg COSURIC immediately after each dialysis without any dosage in between.

Patients with hepatic impairment

Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Treatment of high urate turnover conditions, e.g. neoplasia, Lesch-Nyhan syndrome

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with Cosuric before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinisation of urine to increase solubility of urinary urate/uric acid.

Dosage of Cosuric should be at the lower end of the recommended dosage schedule.

If urate nephropathy or other pathology has compromised renal function, the advice given in 'Patients with renal impairment' should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also section 4.5 and section 4.8.

Monitoring Advice

The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Method of administration:

Cosuric may be taken orally once a day after a meal. It is well tolerated, especially after food. Should the daily dosage exceed 300 mg and gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

4.3 Contraindications

This product is contra-indicated as a treatment for the acute phase of gout. Prophylactic therapy may be instituted when the acute gouty attack has completely subsided provided also that anti-inflammatory agents are also taken.

Cosuric should not be administered to individuals known to be hypersensitive to allopurinol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided as there have been reports of fatal cases (see section 4.5).

Hypersensitivity syndrome, SJS and TEN

Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS, Drug Rash with Eosinophilia and Systemic Symptoms) and SJS/TEN (Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis). 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 and permanently.

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 (and possibly other serious hypersensitivity reactions) in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Thai, Korean, Japanese and European descent. 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*58:01 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 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 of use are thought to exceed the potential associated risks. Patients who are found to be negative for HLA-B*58:01 still have a low risk of SJS/TEN irrespective of their ethnic origin. 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, (see section 4.8).

Chronic renal impairment

Patients with chronic renal impairment and concomitant diuretic use, in particular thiazides, may be at increased 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 or renal impairment

Reduced doses should be used in patients with hepatic or renal impairment (see Section 4.2). Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia

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

Acute gouty attacks

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 Cosuric, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine for at least one month. The literature should be consulted for details of appropriate dosage and 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 agent.

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 Cosuric 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 μ IU/mL) were observed in patients on long-term treatment with allopurinol (5.8%) in a long term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

4.5 Interaction with other medicinal products and other forms of interaction

6-mercaptopurine and azathioprine

Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with Cosuric, a xanthine oxidase inhibitor, inhibition of xanthine oxidase will prolong their activity. Serum concentrations of 6-mercaptopurine or azathioprine may reach toxic levels with consequent life-threatening pancytopenia and myelosuppression when these medicinal products are given concurrently with allopurinol. Therefore, concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided. If it is determined that co-administration with 6-mercaptopurine or azathioprine is clinically needed, dosing should be reduced to one quarter (25%) of the usual dose of 6-mercaptopurine or azathioprine and frequent haematologic monitoring should be ensured (see section 4.4).

Patients should be advised to report any signs or symptoms of bone marrow suppression (unexplained bruising or bleeding, sore throat, fever).

Vidarabine (Adenine Arabinoside)

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

Salicylates and uricosuric agents

Oxipurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of Cosuric, but the significance needs to be assessed in each case.

Chlorpropamide

If Cosuric is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity because allopurinol and chlorpropamide may compete for excretion in the renal tubule.

Coumarin anticoagulants

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

Phenytoin

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

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 drugs. 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.

Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechloroethamine

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (other than leukaemia), in the presence of allopurinol. 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

Reports suggest that the plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered if the drugs 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 drugs 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 Cosuric in human pregnancy, although it has been in wide use for many years without apparent ill

consequence. Use in pregnancy only when there is no safer alternative and when the disease itself carries risks for the mother or unborn child.

Breast-feeding

Reports indicate that allopurinol and oxipurinol are excreted in human breast milk. Concentrations of 1.4 mg/litre allopurinol and 53.7 mg/litre oxipurinol have been demonstrated in breast milk from a woman taking allopurinol 300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on the breastfed baby. Allopurinol during breastfeeding is not recommended.

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 affect ability to drive or operate machinery.

4.8 Undesirable effects

Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The frequency categories assigned to the adverse drug reactions below are estimates: for most reactions, suitable data for calculating incidence are not available. Adverse drug reactions identified through post-marketing surveillance were considered to be rare or very rare. The following convention has been used for the classification of frequency:

Very common $\geq 1/10$ ($\geq 10\%$)

Common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)

Uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)

Rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)

Very rare $< 1/10,000$ ($< 0.01\%$)

Not known: Cannot be estimated from available data

Adverse reactions in association with Cosuric are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder.

Infections and infestations

Very rare: Furuncle

Blood and lymphatic system disorders

Very rare: Agranulocytosis¹, Aplastic anaemia¹, Thrombocytopenia¹

Immune system disorders

Uncommon: Hypersensitivity²

Very rare: Angioimmunoblastic T-cell lymphoma³, Anaphylactic reaction

Metabolism and nutrition disorders

Very rare: Diabetes mellitus, Hyperlipidaemia

Psychiatric disorders

Very rare: Depression

Nervous system disorders

Very rare: Coma, Paralysis, Ataxia, Neuropathy peripheral, Paraesthesia, Somnolence, Headache, Dysgeusia

Not known: Aseptic meningitis

Eye disorders

Very rare: Cataract, Visual impairment,

Maculopathy Ear and labyrinth disorders

Very rare: Vertigo

Cardiac disorders

Very rare: Angina pectoris, Bradycardia

Vascular disorders

Very rare: Hypertension

Gastrointestinal disorders

Uncommon: Vomiting⁴, Nausea⁴, Diarrhoea

Very rare: Haematemesis, Steatorrhoea, Stomatitis, Change of bowel habit

Hepatobiliary disorders

Uncommon: Liver function test abnormal⁵

Rare: Hepatitis (including hepatic necrosis and granulomatous hepatitis)⁵

Skin and subcutaneous tissue disorders

Common Rash

Rare: Stevens-Johnson syndrome/toxic epidermal necrolysis⁶

Very rare: Angioedema⁷, Drug eruption, Alopecia, Hair colour changes

Not known: Lichenoid drug reaction

Renal and urinary disorders

Very rare: Haematuria, Azotaemia

Reproductive system and breast disorders

Very rare: Infertility male, Erectile dysfunction, Gynaecomastia

General disorders and administration site conditions

Very rare: Oedema, Malaise, Asthenia, Pyrexia⁸

Investigations

Common: Blood thyroid stimulating hormone increased⁹

- 1 Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.
- 2 A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia and/or eosinophilia (DRESS), and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), occur rarely (see Skin and subcutaneous tissue disorders). Associated vasculitis and tissue response may be manifested in various ways including hepatosplenomegaly, hepatitis, abnormal liver function tests, vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), renal impairment and, very rarely, seizures. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). Very rarely acute anaphylactic shock has been reported. If such reactions do occur, it may be at any time during treatment. Allopurinol should be withdrawn IMMEDIATELY AND PERMANENTLY. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. 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.
- 3 Angioimmunoblastic T-cell lymphoma has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of Cosuric
- 4 In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking Cosuric after meals.
- 5 Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.
- 6 Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). The highest risk for SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment. The best results in managing such reactions come from early diagnosis and immediate discontinuation of any suspect drug. Treatment should be withdrawn immediately should such reactions occur. After recovery from mild reactions, re-introduction of allopurinol, if desired, may be contemplated at an initially low dose (e.g. 50 mg/day) and gradually increased, only if a mild skin reaction has occurred. The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The use of genotyping as a screening tool to make decisions about treatment with

allopurinol has not been established. If the rash recurs the drug should be withdrawn permanently as more severe hypersensitivity may occur (see Immune system disorders). If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT re-introduce allopurinol due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.

- 7 Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.
- 8 Fever has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction (see section 4.8 Immune system disorders).
- 9 The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies did not report any impact on free T4 levels or had TSH levels indicative of subclinical hypothyroidism.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Ingestion of up to 22.5 g allopurinol 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. Recovery followed general supportive measures. Massive absorption of 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. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary haemodialysis may be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations inhibiting uric acid production, ATC code: M04AA01.

Allopurinol inhibits the action of xanthine oxidase. Allopurinol and its main metabolite oxipurinol reduce the concentration of uric acid in plasma and urine by inhibition of xanthine oxidase, the enzyme catalyzing 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 active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected allopurinol 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 Cosuric, 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 Cosuric 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 allopurinol 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 drug 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 18 to 30 hours in man. Therefore effective inhibition of xanthine oxidase is maintained over a 24 hour period with a single daily dose of Cosuric. 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 is re-absorbed by the kidney tubules. The slow renal clearance of oxypurinol suggests that part of the therapeutic activity of Allopurinol may be due to the maintenance of adequate blood concentrations of oxypurinol. 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 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 Cosuric is therefore required in patients with renal impairment.

Pharmacokinetics in elderly patients

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

5.3 Preclinical safety data

Mutagenicity

Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100 micrograms/ml and in vivo at doses up to 600 mg/day for a mean period of 40 months.

Allopurinol does not produce nitroso compounds in vitro or affect lymphocyte transformation in vitro.

Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

Carcinogenicity

No evidence of carcinogenicity has been found in mice and rats treated with allopurinol for up to 2 years.

Teratogenicity

One study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, however in a similar study in rats at 120 mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in mice up to 100 mg/kg/day, rats up to 200 mg/kg/day and rabbits up to 150 mg/kg/day during days 8 to 16 of gestation produced no teratogenic effects.

An in vitro study using foetal mouse salivary glands in culture to detect embryotoxicity indicated that allopurinol would not be expected to cause embryotoxicity without also causing maternal toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Polyethylene glycol 6000

Dextrose monohydrate

Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for containers, 24 months for blister packs.

6.4 Special precautions for storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

High density polystyrene containers with polythene lids and/or polypropylene containers with polythene lids and polyurethane or polythene inserts:

Pack sizes: 16, 21, 28, 30, 50, 56, 60, 84, 90, 112, 120, 140, 150, 168, 180, 250, 1000, 5000, 50000

PVC/Aluminium blister-packs:

Pack sizes: 16, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 140, 150, 168, 180

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited

11 Boumpoulinas Street,

3rd floor, 1060 Nicosia

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

20/10/1982 09/08/2001

10 DATE OF REVISION OF THE TEXT

08/05/2025