IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0577/013/001
Case No: 2031808

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, **Grange Road**, **Dublin 13**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Allopurinol 100 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/12/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Allopurinol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg allopurinol.

Excipients: Lactose monohydrate

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Round, biconvex, white tablets with breakline and “ALL 100” on one side and twin triangle logo on the reverse.

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 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 phosphoribosyltransferase.

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

Adults
Allopurinol should be introduced at low dosage e.g. 100mg/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:

Mild conditions: 100 to 200 mg daily
Moderately severe conditions: 300 to 600 mg daily
Severe conditions: 700 to 900 mg daily

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

Children
Children under 15 years: 10 to 20mg/Kg bodyweight/day up to a maximum of 400mg daily. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) or 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 *Renal impairment* and *Special Warnins and Precautions for Use*.

Renal impairment
Allopurinol and its metabolites are excreted via the kidney. Impairment of kidney 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 100mg per day or to use single doses of a 100mg at longer dosing 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 400mg 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. 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 renal function is compromised due to renal nephropathy or other pathology, the advice given in *Renal impairment* should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation. See also *Interaction 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

Allopurinol Tablets are contraindicated

- in patients hypersensitive to allopurinol or to any of the excipients.
- in patiens who are breast feeding infants.
- in acute gout.

4.4 Special warnings and precautions for use

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

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 Interaction with other medicinal products and other forms of interaction

6-mercaptopurine and azathioprine
Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with Allopurinol, 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 concurrently 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 or other coumarin anticoagulants when co-administered with allopurinol, therefore, all patients receiving anticoagulants must be carefully be 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 rashes 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.

Cyclosporin
Reports suggest that the plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. 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 allopurinol treatment (300mg daily) without affecting terminal half life. Therefore, dose reductions of didanosine may be required when used concomitantly with allopurinol.

4.6 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. 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 1.4mg/litre allopurinol and 53.7mg/litre oxipurinol have been demonstrated in breast milk from a woman taking Allopurinol 300mg/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 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

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.

Skin and hypersensitivity reactions

These are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Allopurinol 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.

Skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia including Stevens-Johnson syndrome and toxic epidermal necrolysis occur rarely. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment and, very rarely, seizures. 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.

Very rarely acute anaphylactic shock has been reported.

Angioimmunoblastic lymphadenopathy

Angioimmunoblastic lymphadenopathy has been described rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of Allopurinol.

Hepatic function

Rare cases of hepatic dysfunction ranging from asymptomatic rises in liver function tests to hepatitis (including hepatic necrosis and granulomatous hepatitis) have been reported without overt evidence of more generalised hypersensitivity.

Gastrointestinal disorders

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. Recurrent haematemesis has been reported as an extremely rare event, as has steatorrhoea.

Blood and lymphatic system

Occasional 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.

Miscellaneous

The following complaints have been reported occasionally: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesiae, neuropathy visual disorders, cataracts, macular changes, taste

perversion, stomatitis, changed bowel habit, infertility, impotence, diabetes mellitus, hyperlipidaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia, haematuria, angioedema and gynaecomastia.

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

ATC Code M04AA01

Allopurinol is a xanthine oxidase inhibitor.

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 Pharmacokinetic 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 300mg of allopurinol per day will generally have plasma oxipurinol concentrations of 5-10mg/litre.

Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life because it undergoes tubular reabsorption. Reported values for the elimination half-life range from 13.6 hours to 29 hours. The large discrepancies in these values may be accounted for by variations in study design and/or creatinine clearance in the patients.

Pharmacokinetics in patients with renal impairment

Allopurinol and oxipurinol clearance is greatly reduced in patients with poor renal function resulting in higher plasma levels in chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20ml/min, showed plasma oxipurinol concentrations of approximately 30mg/litre after prolonged treatment with 300mg 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.

Pharmacokinetics in elderly patients
The kinetics of the drug are not likely to be altered other than due to deterioration in renal function (see **Pharmacokinetics in patients with renal impairment**).

5.3 Preclinical safety data

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 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

Lactose monohydrate
Maize starch
Pregelatinised maize starch 1500
Sodium starch glycolate (Type A)
Colloidal anhydrous silica
Magnesium stearate

Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. Keep the tablet container tightly closed.

6.5 Nature and contents of container

Polypropylene containers with tamper-evident polyethylene closures. Each container is of suitable size to hold 100 tablets.

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.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited
Trading as Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/13/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th December 1996
Date of last renewal: 13th December 2006

10 DATE OF REVISION OF THE TEXT

December 2007