SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tipuric 100 mg Tablets
Tipuric 300 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tipuric 100 mg Tablets: Each tablet contains 100 mg allopurinol.
Excipients: Lactose monohydrate: 100 mg

Tipuric 300 mg Tablets: Each tablet contains 300 mg allopurinol.
Excipients: Lactose monohydrate: 104.3 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Tipuric 100 mg Tablets
White, circular, biconvex tablets, 9.5 mm in diameter marked with a single breakline and the code 230 on one side with the Clonmel logo on the reverse.

Tipuric 300 mg Tablets
White, circular, biconvex tablets, 11 mm in diameter marked with a single breakline and the code 242 on one side with the Clonmel logo on the reverse.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allopurinol is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy).

The main clinical conditions where urate/uric acid deposition may occur are:

- Idiopathic gout.
- Uric acid lithiasis.
- Acute uric acid nephropathy.
- Neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously, or after cytotoxic therapy.
- Certain enzyme disorders which lead to overproduction of urate for example:
    - hypoxanthine-guanine phosphoribosyltransferase, including Lesch-Nyhan syndrome;
    - Glucose-6-phosphatase including glycogen storage disease;
    - Phosphoribosylpyrophosphate synthetase;
    - Phosphoribosylpyrophosphate amidotransferase;
    - Adenine phosphoribosyltransferase.

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

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

4.2 Posology and method of administration

Dosage in adults:
Allopurinol should be introduced at low dosage e.g. 100 mg/day to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor (see Dosage in renal impairment).
The following dosage schedules are suggested:

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

Dosage higher than 300 mg should be given in divided doses not exceeding 300 mg at any time. If dosage on mg/kg bodyweight basis is required, 2-10 mg/kg bodyweight/day should be used.

Dosage in children:
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.

Dosage 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 '*Dosage in renal impairment*' and '*Special warnings and precautions for use*'**.**

Dosage in 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 metabolities 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 metabolities are removed by renal dialysis. If dialysis is required two or three times a week, consideration should be given to an alternative dosage schedule of 300 – 400 mg Allopurinol immediately after each dialysis with none in the interim.

Dosage in 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, Lesh-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 '*Dosage in renal impairment'* should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also '*Interactions with other medicinal products and other forms of interaction*' and '*Undesirable effects*'.

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

Instructions for use:
Allopurinol may be taken orally once a day after a meal. 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

Known intolerance of allopurinol or any of the excipients. Allopurinol is contra-indicated as a treatment for the acute attack of gout and use in patients who are breast feeding infants. Prophylactic therapy may be started when the acute attack has completely subsided, provided anti-inflammatory agents are also taken.

4.4 Special warnings and precautions for use

Allopurinol should be withdrawn **immediately** when a skin rash or other evidence of sensitivity occurs.

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of allopurinol.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If signs or symptoms of SJS or TEN (e.g., progressive skin rash often with blisters or mucosal lesions) are present, allopurinol treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of allopurinol, allopurinol must not be re-started in this patient at any time.

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.

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.

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

4.5 Interactions with other medicinal products and other forms of interactions

6-mercaptopurine and azathioprine:
Azathioprine is metabolised as 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.

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) allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

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.

4.6 Fertility, pregnancy and lactation

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.

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

Lactation:
Allopurinol is excreted in breast milk and should therefore not be used during lactation.

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 (≥ 10%)
Common	≥ 1/100 and < 1/10 (≥ 1% and <10%)
Uncommon	≥ 1/1000 and <1/100 (≥ 0.1% and <1%)
Rare	≥ 1/10,000 and <1/1000 ≥ (0.01% and < 0.1%)
Very rare	<1/10,000 (< 0.01%)

At the start of treatment with allopurinol, patients may experience a reactive gout attack.

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.

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. Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).
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 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 should be withdrawn IMMEDIATELY AND PERMANENTLY.	
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.	
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
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 allopurinol 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 generalised 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). Allopurinol 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 reactions may occur *(see Immune system disorders)*. The HLA-B*5801 allele has been has been identified as a genetic risk factor for allopurinol associated SJS/TEN in retrospective, case-control, pharmacogenetic studies in patients of Han Chinese, Japanese and European descent. Up to 20-30% of some Han Chinese, African and Indian populations carry the HLA-B*5801 allele whereas only 1-2% of Northern European, US European and Japanese patients are estimated to be HLA-B*5801 carriers. However, the use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. 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.	
Angioedema has been reported to occur with and without signs and symptoms of a more generalised 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 generalised allopurinol hypersensitivity reaction *(see Immune system disorders)* .	

4.9 Overdose

Symptoms and Signs
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.

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: M04AA01

Mode of Action

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 Phamacokinetic properties

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.

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.

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 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.

Pharmocokinetics 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 600mg/day in those with normal renal function. A reduction in the dose of allopurinol is therefore required in patients with renal impairment.

Pharmocokinetics 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

Mutagenicity

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

Allopurinol does not produce nitroso compounds *in vitro* or affect lymphocyte transformation *in vitro.*

Evidence from biochemical and other cytological investigations strongly suggests that allopurinol has no deleterious effects on DNA at any stage of the cell cycle and is not mutagenic.

Carcinogenicity

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

Teratogenicity

One study in mice receiving intraperitoneal doses of 50 or 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 the gestation produced no teratogenic effects.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Starch maize
Povidone
Crospovidone
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed.
Store in the original container.

6.5 Nature and contents of container

Polypropylene containers with LDPE caps. HDPE film may be used as packing material.

Tipuric 100 mg Tablets: Pack sizes: 30, 40, 50, 100, 250 and 500 tablets.
Tipuric 300 mg Tablets: Pack sizes: 40, 50, 100, 250, 500 and 1,000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited,
Waterford Road,
Clonmel,
Co. Tipperary.

8. MARKETING AUTHORISATION NUMBER

Tipuric 100 mg Tablets: PA 126/38/1
Tipuric 300 mg Tablets: PA 126/38/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 27 July 1983
Date of renewal: 27 July 2008

10. DATE OF REVISION OF THE TEXT

May 2012