New Zealand Data Sheet

1. PRODUCT NAME

DP-Allopurinol 100 mg and 300 mg Tablets

2. QUALITATIVE AND QUATITATIVE COMPOSITION

Allopurinol 100 mg

Allopurinol 300 mg

Allopurinol tablets contain lactose. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Each 100 mg tablet is white to off-white, scored, flat cylindrical tablet debossed with 'I' and '56' on either side of the break line on one side and plain on other side.

Each 300 mg tablet is white to off-white, scored, flat cylindrical tablet debossed with 'I' and '57' on either side of the break line on one side and plain on other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DP-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. 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 contra-indicated.

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.

DP-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

DP-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 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 100 mg should be given and increased by 50 mg to 100 mg at weekly intervals until target serum urate is reached (less than 0.36 mmol/L). 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 body weight/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).*

Should the total daily dose exceed 300 mg and/or gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

Paediatric population

Children under 15 years

The average daily dose is 10-20 mg/kg body weight/day or 100 to 400 mg daily. Use in children is rarely indicated except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Elderly population

In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used. Particular attention should be paid to the dosage advice in renal disorder and Precautions. *(see section 4.2 and section 4.4)*.

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 the presence of impaired renal function, serious consideration should be given to initiating treatment with a maximum dose of 100 mg/day and increasing it only if the serum and/or urinary urate response is unsatisfactory. In severe renal insufficiency, it may be advisable to use less than 100 mg/day or to use single doses of 100 mg at longer intervals than one day. Alternative schedules based on creatinine clearances are unsatisfactory because of the imprecision of low clearance values.

If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 µmol/L (15.2 µg/mL).

Renal dialysis

Allopurinol and its metabolites may be removed by renal dialysis. If dialysis is required two to three times a week, consideration should be given to an alternative dosage schedule of allopurinol 300 to 400 mg 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.

Malignancy or cancer therapy hyperuricaemia (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 in the lower range.

If urate nephropathy or other pathology has compromised renal function, the advice given in Renal impairment (above) should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation (see sections 4.5 and 4.8).

<u>Method of Administration</u>

DP-Allopurinol may be taken once daily after a meal. It is normally well tolerated, especially after food. Wherever possible a high fluid intake sufficient to yield a daily urinary output of 2 L and the maintenance of a neutral or alkaline urine are desirable in hyperuricaemic patients whether or not they are on allopurinol therapy.

4.3. Contraindications

DP-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 AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE AN ALLERGIC REACTION.

In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme exudativum), drug rash with eosinophilia and systemic symptoms (DRESS), Lyell's disease, generalised vasculitis, irreversible hepatotoxicity, and on rare occasions death. DRESS is also referred to as drug-induced hypersensitivity syndrome (DIHS) and Lyell's disease is also referred to as toxic epidermal necrolysis.

The occurrence of hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function receiving thiazides and allopurinol concurrently. For this reason, in this clinical setting, such combinations should be administered with caution and patients should be observed closely.

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. 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.

Thyroid disorders

Increased thyroid stimulating hormone (TSH) values (>5.5 µIU/mL) were observed in patients on long-term treatment with allopurinol in a long term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

Impaction of uric acid renal stones

Adequate therapy with allopurinol will lead to the dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

Haematological Effects

Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant drugs with the potential for causing this reaction. This has occurred as early as six weeks to as long as six years after the initiation of therapy of

allopurinol. Rarely a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone.

Haemochromatosis

Allopurinol's primary action in treating gout is to inhibit the enzyme, xanthine oxidase. Xanthine oxidase may be involved in the reduction and clearance of hepatically stored iron. Some rodent studies have found increased iron storage in animals treated with allopurinol, whilst others have not. A study in 28 healthy volunteers found no change in hepatic iron storage with allopurinol treatment. There are no human studies which have investigated the safety of administering allopurinol to patients with haemochromatosis. Administration of allopurinol to patients with abnormal iron storage, including haemochromatosis, should be undertaken with caution.

HLA-B*5801 allele

The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, 8-15% in the Thai population, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin. Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. Chronic kidney disease may increase the risk in these patients. Additionally, in the case that no HLA-B*5801 genotyping is available for patients with Han Chinese, Thai or Korean descent, the benefits should be thoroughly assessed and considered to outweigh the possible higher risks before starting therapy. The use of genotyping has not been established in other patient populations. If the patient is a known carrier of HLA-B*5801 (especially in those who are from Han Chinese, Thai or Korean descent), allopurinol should not be started unless there are no other reasonable therapeutic options and the benefits are thought to exceed risks. Extra vigilance for signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately at the first appearance of symptoms. SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

Use in hepatic impairment

A few cases of reversible clinical hepatotoxicity have been noted in patients taking allopurinol, and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develop in patients on allopurinol, evaluation of liver function should be part of their diagnostic workup. In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy.

Reduced doses should be used in patients with hepatic impairment.

Use in renal impairment

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in serum urea during administration of allopurinol. Although the mechanism responsible for this has not been established, patients with impaired renal function should be

carefully observed during the early stages of allopurinol administration and dosage decreased or the drug withdrawn if increased abnormalities in renal function appear and persist. 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 these patients.

Renal failure in association with administration of allopurinol has been observed among patients with hyperuricemia secondary to neoplastic diseases. Concurrent conditions such as multiple myeloma and congestive myocardial disease were present among those patients whose renal dysfunction increased after allopurinol was begun. Renal failure is also frequently associated with gouty nephropathy and rarely with hypersensitivity reactions associated with allopurinol. Albuminuria has been observed among patients who developed clinical gout following chronic glomerulonephritis and chronic pyelonephritis. A dose reduction will be required in patients with renal impairment, see section 4.2.

Asymptomatic hyperuricaemia

Asymptomatic hyperuricaemia per se is not an indication for the use of allopurinol. Fluid and dietary modifications with management of the underlying cause may correct the condition. If other clinical conditions suggest a need for allopurinol it must be introduced at low dosage (50 to 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 section 4.2.

Allopurinol must be withdrawn immediately and permanently at the first signs of intolerance.

4.5. Interaction with other medicines and other forms of interaction

Azathioprine and mercaptopurine:

Allopurinol inhibits the oxidative metabolism of azathioprine and mercaptopurine by xanthine oxidase. When mercaptopurine or azathioprine is given concurrently with allopurinol, only one quarter of the usual dose of mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity and increase the possibility of toxic effect e.g., an azathioprine dose of 100 mg should be reduced to 25 mg. All patients receiving this combination must be carefully monitored. The risk of overdosage is also increased when allopurinol is being given concomitantly with mercaptopurine or azathioprine (*see section 4.9).*

Vidarabine (Adenine Arabinoside):

Evidence suggests that the plasma half-life of adenine arabinoside is increased in the presence of allopurinol. When the two products are used concomitantly extra vigilance is necessary, to recognise enhanced toxic effects.

Uricosuric Agents and Salicylates:

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 allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity.

Warfarin/Coumarin Anticoagulants:

Patients may need careful monitoring, as there have been reports of an increased response to oral anticoagulants.

Phenytoin:

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

Theophylline and Other Xanthines:

Experimental studies of the effect of allopurinol on theophylline metabolism have produced contradictory findings. Inhibition of the metabolism of theophylline has been reported. Theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Amoxycillin / Ampicillin:

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.

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.

Antacids:

If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

Diuretics:

An increased risk of hypersensitivity has been reported when allopurinol is given with diuretics, in particular thiazides, especially in renal impairment.

Angiotensin-converting-enzyme (ACE) inhibitors:

An increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors especially in renal impairment.
Cytostatics: With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone.

4.6. Fertility, pregnancy and lactation

Fertility

Only rarely has infertility in human males and impotence occurred during allopurinol therapy, however a casual relationship to the drug has not been established.

Pregnancy

There is inadequate evidence of safety of allopurinol in human pregnancy.

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

Breast-feeding

Reports indicate that allopurinol and its metabolite, oxipurinol, are excreted in human breast milk. Concentrations of 1.5 mg/L allopurinol and 53.7 mg/L oxipurinol have been demonstrated in breast milk from a woman taking allopurinol 300 mg/day. There are, however, no data concerning the effects of allopurinol, or its metabolism, on the breast-fed child. Allopurinol during breastfeeding is not recommended.

4.7. Effects 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 where alertness is mandatory until they are reasonably certain that allopurinol does not adversely affect performance.

4.8. Undesirable effects

Adverse reactions are usually reversed by the reduction of dosage or complete withdrawal of allopurinol. Taking allopurinol after meals may minimise gastrointestinal disturbances. Where hypersensitivity reactions occur, allopurinol should be withdrawn immediately. Corticosteroids may be beneficial in overcoming such reactions.

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.

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
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10,000 to <1/1000
Very rare	<1/10,000

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.

Table 1 Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very rare	Furuncle
Blood and lymphatic system disorders	Very rare	Agranulocytosis[1] Aplastic anaemia[1] Thrombocytopenia[1]
Immune system disorders	Uncommon	Hypersensitivity [2]
	Very rare	Angioimmunoblastic T-cell lymphoma [3] Anaphylactic reaction
Metabolism and nutrition disorders	Very rare	Diabetes mellitus Hyperlipidaemia
Psychiatric disorders	Very rare	Depression
Nervous system disorders	Very rare	Coma Paralysis Ataxia Neuropathy peripheral Paraesthesia Somnolence Headache Dysgeusia
	Not known	Aseptic meningitis
Eye disorders	Very rare	Cataract Visual impairment Maculopathy
Ear and labyrinth disorders	Very rare	Vertigo
Cardiac disorders	Very rare	Angina pectoris Bradycardia
Vascular disorders	Very rare	Hypertension
Gastrointestinal disorders	Uncommon	Vomiting[4] Nausea[4] Diarrhoea

	Very rare	Haematemesis Steatorrhoea Stomatitis Change of bowel habit
Hepatobiliary disorders	Uncommon	Liver function test abnormal[5]
	Rare	Hepatitis (including hepatic necrosis and granulomatous hepatitis) [5]
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Stevens-Johnson syndrome/toxic epidermal necrolysis [6]
	Very rare	Angioedema[7] Drug eruption Alopecia Hair colour changes
Renal and urinary disorders	Very rare	Haematuria Azotaemia
Reproductive system and breast disorders	Very rare	Infertility male Erectile dysfunction Gynaecomastia
General disorders and administration site conditions	Very rare	Oedema Malaise Asthenia Pyrexia [8]
Investigations	Common	Blood thyroid stimulating hormone increased[9]

1 Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.

2 A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis,lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia hepato-splenomegaly, abnormal liver function tests, and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn IMMEDIATELY AND PERMANENTLY.

Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.

3 Angioimmunoblastic T-cell lymphoma has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of Allopurinol.

4 In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking Allopurinol after meals.

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

6 Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). 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. 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. The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the rash recurs, Allopurinol should be permanently withdrawn as more severe hypersensitivity may occur (see section 4.8 *Immune system disorders*). 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 remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.

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

8 Fever has been reported to occur with and without signs and symptoms of a more generalised Allopurinol hypersensitivity reaction (see section 4.8 *Immune system disorders*).

9 The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies did not report any impact on free T4 levels or had TSH levels indicative of subclinical hypothyroidism.

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

<u>Symptoms</u>

These include nausea, vomiting, diarrhoea and dizziness.

Treatment

Recovery followed general supportive measures.

Massive absorption of allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine and/or azathioprine is being taken concomitantly. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary, haemodialysis may be used.

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

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

Allopurinol inhibits xanthine oxidase, the enzyme which catalyses the conversion of hypoxanthine to xanthine, and of xanthine to urate/uric acid.

	XO		XO	
Hypoxanthine	→	Xanthine	→	Urate /uric acid

Allopurinol decreases urate formation in two ways:

1. The inhibition of xanthine oxidase reduces the amount of hypoxanthine and xanthine converted to urate/uric acid.
2. This action makes more hypoxanthine and xanthine available for reutilisation in the purine metabolic cycle, which in turn, by a feedback mechanism, decreases overall de novo purine formation.

Since allopurinol decreases urate formation, it reduces urate/uric acid concentrations in both body fluids and urine. In contrast, the uricosuric agents which increase urate/uric acid excretion via the kidney will reduce the urate concentration in body fluids, but increase urate/uric acid concentration in urine. Reduction of the urate concentrations in body fluids by allopurinol permits mobilisation and dissolution of urate deposits anywhere in the body, the commonest sites being those in the skin, bones, joints and kidney interstitial tissue.

Therapeutic effects therefore include: the resolution of skin tophi and the healing of urate sinuses; eventual reduction in the frequency of attacks of acute gouty arthritis,

improvement in joint mobility; reduction of the urate load to be excreted via the kidney; prevention and treatment of acute uric acid nephropathy; and, in the long-term, reduced risk of renal impairment by urate/uric acid and prevention and dissolution of uric acid renal stones.

5.2. Pharmacokinetic properties

Absorption:

Allopurinol is approximately 90% absorbed from the gastrointestinal tract.

Distribution:

Allopurinol is uniformly distributed in total tissue water with the exclusion of the brain, where concentrations of the drugs are approximately 50% those of other tissues. Within muscle, small amounts of allopurinol and oxypurinol crystals have been found. Allopurinol and oxypurinol are not bound to plasma proteins. Allopurinol and oxypurinol are distributed into breast milk.

Biotransformation:

Allopurinol is rapidly converted in the body to the pharmacologically active principal metabolite oxypurinol and other metabolites including allopurinol riboside and oxypurinol-7-riboside. Peak plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively. Oxypurinol is also an inhibitor of xanthine oxidase.

Elimination:

The renal clearance of hypoxanthine and xanthine is at least 10 times greater than that of uric acid. The increased xanthine and hypoxanthine in the urine have not been accompanied by problems of nephrolithiasis.

Approximately 20% of the ingested allopurinol is excreted in the faeces. Because of its rapid oxidation to oxypurinol and a renal clearance rate approximately that of glomerular filtration rate, allopurinol has a plasma half-life of about 1 to 2 hours. Little allopurinol is found in the urine 6 hours after administration. Allopurinol and oxypurinol are mainly excreted in the urine. Oxypurinol, however, has a longer plasma half-life (approximately 15.0 hours) and therefore effective xanthine oxidase inhibition is maintained over a 24 hour period with single daily doses of allopurinol. Whereas allopurinol is cleared essentially by glomerular filtration, oxypurinol is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

5.3. Preclinical safety data

<u>Carcinogenicity</u>

No data is available on whether or not allopurinol has carcinogenic effects within humans or animals. No evidence of carcinogenicity has been found in mice treated with allopurinol for up to 2 years.

Mutagenicity

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

Teratogenicity

While one study in mice receiving intraperitoneal doses of 50 or 100 mg/kg on days 10 or 13 of gestation resulted in foetal abnormalities, 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 (up to 100 mg/kg/day in mice, up to 200 mg/kg/day in rats and up to 150 mg/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.

Reproductive toxicity

Reproduction studies in rabbits and rats using dosages up to 20 times the usual human dosage have not revealed any evidence of impaired fertility.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate

Maize Starch

Povidone

Magnesium Stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months. This medicine should not be used after the expiry date shown on the pack.

6.4. Special precautions for storage

Store at or below 25°C. Store in the original package in order to protect from moisture and light.

6.5. Nature and contents of container

DP-Allopurinol 100mg tablets

PVC/aluminium foil blister packs of 28 and 56

HDPE bottles of 500

DP-Allopurinol 300mg tablets

PVC/aluminium foil blister packs of 28 and 56

HDPE bottles of 100 and 500

6.6. Special precautions for disposal and other handling

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

29 September 2016

10.DATE OF REVISION OF THE TEXT

27 March 2023

Summary table of changes

Section Changed	Summary of new information
4.4, 4.5, 4.6, 4.8,	Aligned with International Product Information.