# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

ZYLORIC 300mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Qualitative Declaration**

Allopurinol Ph. Eur.

**Quantitative Declaration**

Each ZYLORIC 300mg tablet contains 300mg

Allopurinol Excipients with known effect:

Contains 150mg Lactose Monohydrate *(Refer to Section 4.4 Special Warnings and Precautions for Use)*

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

Round, white to off white biconvex, bisected tablets, debossed with Z1 on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

ZYLORIC® 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.
- lacute 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

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

ZYLORIC® is indicated for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary and similar measures have failed**.**

## 4.2 Posology and Method of Administration

**Posology**

– **General**

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

– **Populations**

*Adults*

ZYLORIC® 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 Posology and method of administration – Renal impairment and Special warnings and precautions for use).

The following dosage schedules are suggested:

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

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

*Paediatric population (under 15 years)*

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

*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 Posology and method of administration – Renal impairment and Special warnings and precautions for use.

*Renal impairment*

Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the drug and/or its metabolites with consequent prolongation of plasma half-lives. 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 facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15,2 mg/litre). 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 mg to 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*

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with allopurinol before starting cytotoxic therapy. Adequate hydration is important to maintain optimum diuresis and alkalinisation of the urine is advisable to increase solubility of urinary urate/uric acid. Dosage of ZYLORIC® 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 Posology and method of administration – Renal impairment should be followed. These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation *(Refer to Sections 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction and 4.8 Undesirable Effects).*

**Method of Administration**

Oral Administration

The tablets are to be swallowed as is with a large glass of water, after meals. If the daily dose must be greater than 300 mg and in the event of manifest gastrointestinal intolerance, it may be appropriate to split the doses.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Pharmaceutical Particulars – List of excipients.

## 4.4 Special Warnings and Precautions for Use

**Special Warnings**

- Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This is due to the indigestion of lactose, leading to digestive symptoms like gas, bloating, diarrhea, and stomach cramps.

- 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.

- 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 greatly between ethnic groups: up to 20% in the Han Chinese ethnic group, about 12% in the Korean population and in 1 to 2% of individuals of Japanese or European. The use of genotyping as a diagnostic tool in making allopurinol treatment decisions has not been established. If the patient is found to carry the HLA-B*5801 allele, the use of allopurinol may be considered if the benefits are thought to outweigh the risks. Extra vigilance is required to detect any signs of hypersensitivity syndrome and SJS/TEN and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms.

- Hepatic and renal 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 ZYLORIC® 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 ZYLORIC®. Fluid and dietary modification with management of the underlying cause may correct the condition.

**Precautions for Use**

- Acute attacks of gout

ZYLORIC® 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 ZYLORIC®, 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 a few months. The literature should be consulted for details of appropriate dosage and precautions and warnings. If acute attacks develop in patients receiving ZYLORIC®, 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.

- Impact of uric acid renal stones

Adequate therapy with ZYLORIC® 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.

## 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

**Unadvisable Combinations**

- 6-mercaptopurine and Azathioprine:

Azathioprine is metabolized to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6mercaptopurine or azathioprine is given concurrently with

ZYLORIC®, 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 major metabolite of ZYLORIC® 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 therapeutic activity of ZYLORIC®, but the significance needs to be assessed in each case.

- Chlorpropamide

If ZYLORIC® is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemia 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 ZYLORIC®, therefore, all patients receiving anticoagulants must be carefully monitored.

- Phenytoin:

ZYLORIC® 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 ZYLORIC® therapy.

- Ampicillin/Amoxicillin

An increase in the frequency of skin rash has been reported among patients receiving Ampicillin or Amoxicillin concurrently with ZYLORIC® 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 ZYLORIC® an alternative to Ampicillin or Amoxicillin is used where available.

- Cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechloroethamine

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease (other than leukaemia) in the presence of allopurinol. However, in a well - controlled study of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechloroethamine (mustine hydrochloride) ZYLORIC® did not appear to increase the toxic reaction of these cytotoxic agents.

- Cyclosporin

Reports suggest that the plasma concentration of cyclosporin may be increased during concomitant treatment with ZYLORIC®.

The possibility of enhanced cyclosporine toxicity should be considered if the drugs 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 ZYLORIC® and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported.

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

## 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 (*Refer to Section 5.3 Preclinical Safety Data*).

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

**Breastfeeding**

Reports indicate that allopurinol and oxipurinol are excreted in human breast milk. Concentrations of 1.4 mg/litre allopurinol and 53,7 mg/litre oxipurinol have been demonstrated in breast milk from a woman taking allopurinol 300 mg/day.

However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed baby

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

**4.8 Undesirable Effects**

For this product there in 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 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 rare or very rare.

The following convention has been used for the classification of frequency:

Very common: ≥ 1/10

Common: ≥ 1/100 and < 1/10

Uncommon: ≥ 1/1000 and < 1/100

Uncommon: ≥ 1/10000 and < 1/1000

Very rare: < 1/10000

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.

**Tabulated summary of adverse reactions**

| System Organ Class | Frequency | Adverse reaction |
|---|---|---|
| **Infections and infestations** | Very rare | Furuncle |
| **Blood and lymphatic system disorders** | Very rare | Agranulocytosis[1]<br>Aplastic anaemia[1]<br>Thrombocytopenia[1] |
| **Immune system disorders** | Uncommon | Hypersensitivity[2] |
| | Very rare | Angioimmunoblastic T-cell lymphoma[2] |
| **Metabolism and nutrition disorders** | Very rare | Diabetes mellitus<br>Hyperlipidaemia |
| **Psychiatric disorders** | Very rare | Depression |
| **Nervous system disorders** | Very rare | Coma<br>Paralysis<br>Ataxia<br>Neuropathy peripheral<br>Paraesthesia<br>Somnolence<br>Headache<br>Dysgeusia |
| **Eye disorders** | Very rare | Cataract<br>Visual impairment<br>Maculopathy |
| **Ear and labyrinth disorders** | Very rare | Vertigo |
| **Cardiac disorders** | Very rare | Angina pectoris<br>Bradycardia |
| **Vascular disorders** | Very rare | Hypertension |
| **Gastrointestinal disorders** | Uncommon | Vomiting[4]<br>Nausea[4] |
| | Very rare | Haematemesis<br>Steatorrhoea<br>Stomatitis<br>Change of bowel |
| **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]<br>Drug eruption<br>Alopecia<br>Hair colour change |
| **Renal and urinary disorders** | Very rare | Haematuria<br>Azotaemia |
| **Reproductive system and breast disorders** | Very rare | Infertility male<br>Erectile dysfunction<br>Gynaecomastia |
| **General disorders and administration site conditions** | Very rare | Oedema<br>Malaise<br>Asthenia<br>Pyrexia[8] |

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, 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, ZYLORIC® 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 ZYLORIC®.
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 ZYLORIC® 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). ZYLORIC should be withdrawn IMMEDIATELY in any patient developing signs or symptoms of a SJS/TEN, or other serious hypersensitivity reactions. 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. If ZYLORIC® treatment has been discontinued due to mild skin reactions (i.e. not signs or symptoms of SJS/TEN, or other serious hypersensitivity reaction), ZYLORIC® may be reintroduced at a low dose (e.g. 50 mg/day) and then 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 ZYLORIC® has not been established. If the original symptoms recur allopurinol should be PERMANENTLY withdrawn as more severe hypersensitivity reactions may occur (*Refer to Section 4.8 Undesirable Effects - Immune system disorders*). If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT reintroduce ZYLORIC® 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 (*Refer to Section 4.8 Undesirable Effects - Immune system disorders*).

## 4.9 Overdose

### Signs and Symptoms

Ingestion of up to 22,5 g allopurinol without adverse eect 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.

### Treatment

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 and ATC Code

Preparations inhibiting uric acid production**;** 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.

## 5.2 Pharmacokinetic Properties

### Absorption

Allopurinol is active when given orally and is rapidly absorbed from the upper gastrointestinal tract. Studies have detected the presence of allopurinol in the blood 30 to 60 minutes after taking it. Estimates of its bioavailability range from 67% to 90%. Peak plasma concentrations of allopurinol are usually reached 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 to 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.

**Metabolism**

The main metabolite of allopurinol is oxypurinol . Other metabolites of allopurinol include allopurinol - riboside and oxypurinol 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 to 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. ***Special patient populations***

- *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.

- *Elderly*

The kinetics of the medicinal product are not likely to be altered except in the event of impaired renal function *(Refer to the information mentioned above on Renal Impairment).*

### 5.3 Preclinical Safety Data

- Carcinogenesis, Mutagenesis

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

Allopurinol does not produce nitraso 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.

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

- Teratogenicity

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

- Lactose Monohydrate
- Mazie Starch
- Povidone
- Magnesium Stearate
- Purified Water

### 6.2 Incompatibilities

Unknown

**6.3 Shelf life**

The expiry date is indicated on the packaging.

**6.4 Special Precautions for Storage** Store below $30^0$C in a dry place.

KEEP OUT OF REACH OF CHILDREN.

**6.5 Nature and Contents of Container**

Clear plastic/silver aluminium blister packs of 28 or 100 tablets packed in a cardboard box.

**6.6 Special Precautions for Disposal and Other Handling** Do not throw away any medicines you no longer use.

Ask your pharmacist or medical facility on how to properly dispose them. This will help protect the environment.

**7. MARKETING AUTHORISATION HOLDER**

BETA HEALTHCARE INTERNATIONAL LTD,

Plot No. Nairobi/Block59/135,

Mogadishu Road, Off Lunga Lunga Road,

Industrial Area, Nairobi, Kenya.

**8. MARKETING AUTHORIZATION NUMBER**

H2008/1248/R1

**9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION**

26/02/2026

**10. DATE OF REVISION OF THE TEXT**

22/08/2026