

# NEW ZEALAND DATASHEET

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## 1. PRODUCT NAME

Ipca-Allopurinol 100 mg and 300 mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Allopurinol 100 mg

Allopurinol 300 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

IPCA-ALLOPURINOL 100mg tablets are white to off white, round, biconvex, uncoated tablets, engraved "AL" and "100" separated by breakline on one side and plain on other side.

Each tablet contains 100mg allopurinol and typically weighs 173mg.

IPCA-ALLOPURINOL 300mg tablets are peach colored, round, biconvex, uncoated tablets and engraved Each tablet contains 300mg allopurinol and typically weighs 520mg.

## 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.  
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.
- 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
- 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

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

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### **Adults:**

The average daily dose is 2-10 mg/kg bodyweight, or 100mg to 200mg for mild conditions, 300mg to 600mg daily for moderately severe conditions and 700mg to 900mg for severe conditions.

### **Initiating therapy:**

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.

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.

### **Hyperuricaemia of malignancy or cancer therapy:**

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.

### **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.

### **Use in renal dysfunction:**

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.

### **Use in the elderly:**

The lowest dose, which produces satisfactory urate reduction, should be used. Special attention to dosage is necessary if there is overt renal dysfunction.

## **4.3. Contraindications**

Hypersensitivity to allopurinol or its metabolites

## **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

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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.

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.

To avoid precipitating an acute attack of gout, allopurinol should be introduced slowly and the patient should usually be given initial prophylactic cover (see under Dosage and 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.

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

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. It is advisable to maintain a high fluid intake.

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

### 4.5. Interaction with other medicines and other forms of interaction

#### **Antineoplastic Agents:**

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.

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### **Didanosine:**

Plasma didanosine C<sub>max</sub> 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.

### **Coumarin Anticoagulants:**

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

### **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 patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine and/or mechloroethamine 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.

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### 4.6. Fertility, pregnancy and lactation

#### **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.

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 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 warnings and precautions)

#### **Eye Disorders**

Some patients develop cataracts but a casual 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.

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## **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 hepatomegaly, 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 Dosage and Administration).

## **Reproductive System and Breast Disorders**

Impotence, male infertility, gynaecomastia

## **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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

**Pharmacotherapeutic Group:** Antigout preparations inhibiting uric acid production

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### **ATC code:** M04 AA01

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. However to avoid xanthine stones being deposited, it is advisable to maintain a high fluid intake and a neutral or alkaline urinary pH, especially if initial uric acid concentrations are high and the patient is symptomatic.

### **5.2. Pharmacokinetic properties**

#### **Absorption**

Up to 90% of an oral dose of allopurinol is absorbed in the gastrointestinal tract. The allopurinol is rapidly metabolised to the active metabolite oxypurinol (alloxanthine). After allopurinol tablet administration, peak plasma levels occur generally at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively. 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. A reduction in the dose is required in patients with renal impairment. Both allopurinol and oxypurinol are conjugated to form their respective ribonucleosides (Allopurinol-ribose and oxypurinol-7-ribose). 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.

Allopurinol and oxypurinol are not bound to plasma proteins and distribute in the total tissue water.

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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. Allopurinol and its metabolites may be removed by renal dialysis.

### 5.3. Preclinical safety data

#### Mutagenicity, Carcinogenicity and Teratogenicity

Cytogenic studies show that allopurinol does not induce chromosome aberrations in human blood cells in vitro at concentrations up to 100mg/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.

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

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

Lactose  
Corn-starch  
Povidone  
Sodium starch glycolate-type A  
Sunset yellow FCF aluminium lake CI15985  
Purified water  
Corn-starch (Dried)  
Stearic acid (micronised).

Ipca-Allopurinol tablets contain lactose and are gluten free.

### 6.2. Incompatibilities

Not applicable.



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## 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 below 25°C. Protect from moisture. Keep container tightly closed.

## 6.5. Nature and contents of container

Ipca Allopurinol 100 mg and 300 mg tablets are packed in Bottles of 30 and 1000 tablets

## 6.6. Special precautions for disposal and other handling

No special requirements

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Ipca Pharma (NZ) Pty Limited,  
3-A, Oswalds Road,  
Greenlane,  
Auckland 1061  
Phone: (09) 634 7266

## 9. DATE OF FIRST APPROVAL

**21<sup>st</sup> April 2016**

## 10. DATE OF REVISION OF THE TEXT

**6<sup>th</sup> May 2022**

### Summary table of changes

Section changed	Summary of new information
Full datasheet	In line with new datasheet format