

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Allopurinol Orion 300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg allopurinol.

Excipients with known effects:

Each tablet contains 145.9 mg lactose (as monohydrate).

Each tablet contains 2.6 mg Sunset Yellow FCF aluminium lake (azo colouring agent).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Peach colored, approximately 11 mm round, biconvex uncoated tablets with “AL” & “300” separated by breakline on one side & plain on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- all forms of hyperuricaemia not controllable by diet including secondary hyperuricaemia of differing origin and in clinical complications of hyperuricaemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones
- the management of recurrent mixed calcium oxalate stones in concurrent hyperuricaemia, when fluid, dietary and similar measures have failed.

4.2 Posology and method of administration

For oral use

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.

2–10 mg/kg bodyweight/day or 100–200 mg daily in mild conditions, 300–600 mg daily in moderately severe conditions, or 700–900 mg daily in severe conditions. 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 *Dosage recommendations in renal disorders*).

Paediatric population

The tablets contain Sunset Yellow FCF aluminium lake (azo colouring agent) and should not be given to children.

Elderly

No specific dosage recommendation, the lowest dosage which produces satisfactory urate reduction should be used. Refer to dosage advice in *Patients with renal impairment* (also see section 4.4).

Patients with renal impairment

Allopurinol and its metabolites are excreted by the kidney, therefore impairment of renal function may lead to retention of the drug and/or its metabolites. The plasma half-lives may as a consequence be prolonged. The following schedule may serve as guidance for dose adjustments at renal impairment:

<u>Creatinine clearance</u>	<u>Dosage</u>
> 20 mL/min	normal dose
10–20 mL/min	100–200 mg per day
< 10 mL/min	100 mg/day or longer dose intervals

Serious consideration should be given in the presence of impaired renal function, to initiating treatment with a maximum dose of 100 mg/day and increasing it only if the serum and/or urinary rate response is unsatisfactory. In severe renal insufficiency, it may be advisable to use less than 100 mg per day or to use single doses of 100 mg at longer intervals than one day.

If plasma oxipurinol concentration monitoring is available, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2 microgram/mL).

Dose recommendation in renal dialysis

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 Orion immediately after each dialysis with none in the interim.

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 Allopurinol Orion before commencing cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalisation of urine to increase solubility of urinary urate/uric acid. The dose of Allopurinol Orion should be in the lower range.

If urate nephropathy or other pathology has compromised renal function, advice provided 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 sections 4.5 and 4.8).

Monitoring advice

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

Method of administration

Allopurinol Orion tablets 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

Hypersensitivity 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).

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.

Hepatic and renal impairment

Reduced doses should be used in patients with hepatic or renal impairment. There is a risk for allopurinol accumulation in patients with 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.

Patients with chronic renal impairment may be at increased risk of developing hypersensitivity reactions including SJS/TEN associated with allopurinol and concomitant use of diuretics, especially thiazide diuretics. 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).

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.

In very rare cases thrombocytopenia, agranulocytosis and aplastic anaemia may appear, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients. In case of signs and symptoms of hematologic adverse effects, discontinuation of allopurinol should be considered.

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.

In the treatment of renal gout and uric acid stones, the volume of urine produced should be at least 2 litres per day and the urinary pH should be kept in the range of 6.4–6.8.

Hypersensitivity syndrome, SJS and TEN

Allopurinol should be withdrawn IMMEDIATELY when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions (see section 4.8 –Immune system disorders and Skin and subcutaneous tissue disorders). 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.

*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 HLAB*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.

Thyroid disorders

Increased TSH values (> 5.5 $\mu\text{IU/mL}$) 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.

Excipients

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

Sunset Yellow FCF aluminium lake (azo colouring agent) may cause allergic reactions.

This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially 'sodium-free'.

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, 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 recognize 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 allopurinol, but the significance needs to be assessed in each case.

Chlorpropamide: If Allopurinol Orion 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.

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: 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.

Angiotensin-converting-enzyme (ACE) inhibitors: An increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors especially in renal impairment. E.g. with concomitant administration of allopurinol and captopril, the risk of skin reactions can be raised, especially in cases of chronic renal failure.

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.

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 insufficient evidence of the safety of allopurinol in human pregnancy. Animal reproductive toxicity studies have shown conflicting results (see section 5.3).

Allopurinol should be used in pregnancy only where there is no safer alternative and when the disease itself carries risks for the mother or child.

Breast-feeding

Allopurinol and its metabolite oxipurinol is excreted in the human breast milk. Allopurinol during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

Since adverse reactions such as vertigo, somnolence 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 sure that allopurinol does not adversely affect performance.

4.8 Undesirable effects

For this 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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1\ 000$ to $< 1/100$)

Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$)

Very rare ($< 1/10\ 000$)

Not known (cannot be estimated from the available data)

The incidence of adverse reactions is higher in the presence of renal and/or hepatic disorder.

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations				Furunculosis	
Blood and lymphatic system disorders				Agranulocytosis ¹ , aplastic anaemia ¹ , thrombocytopenia ¹ , leukopenia, leukocytosis, eosinophilia and pure red cell aplasia	
Immune system disorders		Hypersensitivity reactions ²		Angioimmunoblastic lymphadenopathy, anaphylactic reaction	

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders				Diabetes mellitus, hyperlipidaemia	
Psychiatric disorders				Depression	
Nervous system disorders				Coma, paralysis, ataxia, neuropathy, paraesthesiae, somnolence, headache, taste perversion	Aseptic meningitis
Eye disorders				Cataract, visual disorder, macular changes	
Ear and labyrinth disorders				Vertigo	
Cardiac disorders				Angina, bradycardia	
Vascular disorders				Hypertension	
Gastrointestinal disorders		Vomiting, nausea ³ , diarrhoea		Recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit	
Hepatobiliary disorders		Asymptomatic increases in liver function tests	Hepatitis (including hepatic necrosis and granulomatous hepatitis) ⁴		
Skin and subcutaneous tissue disorders	Rash ⁵		Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) ⁶	Angioedema ⁷ , fixed drug eruption, alopecia, discoloured hair	Lichenoid drug reaction
Musculoskeletal and connective tissue disorders				Muscle pain	
Renal and urinary disorders			Urolithiasis	Haematuria, azotemia/uraemia	
Reproductive system and breast disorders				Male infertility, erectile dysfunction, gynaecomastia	
General disorders and administration site conditions				Oedema, general malaise, asthenia, fever ⁸	
Investigations	Blood thyroid				

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
	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. Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis occur rarely (see *Skin and subcutaneous tissue disorders*). Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment, acute cholangitis, xanthine stones and very rarely, seizures. Very rarely acute anaphylactic shock has been reported. If such reactions do occur, it may be at any time during treatment, Allopurinol Orion 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.

Angioimmunoblastic lymphadenopathy has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of allopurinol. A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, 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*.

When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

3. In early clinical studies, nausea and vomiting were reported. To increase gastrointestinal tolerability, Allopurinol Orion tablets should be taken after a meal.

4. Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.

5. 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. Allopurinol Orion should be withdrawn *immediately* should such reactions occur. After recovery from mild reactions, allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. If the rash recurs, allopurinol should be permanently withdrawn as more severe hypersensitivity may occur.

6. 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 generalized allopurinol hypersensitivity reaction (see *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 national reporting system** listed in [Appendix V](#).

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 Orion 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.

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. 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 levels of oxipurinol generally occur after 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-ribose and oxipurinol-7-ribose.

Elimination

Approximately 20% of the ingested allopurinol is excreted in the faeces in 48–72 hours. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol by xanthine oxidase and aldehyde oxidase, with less than 10% of the unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1 to 2 hours.

Oxipurinol is a less potent inhibitor of xanthine oxidase than allopurinol, but the plasma half-life of oxipurinol is far more prolonged. Estimates range from 13 to 30 hours in man. Therefore, effective inhibition of xanthine oxidase is maintained over a 24-hour period with a single daily dose of allopurinol. Patients with normal renal function will gradually accumulate oxipurinol until a steady-state plasma oxipurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5–10 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 is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20 mL/min, showed plasma oxipurinol concentrations of approximately 30 mg/litre after prolonged treatment with 300 mg allopurinol per day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function. A reduction in the dose of allopurinol is therefore required in patients with renal impairment.

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

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.

In animal experiments, long-term application of high doses of allopurinol resulted in formation of xanthin precipitates (urolithiasis), which led to morphological changes in uriniferous organs.

There are no additional non-clinical data considered relevant to clinical safety beyond those included in other sections of this SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Sodium starch glycolate
Colour Sunset Yellow FCF al. lake (E110)
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVDC/PVC/Aluminium blisters with 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

27-Feb-2025