1. PRODUCT NAME
APPO-ALLOPURINOL 100mg and 300mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Allopurinol 100mg
Allopurinol 300mg

Excipient(s) with known effect
Nil.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Apo-ALLOPURINOL 100mg tablets are white, round, biconvex tablets, scored and engraved “ALL” over “100” on one side and engraved “APO” on the other side. Each tablet contains 100mg allopurinol and typically weighs 113mg.

Apo-ALLOPURINOL 300mg tablets are orange, round, biconvex tablets, scored and engraved “ALL” over “300” on one side and engraved “APO” on the other side. Each tablet contains 300mg allopurinol and typically weighs 340mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Allopurinol is mainly used in the management of primary gout or secondary hyperuricaemia associated with chronic gout. It is not, however, used to treat an acute attack of gout as it has no analgesic, anti-inflammatory or uricosuric activity and may prolong the attack. It is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition may occur such as: uric acid nephropathy; recurrent uric acid stone formation; certain enzyme disorders or blood disorders which lead to overproduction of urate (e.g. Lesch-Nyhan syndrome; haemolytic anaemia); hyperuricaemia associated with malignancy and cytotoxic therapy which result in a high cell turnover rate.

Allopurinol is indicated for the prevention and treatment of calcium oxalate/phosphate renal stones in the presence of high uric acid levels of the blood and/or urine.

4.2 Dose and method of administration
Dose
Allopurinol may increase the frequency of acute attacks during the first few months of therapy; it is therefore recommended that low doses be given initially and slowly increased, and that anti-inflammatory agents or colchicine should be given concomitantly during this period as prophylactic cover. The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Adults
Initiating therapy: In patients with good renal function, doses of 100mg should be given and increased by 50mg to 100mg at weekly intervals until serum urate levels of 0.6 mg per ml are achieved. The following dosage schedules are suggested:

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

If dosage on a mg/kg bodyweight basis is required, 2 to 10 mg/kg bodyweight/day should be used.
If changing therapy from a uricosuric agent alone, the dose should be reduced gradually while allopurinol is introduced.
In severe cases of chronic gout, allopurinol can be used together with a uricosuric agent unless the latter is contraindicated (see section 4.3 Contraindications)

Paediatric population
Children
The average daily dose is 10-20 mg/kg bodyweight up to a maximum of 400mg per day. Use in children is rarely indicated except in malignant conditions and certain enzyme disorders.

Elderly population
The lowest dose, which produces satisfactory urate reduction, should be used. Special attention to dosage is necessary if there is overt renal dysfunction (see section 4.2 Renal impairment and section 4.4 Special warnings and precautions for use).

Renal impairment
The excretion of allopurinol and its metabolites is prolonged, so dosage reductions are recommended. Doses of 100 to 200mg daily should be used if creatinine clearance is between 10 - 20mL/min. and not more than 100mg per day should be used if clearance is less. These doses may be halved or reduced even further when initiating therapy and then slowly increased depending on response. Allopurinol and its metabolites may be removed by renal dialysis.

Hepatic impairment
Dosage reductions are necessary if hepatic function is compromised. Liver function tests and complete blood counts should be performed before, and periodically during allopurinol therapy.

Malignancy or cancer therapy hyperuricaemia
Therapy should be initiated 2 to 3 days prior to cytotoxic therapy after which maintenance doses are given according to response. Adequate hydration is essential throughout.

Method of Administration
Allopurinol may be taken once daily after a meal. It is normally well tolerated, especially after food. Should the total daily dose exceed 300mg and/or gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

4.3 Contraindications
Allopurinol should not be administered to individuals known to be hypersensitive to allopurinol or to any of the components of the formulation, listed in section 6.1.

4.4 Special warnings and precautions for use
Hypersensitivity syndrome, SJS and TEN
Allopurinol should be discontinued immediately at the first sign of a rash or other sign of immediate allergic reactions.

The risk of skin reactions appears to be highest in the first 2 months of treatment and in patients taking higher doses. However, reactions may also be delayed. Skin reactions can include erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis or a diffuse maculopapular or exfoliative dermatitis, fatal cases have been reported.

Skin reactions may also occur as part of a generalised hypersensitivity reaction. A DRESS syndrome (drug rash with eosinophilia and systemic symptoms) characterised by exfoliative dermatitis with eosinophilia complicated by symptoms such as hepatitis and interstitial nephritis has been described in association with allopurinol treatment. Risk factors include renal impairment and use with thiazide diuretics. Patients have been successfully treated by immediate withdrawal of allopurinol and use of corticosteroids.
Chronic renal impairment
Patients with chronic renal impairment and concomitant diuretic use, in particular thiazides, may be at increased risk of developing hypersensitivity reactions including SJS/TEN associated with allopurinol. Extra vigilance, for the signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms (see section 4.8).

Acute gout attacks
To avoid precipitating an acute attack of gout, allopurinol should be introduced slowly, and the patient should usually be given initial prophylactic cover (see section 4.2 Dose and method of administration). Allopurinol should not be started during an acute attack as it may prolong the attack. However, allopurinol is continued when acute attacks occur in patients already on treatment.

Xanthine deposition
In conditions where the rate of urate formation is greatly increased, the concentration of xanthine in the urine could result in the formation of xanthine stones in the urinary tract. To avoid xanthine stones being deposited, it is advisable to maintain a high fluid intake and a neutral alkaline urinary pH, especially if initial uric acid concentrations are high and the patient is symptomatic.

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.

Asymptomatic hyperuricaemia
Allopurinol is not recommended for the treatment of mild asymptomatic hyperuricaemia. It should generally only be considered if serum urate concentrations exceed 0.8 to 0.9 mg/ml with an aim of reducing levels to 0.6 mg/ml.

4.5 Interaction with other medicines and other forms of interaction

Warfarin/Coumarin Anticoagulants:
Patients may need careful monitoring, as there have been reports of an increased response to oral anticoagulants.

Azathioprine and mercaptopurine
In doses of 300-600 mg daily, allopurinol inhibits the oxidative metabolism of azathioprine and mercaptopurine by xanthine oxidase. The doses of the latter agents should be decreased by 25-30% initially if allopurinol is used concomitantly and adjusted according to the patient's response and toxic effects.

Amoxycillin / Ampicillin
Allopurinol or hyperuricaemia may potentiate aminopenicillin allergenicity and the combination should be avoided if possible.

Uricosuric Agents and Salicylates
Medicines with uricosuric activity may accelerate the excretion of oxipurinol the active metabolite of allopurinol. This may decrease the therapeutic activity of allopurinol, but the significance should be assessed in each case.

Didanosine
Plasma didanosine Cmax and AUC levels were approximately doubled with concomitant allopurinol treatment without affecting the terminal half-life. Therefore, co-administration is not recommended. If concomitant use is unavoidable a dose reduction of didanosine may be required and patients should be closely monitored.

Diuretics
Thiazide diuretics may increase the risk of serious allopurinol toxicity, including hypersensitivity reactions and the combination should be monitored, especially if renal function is compromised.
Theophylline and Other Xanthines
High dose allopurinol (600 - 900 mg) can reduce the clearance of theophylline and other xanthines and may cause theophylline toxicity unless the dosage of the latter is reduced.

Chlorpropamide
Caution is indicated as allopurinol may enhance the hypoglycaemic effect of chlorpropamide by competing for renal tubular secretion.

Vidarabine (Adenine Arabinoside)
Extra vigilance is necessary when vidarabine and allopurinol are used concomitantly as the plasma half-life of vidarabine may be increased resulting in enhanced toxic effects.

Phenytoin
Allopurinol may inhibit hepatic oxidation of phenytoin, but the clinical significance has not been established.

Angiotension Converting Enzyme Inhibitors
Isolated reports indicate that concurrent administration of captopril and allopurinol may predispose to hypersensitivity reactions e.g. Stevens-Johnson syndrome. Patients on the combination should be monitored and if a reaction occurs, use of the medications discontinued.

Cyclophosphamide and other Cytotoxic Agents
Concurrent cyclophosphamide or other cytotoxic therapy and allopurinol therapy may increase the incidence of bone marrow depression as compared with cyclophosphamide alone. The mechanism for this interaction is not known. However, in a well-controlled study patient treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechloerethamine allopurinol did not appear to increase the toxic reaction of these cytotoxic agents.

Cyclosporin
Plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporin toxicity should be considered if the medicines are co-administered.

4.6 Fertility, pregnancy and lactation

Pregnancy
Category B2
Although animal studies have not indicated any incidence of teratogenicity, the effect of allopurinol on the human foetus is unknown and it should be used in pregnancy only if clearly indicated.

Breast-feeding
Allopurinol and oxypurinol are distributed into breast milk. Allopurinol should thus be used with caution in view of the potential for adverse effects, especially hypersensitivity reactions.

4.7 Effects on ability to drive and use machines
Drowsiness may occur. Patients should be warned not to engage in activities where alertness is mandatory until their response to allopurinol is known.

4.8 Undesirable effects
The most common adverse effect of allopurinol is a pruritic, maculopapular rash (10%) which may occur more frequently in patients with renal failure.

Skin and Subcutaneous Tissue Disorders
Rash, alopecia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Skin reactions may be delayed and rarely have been followed by severe hypersensitivity reactions which may be fatal. It is therefore recommended that allopurinol be withdrawn immediately if a rash or other signs of allergy occur.

**Immune System Disorders**
Hypersensitivity reactions, angioimmunoblastic lymphadenopathy, DRESS. Serious hypersensitivity reactions, including skin reactions and characterised by fever, chills, leucopenia or leucocytosis, eosinophilia, arthralgia, pruritus, have occurred occasionally. A generalised hypersensitivity vasculitis can lead to renal and hepatic damage and very rarely seizures. These above reactions may be severe, and life threatening and may occur more frequently in patients with renal impairment and/or taking thiazide diuretics. Allopurinol should be withdrawn immediately and permanently (see section 4.4 Special warnings and precautions for use)

**Eye Disorders**
Some patients develop cataracts but a causal relationship to allopurinol is still uncertain.

**General Disorders and Administration Site Conditions**
Asthenia, oedema, fever (can occur with or without symptoms of a generalised hypersensitivity reaction)

**Nervous System Disorders**
Headache, vertigo, ataxia, peripheral neuritis, drowsiness, confusion, coma, paraesthesiae, taste perversion.

**Blood and Lymphatic System Disorders**
Agranulocytosis, aplastic anaemia, thrombocytopenia

**Metabolism and Nutrition Disorders**
Diabetes mellitus, hyperlipidaemia

**Psychiatric Disorders**
Depression

**Cardiac Disorders**
Angina, bradycardia

**Gastrointestinal Disorders**
Nausea, vomiting, diarrhoea, abdominal pain, gastritis and dyspepsia. Patients can be advised to take allopurinol after food.

**Hepatobiliary Disorders**
Alterations in liver function tests hepatatomegaly, hepatitis and jaundice Hepatic dysfunction has occasionally been reported with or without signs of hypersensitivity.

**Renal and Urinary Disorders**
Interstitial nephritis, xanthine stone deposition, impaction of partly dissolved renal uric acid stones in the ureter.

Adequate hydration is important especially in patients with significant hyperuricaemia and tophaceous deposits. Alkalinization of the urine will further reduce crystalluria. On initiating therapy, patients may experience an increase in acute gouty attacks (see section 4.2 Dose and method of administration).

**Reproductive System and Breast Disorders**
Impotence, male infertility, gynaecomastia
APO-ALLOPURINOL

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms
Nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20g of allopurinol. Ingestion of larger doses have been reported without adverse effects.

Treatment
The patient should be monitored and receive normal supportive measures and should be adequately hydrated to maintain urinary excretion of allopurinol and its metabolites. Concomitant medication may affect the effects noted. Haemodialysis may be used if necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antigout preparations – inhibiting uric acid production

ATC code: M04 AA01

Mechanism of action
Allopurinol is used to decrease uric acid concentrations in plasma and/or urine when hyperuricaemia is clinically significant.

Allopurinol and its active metabolite oxypurinol inhibit xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid. Inhibition of this enzyme accounts for the major pharmacological effects of allopurinol. In addition, allopurinol increases reutilization of hypoxanthine and xanthine for nucleotide and nucleic acid synthesis via an action involving the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRTase). The resultant increase in nucleotide concentration leads to feedback inhibition of de novo purine synthesis. Allopurinol thereby decreases uric acid concentrations in both serum and urine.

Accompanying the decreases in uric acid produced by allopurinol is an increase in serum and urine concentrations of hypoxanthine and xanthine. Plasma concentrations of these oxypurines are only slightly increased and renal clearance is rapid and greater than that of uric acid. In the absence of allopurinol, normal urinary output of oxypurines is almost solely in the form of uric acid. After administration of allopurinol, it is composed of hypoxanthine, xanthine and uric acid. Since each has its independent solubility, the concentration of uric acid in plasma is reduced without exposing the urinary tract to an excessive load of uric acid, thus decreasing the risk of crystalluria. By lowering the uric acid concentration in the plasma below its limits of solubility, allopurinol facilitates dissolution of tophi. Although the levels of hypoxanthine and xanthine are increased, the risk of their deposition is less than that of uric acid as they are more soluble and are rapidly cleared by the kidney (see section 4.4 Special warnings and precautions for use).

5.2 Pharmacokinetic properties

Absorption
Up to 90% of an oral dose of allopurinol is absorbed in the gastrointestinal tract. After allopurinol tablet administration, peak plasma levels occur generally at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively.
Distribution
Allopurinol and oxypurinol are not bound to plasma proteins and distribute in the total tissue water.

Biotransformation
The allopurinol is rapidly metabolised to the active metabolite oxypurinol (alloxanthine). Both allopurinol and oxypurinol are conjugated to form their respective ribonucleosides (Allopurinol-riboside and oxypurinol-7-riboside).

Elimination
Allopurinol has a plasma half-life of 1 to 3 hours. It is converted in the liver primarily to the active metabolite oxypurinol, which has a plasma half-life of 12 to 30 hours in people with normal renal function; this is prolonged in the presence of renal dysfunction. Excretion is mainly through the kidneys with up to 10% being excreted unchanged in the urine. 70% is excreted in the urine as oxypurinol but this occurs more slowly since it also undergoes tubular reabsorption. The remainder of the dose is excreted in the faeces as unchanged drug. Serum urate concentrations usually begin to decline slowly within 48 to 72 hours reaching a plateau after 1 to 3 weeks of therapy. However, in patients with tophaceous gout or those who are undersecretors of uric acid, a decline in serum urate levels may be delayed for the first few months.

5.3 Preclinical safety data
Mutagenicity
Cytogenic 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 60mg/day for a mean period of 40 months. Allopurinol does not produce nitroso compounds or affect lymphocyte transformation in vitro.

Evidence 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 treated with allopurinol for up to 2 years.

Teratogenicity
While one study in mice receiving intraperitoneal doses of 50 or 100mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, 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 (up to 100mg/kg/day in mice, up to 200mg/kg/day in rats and up to 150mg/kg/day in rabbits) 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
- Colloidal silicon dioxide
- Croscarmellose sodium
- Magnesium stearate
- Sunset yellow aluminium lake (Allopurinol 300mg)

6.2 Incompatibilities
Not applicable
6.3 Shelf life
Shelf life: 36 months from data of manufacture.

6.4 Special precautions for storage
Store at or below 25°C.
Protect from heat, light and moisture. Keep container tightly closed.

6.5 Nature and contents of container
APO-ALLOPURINOL 100mg tablets:
HDPE Bottles of 100, 250, 500 and 1000 tablets.

APO-ALLOPURINOL 300mg tablets:
HDPE Bottles of 100, 250 and 500 tablets
Calendar Packs of 30 tablets.

6.6 Special precautions for disposal
No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Aponex NZ Ltd.
32 Hillside Road
Wairau Valley
AUCKLAND 0627
Telephone: (09) 444 2073
Fax: (09) 444 2951
E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL
03 November 2005

10. DATE OF REVISION OF THE TEXT
18 March 2019

SUMMARY TABLE OF CHANGES

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