Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg Allopurinol.

Excipients with known effect:
Each 100 mg tablet contains 33 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off white, round, biconvex, uncoated tablet with inscription "AW" on one side and plain on the other side having approximate diameter of 8.0 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Allopurinol 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;
-Phosphoribosylpyrophosphate synthetase;
-Phosphoribosylpyrophosphate amidotransferase;
-Adenine phosphoribosyltransferase;

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

Allopurinol 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.

Children and adolescents
-Secondary hyperuricaemia of differing origin
-Uric acid nephropathy during treatment of leukaemia
-Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl transferase deficiency) and adenine phosophoribosyl transferase deficiency.

4.2 Posology and method of administration

Posology

Adults

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 (see section 4.2 *Renal impairment*). The following dosage schedules are suggested:

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

To reduce gastrointestinal undesirable effects, doses higher than 300 mg should be given in divided doses not exceeding 300 mg at any time. If dosage on a mg/kg bodyweight basis is required, 2 to 10 mg/kg bodyweight/day should be used.

Monitoring Advice

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

Special populations

Elderly

In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used. Particular attention should be paid to advice in "section 4.2 *Renal impairment*" and section 4.4.

Renal impairment

Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the allopurinol and/or its metabolites with consequent prolongation of plasma half-lives. The following schedule may serve as guidance for adults:

Creatinine clearance (normal value 60 to 120 ml/min)	Dosage at reduced renal function
>20 ml/min	normal dose
10 to 20 ml/min	100 to 200 mg per day
<10 ml/min	100 mg/day or longer dose intervals

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

Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two to three times a week consideration should be given to an alternative dosage schedule of 300-400 mg allopurinol immediately after each dialysis with none in the interim.

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

Dosage of allopurinol 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 section 4.2 *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.

Paediatric population

Children and adolescents under 15 years: 10 to 20 mg/kg bodyweight/day up to a maximum of 400 mg daily in three divided doses. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Method of administration

Allopurinol is for oral use.
The tablets are recommended to be taken orally after a meal to increase gastro-intestinal tolerability
Should the daily dosage exceed 300 mg divided dose regime may be appropriate (see posology).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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 Stevens - Johnson Syndrome (SJS) /toxic epidermal necrolysis (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. (See section 4.8 *Adverse Reactions – Immune system disorders and Skin and subcutaneous tissue disorders).*

*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 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.

Renal or hepatic impairment:

Reduced doses should be used in patients with hepatic or renal impairment. 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.

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with Allopurinol 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.

Chronic renal insufficiency and concomitant diuretic use, in particular thiazides, has been associated with an increased risk of allopurinol induced SJS/TEN, and other serious hypersensitivity reactions.

Asymptomatic hyperuricaemia:

Asymptomatic hyperuricaemia per se is generally not considered an indication for use of allopurinol. 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 allopurinol, 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 allopurinol 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 microIU/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.

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

Lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 allopurinol, a xanthine oxidase inhibitor, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because 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 medicinal products are used concomitantly extra vigilance is necessary, to recognise enhanced toxic effects.

Salicylates and uricosuric agents:

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

Chlorpropamide:

If allopurinol 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 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 medicinal products. 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.

Cyclosporin:

Reports suggest that the plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporin toxicity should be considered if the medicinal products are co-administered.

Didanosine:

In healthy volunteers and HIV patients receiving didanosine, plasma didanosine Cmax and AUC values were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting terminal half-life. Therefore, dose reductions of didanosine may be required when used concomitantly with allopurinol.

Diuretics:

An interaction between allopurinol and furosemide that results in increased serum urate and plasma oxipurinol 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 safety of allopurinol in human pregnancy, although it has been in wide use for many years without apparent ill consequence. Animal reproductive toxicity studies have shown teratogenic effect in a single study (see section 5.3).

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

Allopurinol and its metabolite oxipurinol is excreted in the 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 breast-fed baby. Allopurinol during breastfeeding is not recommended.

Fertility

There are insufficient clinical data on the effect of allopurinol on fertility.

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

For this medicinal product there is no modern clinical documentation which can be used as support for determining the frequency of 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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Adverse reactions in association with allopurinol 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.

Table 1 Tabulated summary of adverse reactions.

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Very rare	Furuncle
Blood and lymphatic system disorders	Very rare	Agranulocytosis[1]
		Granulocytosis
		Aplastic anaemia[1]
		Thrombocytopenia[1]
		Leukopenia
		Leukocytosis
		Eosinophilia
		Pure red cell aplasia
Immune system disorders	Uncommon	Hypersensitivity[2]
	Very rare	Angioimmunoblastic T-cell lymphoma[3]
		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	Vomiting[4]
		Nausea[4]
		Diarrhoea
	Very rare	Haematemesis
		Steatorrhoea
		Stomatitis
		Change of bowel habit
Hepatobiliary disorders	Uncommon	Liver function test abnormal[5]
	Rare	Hepatitis (including hepatic necrosis and granulomatous hepatitis)[5]
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Stevens-Johnson syndrome/toxic epidermal necrolysis[6]
	Very rare	Angioedema[7]
		Drug eruption
		Alopecia
		Hair colour changes
	Not known	Lichenoid drug reaction
Musculoskeletal and connective tissue disorders	Very rare	Muscle pain
Renal and urinary disorders	Rare	Urolithiasis
	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
		Pyrexia[8]
Investigations	Common	Blood thyroid stimulating hormone increased[9]

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) with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia hepato-splenomegaly, 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 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 generalized lymphadenopathy. It appears to be reversible on withdrawal of allopurinol.

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 allopurinol 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). Allopurinol should be withdrawn IMMEDIATELY should such reactions occur. 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. After recovery from mild reactions, allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. 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 reoccurs, allopurinol should be permanently withdrawn as more severe hypersensitivity reactions may occur (see section 4.8 *Immune system disorders*). If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, allopurinol should not be reintroduced due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN, or other serious hypersensitivity reactions remain the basis for decision making.

7. Angioedema has been reported to occur with and without signs and symptoms of a more generalised allopurinol hypersensitivity reaction.

8. Fever has been reported to occur with and without signs and symptoms of a more generalised allopurinol 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
HPRA Pharmacovigilance
Website: www.hpra.i

4.9 Overdose

Symptoms and Signs:

Ingestion of up to 22.5g allopurinol without adverse effect has been reported. Symptoms and signs including nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20g allopurinol. Recovery followed general supportive measures.

Management:

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: Antigout preparations; Preparations inhibiting uric acid production

ATC code: M04AA01

Mechanism of action

Allopurinol is a xanthine-oxidase inhibitor. Allopurinol and its main metabolite oxipurinol lower the level 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.

Pharmacodynamic effects

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 Allopurinol, but fall rapidly and are barely detectable after 6 hours. Peak plasma levels of oxipurinol generally occur 3-5 hours after oral administration of Allopurinol 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 allopurinol 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 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 5-10mg/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 is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal 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.

Pharmacokinetics in elderly patients

The kinetics of the allopurinol are not likely to be altered other than due to deterioration in renal function (see section 5.2 *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 microgram/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 100mg/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 the 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

Lactose monohydrate
Crospovidone Type B
Maize starch
Povidone K 30
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC-ALU blister containing 25, 28, 30, 50, 60, 90 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/219/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th July 2019
Date of Last Renewal: 20th March 2024

10 DATE OF REVISION OF THE TEXT

February 2025