Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol 300mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg Allopurinol.

Excipients with known effect - contains Lactose monohydrate 93.0mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, circular, biconvex, uncoated tablets impressed with the identifying letters 'AG' and 'C' on either side of a central scoreline imprinted on one face.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Allopurinol and its major metabolite, oxipurinol, act by inhibiting the enzyme xanthine oxidase, which catalyses the end stage of the metabolism of purines to uric acid. Allopurinol and its metabolites are excreted by the kidney but the renal handling is such that allopurinol has a plasma half-life of about 1 hour whereas that of oxipurinol exceeds 18 hours. Thus therapeutic effect may be achieved by once-a-day dosage.

1) *Prophylactic management of gout and other conditions of excess body urate:*
Allopurinol is used to reduce excessive urate levels (serum is theoretically saturated with urate at a concentration between 0.38-0.42mmol/l). The higher levels seen in practice may be accounted for by: a) the formation of saturated solutions; b) protein binding of urate. Excess body urate may be indicated by hyperuricaemia and/or hyperuricosuria. It may lead to disposition of urate in the tissues or it may be present with no obvious signs or symptoms.
The main clinical manifestations of urate disposition are gouty arthritis, skin tophi and/or renal involvement: Excess body urate is frequently of idiopathic origin but may also be found in association with the following other conditions: neoplastic disease and its treatment; certain enzyme disorders (especially Lesch-Nyhan syndrome); renal failure; renal calculus formation; diuretic therapy and psoriasis.

2) *Calcium renal lithiasis:*
Allopurinol is of benefit in the prophylaxis and treatment of calcium renal lithiasis in patients with raised serum or urinary uric acid.

4.2 Posology and method of administration

Posology
Initiation of therapy:
In the initial stages of treatment with allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. It is therefore advisable to give a suitable anti-inflammatory agent or colchicine for at least one month prophylactically.

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).

Adults:
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.

Dosage 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.

Paediatric population:
Use in children is mainly indicated for malignant conditions especially leukaemia, and certain enzyme disorders (*eg* Lesch-Nyhan syndrome) when the dosage is 10-20mg/kg bodyweight daily up to a maximum of 400 mg daily.

Use in the 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.

Use with uricosurics:
Oxipurinol, allopurinol's major metabolite which is itself therapeutically active, is excreted by the kidney in a similar way to urate. Drugs with uricosuric activity (*eg* probenecid or large doses of salicylate) may therefore accelerate the excretion of oxipurinol. This may decrease the therapeutic effect of allopurinol, however, the significance should be assessed on an individual basis.
In order to prevent acute uric acid nephropathy in neoplastic conditions, treatment with allopurinol should precede treatment with cytotoxic drugs.

Dose recommendations with impaired renal function:
Impairment of renal function may lead to retention of allopurinol and its metabolites (which are excreted via the kidney) with consequent prolongation of action. Serum uric acid levels should therefore be monitored and the dose adjusted accordingly. The following dose recommendation is for use in adults:

Creatinine clearance:	**Dosage:**
Over 20 ml/minute	Standard dose
10-20 ml/minute	100-200 mg daily
Under 10 ml/minute	100 mg daily or less frequently

Allopurinol and its metabolites are removed by renal dialysis. If frequent dialysis is required, an alternative schedule of 300-400mg after each dialysis, with none in the interim, should be considered.

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 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 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.

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

Method of administration
Allopurinol tablets are to be administered orally. It is well tolerated, especially after food. Should the daily dosage exceed 300mg and gastrointestinal intolerance be manifested, a divided dose regimen may be appropriate.

4.3 Contraindications

Hypersensitivity to the active substances or to excipients listed in section 6.1.

Treatment for an acute attack of gout; prophylactic therapy may be commenced when the acute attack has completely subsided, provided anti-inflammatory agents are also taken.

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, SJS and TEN
Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN. These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions (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.

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 µIU/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.

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

4.5 Interaction with other medicinal products and other forms of interactions

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, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.

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 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 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 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. 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 (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.

Breastfeeding
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.

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 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 <1/1000

Very Rare <1/10,000

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.

Frequency Organ Class	Very common (>1/10)	Common (>1/100 and <1/10)	Uncommon (>1/1.000 and <1/100)	Rare (>1/10.000 and <1/1.000)	Very rare (<1/10.000)	Not known (cannot be estimated from available data)
Infections and infestations					Furuncle	
Blood and lymphatic system disorders				Eosinophilia	Agranulocytosis[1], Aplastic anaemia[1], Thrombocytopenia[1] Haemolytic anaemia, Angioimmunoblastic lymphadenopathy.	
Immune system disorders			Hypersensitivity[2]		Angioimmunoblastic T-cell lymphoma[3], Anaphylactic reaction	
Metabolism and nutrition disorders					Diabetes mellitus, Hyperlipidaemia	
Psychiatric disorders					Depression	
Nervous system disorders					Coma, Paralysis, Ataxia, Somnolence, Headache, Parageusia, Paraesthesia, Neuropathy peripheral, Dysgeusia	Aseptic meningitis
Eye disorders					Cataract, Visual impairment, Maculopathy	
Ear and labyrinth disorders					Vertigo	
Cardiac disorder					Angina pectoris, Bradycardia	
Vascular disorders				Vasculitis	Hypertension	
Gastrointestinal disorders			Vomiting[4], Nausea[4], Diarrhoea, Abdominal pain		Haematemesis, Steatorrhoea, Stomatitis, Changed bowel habit	
Hepatobiliary disorders			Liver function test abnormal[5]	Hepatitis (including hepatic necrosis and granulomatous hepatitis)[5]		
Skin and subcutaneous disorders		Rash		Stevens-Johnson syndrome/toxic epidermal necrolysis[6] Erythema	Angioedema[7], Drug eruption, Alopecia, Hair colour changes Drug rash with eosinophilia and systemic	.

				multiforme,	symptoms (DRESS)	
Musculoskeletal and connective tissue disorders				Arthralgia Gout		
Renal and urinary disorders				Nephrolithiasis	Haematuria, Uraemia, Azotaemia	
Reproductive system and breast disorders					Infertility male, Erectile dysfunction, Gynaecomastia	
General disorders and administration site conditions					Oedema, Malaise, Asthenia, Fever, pyrexia[8]	
Investigations		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 generalised 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, DO NOT re-introduce allopurinol 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 authorization 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.ie

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: Preparations inhibiting uric acid production

ATC code: M04A A01

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 of 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 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-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 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 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 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 100µg/ml and in vivo at doses up to 600mg/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 120mg/kg on day 12 of gestation no abnormalities were observed. Extensive studies of high oral doses of allopurinol in mice up to 100mg/kg/day, rats up to 200mg/kg/day and rabbits up to 150mg/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

Croscarmellose sodium
Powdered Cellulose
Lactose monohydrate
Magnesium stearate
Maize starch

Sodium laurilsulfate
Pregelatinised maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.
Blisters: Store in the original package in order to protect from moisture.
PP or PE containers: Store in the original container in order to protect from moisture.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:
a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M^2 PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes:
PP container: 10's, 14's, 20's, 28's, 30's, 49's, 50's, 60's, 98's, 100's
Al/PVC/PVDC blister pack: 10's, 14's, 20's, 28's, 30's, 49's, 50's, 60's, 98's, 100's

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. 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

PA2315/056/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 March 1985

Date of last renewal: 06 March 2010

10 DATE OF REVISION OF THE TEXT

January 2022