

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZYLORIC TABLETS

1. GENERIC NAME

Allopurinol Tablets IP 100 mg / 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYLORIC TABLETS

Each uncoated tablet contains:

Allopurinol IP 100 mg

ZYLORIC 300 TABLETS

Each uncoated tablet contains:

Allopurinol IP 300 mg

3. DOSAGE FORM AND STRENGTH

Uncoated tablets

ZYLORIC TABLETS

Each uncoated tablet contains:

Allopurinol IP 100 mg

ZYLORIC 300 TABLETS

Each uncoated tablet contains:

Allopurinol IP 300 mg

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;
- 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;

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

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

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 4.2 *Posology and Method of Administration* and 4.4 *Special Warnings and Precautions for Use*).

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.

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

Children (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.

Special population

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 *4.2 Posology and Method of Administration* and *4.4 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 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 *ZYLORIC* 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 *4.2 Posology and Method of Administration* should be followed. These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation (*see 4.5 Drug Interactions* and *4.8 Undesirable Effects*).

4.3. Contraindications

ZYLORIC tablets should not be administered to individuals known to be hypersensitive to allopurinol or to any of the components of the formulation.

4.4. Special Warnings and Precautions for Use

ZYLORIC should be withdrawn IMMEDIATELY when a skin rash or other evidence of sensitivity occurs as this could result in more serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome (also known as Drug Rash with Eosinophilia and Systemic Symptoms, DRESS) (*see 4.8 Undesirable Effects*).

The *HLA-B*58:01* allele has been identified as a genetic risk factor for allopurinol associated SJS/TEN (and possibly other serious hypersensitivity reactions) in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Thai, Korean, Japanese and European descent. Up to 20-30% of people of Han Chinese, African and Indian ancestry carry the *HLA-B*58:01* allele whereas only 1-2% of Northern European, US European and Japanese are estimated to be *HLA-B*58:01* carriers.

Screening for *HLA-B*58:01* should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. If these individuals test positive, allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits of use outweigh the potential associated risks. Patients who are found to be negative for *HLA-B*58:01* still have a low risk of SJS/TEN. The clinical diagnosis of SJS/TEN, and other hypersensitivity reactions, remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently. (see 4.8 *Undesirable Effects*).

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 has been associated with an increased risk of allopurinol induced SJS/TEN, and other serious hypersensitivity reactions.

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.

Acute gouty attacks

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.

Impaction 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.

4.5. Drug 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 *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 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 *ZYLORIC* 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 *ZYLORIC*, 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 *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 cyclosporin 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 *ZYLORIC* treatment (300 mg daily) without affecting terminal half-life. Therefore, dose reductions of didanosine may be required when used concomitantly with *ZYLORIC*.

4.6. Use in 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 *4.2 Posology and Method of Administration* and *4.4 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 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 *ZYLORIC* 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 4.2 *Posology and Method of Administration* should be followed. These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation (see 4.5 *Drug Interactions* and 4.8 *Undesirable Effects*).

Pregnancy and Lactation

Pregnancy (see 6. *Nonclinical Properties*)

There is inadequate evidence of safety of *ZYLORIC* in human pregnancy, although it has been in wide use for many years without apparent ill consequence.

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

Lactation

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 is no modern clinical documentation which can be used as support or 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	$\geq 1/10$ ($\geq 10\%$)
Common	$\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)
Uncommon	$\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)
Rare	$\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
Very rare	$< 1/10,000$ ($< 0.01\%$)

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

Infections and infestations

Very rare Furunculosis

Blood and lymphatic system disorders

Very rare Agranulocytosis, aplastic anaemia, thrombocytopenia

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.

Immune system disorders

Uncommon Hypersensitivity reactions.

Very rare Angioimmunoblastic lymphadenopathy.

Serious hypersensitivity reactions, including skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia (DRESS), and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), occur rarely (*see 4.8 Undesirable Effects*). Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment 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. *ZYLORIC* should be withdrawn IMMEDIATELY AND PERMANENTLY.

Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalized 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 generalized lymphadenopathy. It appears to be reversible on withdrawal of *ZYLORIC*.

Metabolism and nutrition disorders

Very rare Diabetes mellitus, hyperlipidaemia

Psychiatric disorders

Very rare Depression

Nervous system disorders

Very rare Coma, paralysis, ataxia, neuropathy, paraesthesiae, somnolence, headache, taste perversion, aseptic meningitis

Eye disorders

Very rare Cataract, visual disorder, macular changes

Ear and labyrinth disorders

Very rare Vertigo

Cardiac disorders

Very rare Angina, bradycardia

Vascular disorders

Very rare Hypertension

Gastrointestinal disorders

Uncommon Vomiting, nausea

Very rare Recurrent haematemesis, steatorrhoea, stomatitis, changed bowel habit

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.

Hepatobiliary disorders

Uncommon Asymptomatic increases in liver function tests

Rare Hepatitis (including hepatic necrosis and granulomatous hepatitis)

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

Skin and subcutaneous tissue disorders

Common	Rash
Rare	Stevens- Johnson syndrome / toxic epidermal necrolysis
Very rare	Angioedema, fixed drug eruption, alopecia, discoloured hair

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 allopurinol treatment has been discontinued due to mild skin reactions (i.e. not signs or symptoms of SJS/TEN, or other serious hypersensitivity reaction), allopurinol may be re-introduced at a low dose (e.g. 50 mg/day) and then gradually increased. Consideration should be given to screening for the presence of the *HLA-B*58:01* allele before allopurinol is reintroduced. If the original symptoms recur allopurinol should be PERMANENTLY withdrawn as more severe hypersensitivity reactions may occur (see 4.8 *Undesirable Effects*). 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 remains the basis for decision making.

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

Renal and urinary disorders

Very rare Haematuria, uraemia

Reproductive system and breast disorders

Very rare Male infertility, erectile dysfunction, gynaecomastia

General disorders and administration site conditions

Very rare Oedema, general malaise, asthenia, fever

Fever has been reported to occur with and without signs and symptoms of a more generalized allopurinol hypersensitivity reaction (see 4.8 *Undesirable Effects*).

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.

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. 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.

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. Pharmacodynamic Properties

ATC Code

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

For further details see *5.1 Mechanism of Action*

5.3. 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 to 60 min after dosing. Estimates of bioavailability vary from 67% to 90%.

Peak plasma levels of allopurinol generally occur approximately 1.5 h after oral administration of allopurinol but fall rapidly and are barely detectable after 6 h. Peak plasma levels of oxipurinol generally occur after 3 to 5 h 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 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 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 drug are not likely to be altered other than due to deterioration in renal function (see 5.3 *Pharmacokinetic Properties*).

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology and Pharmacology

Carcinogenesis, mutagenesis

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.

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.

7. DESCRIPTION

Uncoated tablets

ZYLORIC TABLETS

Each uncoated tablet contains:
Allopurinol IP 100 mg

ZYLORIC 300 TABLETS

Each uncoated tablet contains:
Allopurinol IP 300 mg

8. PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose, Starch - maize, Sodium Starch glycollate, Magnesium Stearate, Purified water.

8.1. Incompatibilities

No data available

8.2. Shelf Life

The expiry date is indicated on the label and packaging.

8.3. Packaging Information

CRSF (Child Resistant Senior Friendly) blisters in a carton.

or

High density polyethylene (HDPE) container with induction sealing for 100/300mg.

ZYLORIC 100/300 mg comes in special packaging to prevent children removing them.

To take out a tablet gently push one end of the tablet through the foil layer.

For more information open the link below:

<https://www.youtube-nocookie.com/embed/OYXJcPkJrVA>

All presentations may not be marketed in India.

8.4. Storage and Handling Information

Store in dry place at a temperature not exceeding 30°C.

Keep out of reach of children.

There are no special requirements for use or handling of this product.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or patient's caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contra-indications of *ZYLORIC*. Patients (and/or patient's caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited.

Registered Office:
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Manufacturing License number is indicated on the label and packaging.

12. DATE OF REVISION

15-MAR-2022

Trademarks are owned by or licensed to the GSK group of companies.

Version: ZYL/PI/IN/2022/01

Adapted from ZYLORIC (Allopurinol) IPI 05 dated 14th May 2019