

ALLOPURINOL SODIUM- allopurinol sodium injection, powder, lyophilized, for solution

Hikma Pharmaceuticals USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Allopurinol Sodium for Injection safely and effectively. See full prescribing information for Allopurinol Sodium for Injection.

**Allopurinol Sodium for Injection for intravenous use
Initial U.S. Approval: 1966**

----- **INDICATIONS AND USAGE** -----

Allopurinol Sodium for Injection is a xanthine oxidase inhibitor indicated for the management of adult and pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Recommended Dosage (2.2)

Adult Patients	200 mg/m ² /day to 400 mg/m ² /day Maximum 600 mg/day
Pediatric Patients	Starting Dose 200 mg/m ² /day Maximum 400 mg/day

- Recommended Dosage in Adult Patients with Renal Impairment (2.2, 5.2, 8.6)

Creatinine Clearance	Recommended Daily Dose
10 to 20 mL/min	200 mg/day
Less than 10 mL/min	100 mg/day
On dialysis	50 mg every 12 hours, or 100 mg every 24 hours

----- **DOSAGE FORMS AND STRENGTHS** -----

For injection: 500 mg as a white lyophilized powder or cake in a single-dose vial for reconstitution (3)

----- **CONTRAINDICATIONS** -----

Known hypersensitivity to allopurinol. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- **Skin Rash and Hypersensitivity:** Discontinue Allopurinol Sodium for Injection at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction. Allopurinol has been associated with serious and sometimes fatal dermatologic reactions. (5.1)
- **Renal Function Impairment:** Patients with decreased renal function require lower doses of allopurinol. (5.2)
- **Hepatotoxicity:** If signs and symptoms of hepatotoxicity develop, liver function evaluation should be performed. (5.3)
- **Myelosuppression:** Bone marrow suppression has been reported with allopurinol. (5.4)
- **Drowsiness:** Drowsiness has been reported in patients taking Allopurinol Sodium for Injection. (5.5)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (incidence > 1%) are skin rash, nausea, vomiting, and renal failure/insufficiency. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- **Capecitabine:** Avoid the concomitant use of allopurinol (7.2).
- **Pegloticase:** Discontinue and do not institute allopurinol therapy during treatment with pegloticase

(7.2).

- Mercaptopurine or Azathioprine: Reduce mercaptopurine or azathioprine dose as recommended in the respective prescribing information (7.2).
- See full prescribing information for complete list of significant drug interactions (7).

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Allopurinol Sodium for Injection is indicated for the management of adult and pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels and who cannot tolerate oral therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Initiate therapy with Allopurinol Sodium for Injection 24 to 48 hours before the start of chemotherapy known to cause tumor cell lysis. Additionally, administer fluids sufficient to yield a daily urinary output of at least two liters in adults with a neutral or, preferably, slightly alkaline urine.

The recommended daily dose of Allopurinol Sodium for Injection is shown in Table 1. Administer the daily dose as single infusion or in equally divided infusions at 6-, 8-, or 12-hour intervals at a rate appropriate for the volume of infusate.

Table 1: Recommended Daily Dose of Allopurinol Sodium for Injection

Adult Patients	200 mg/m ² /day to 400 mg/m ² /day intravenously Maximum 600 mg/day
Pediatric Patients	Starting Dose 200 mg/m ² /day intravenously Maximum 400 mg/day

The dosage of Allopurinol Sodium for Injection to lower serum uric acid to normal or near-normal varies with the severity of the disease. Monitor serum uric acid levels at least daily and administer Allopurinol Sodium for Injection at a dose and frequency to maintain the serum uric acid within the normal range. Discontinue Allopurinol Sodium for Injection when the patient is able to take oral therapy or when the risk of tumor lysis has abated.

2.2 Dosage Modifications in Patients with Renal Impairment

Reduce the dose of Allopurinol Sodium for Injection in patients with impaired renal function [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. The recommended dosage reductions of Allopurinol Sodium for Injection in adult patients

with renal impairment are shown in Table 2.

Table 2: Recommended Daily Dose of Allopurinol Sodium for Injection in Adult Patients with Renal Impairment

Creatinine Clearance	Recommended Daily Dose
10 to 20 mL/min	200 mg/day
Less than 10 mL/min	100 mg/day
On dialysis	50 mg every 12 hours, or 100 mg every 24 hours

Treatment with Allopurinol Sodium for Injection has not been studied in pediatric patients with severe renal impairment or on dialysis. For pediatric patients with severe renal impairment or on dialysis, consider the risks and potential benefits before initiating treatment with Allopurinol Sodium for Injection [see *Warnings and Precautions (5.2) and Use In Specific Populations (8.6)*].

2.3 Preparation Instructions

Reconstitute and further dilute Allopurinol Sodium for Injection prior to intravenous infusion.

Reconstitution

- Reconstitute each vial of Allopurinol Sodium for Injection with 25 mL of Sterile Water for Injection, USP to obtain a concentration of 20 mg/mL of allopurinol.
- Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear as a clear, almost colorless solution with no more than a slight opalescence. Do not use if the reconstituted solution contains particulate matter or discoloration is present.

Dilution

- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose for Injection, USP to obtain a final concentration of less than 6 mg/mL.
- Inspect the diluted solution for particulate matter or discoloration and discard if present.
- If not used immediately, the diluted Allopurinol Sodium for Injection solution can be stored at 20° to 25°C (68° to 77°F) for up to 10 hours after initial reconstitution. The storage includes time for infusion. Do not refrigerate the reconstituted and/or diluted product.
- If stored, the administration should be completed within 10 hours after reconstitution.
- Discard unused portion.

2.4 Administration Instructions

Do not mix Allopurinol Sodium for Injection with or administer it through the same intravenous port as agents which are incompatible in solution with Allopurinol Sodium for Injection. The following table lists drugs that are known to be physically incompatible in solution with Allopurinol Sodium for Injection.

Table 3: Drugs That Are Physically Incompatible in Solution with Allopurinol Sodium for Injection

Amikacin sulfate	Hydroxyzine HCl
Amphotericin B	Idarubicin HCl
Carmustine	Imipenem-cilastatin sodium
Cefotaxime sodium	Mechlorethamine HCl
Chlorpromazine HCl	Meperidine HCl
Cimetidine HCl	Metoclopramide HCl
Clindamycin phosphate	Methylprednisolone sodium succinate
Cytarabine	Minocycline HCl
Dacarbazine	Nalbuphine HCl
Daunorubicin HCl	Ondansetron HCl
Diphenhydramine HCl	Prochlorperazine edisylate
Doxorubicin HCl	Promethazine HCl
Doxycycline hyclate	Sodium bicarbonate
Droperidol	Streptozocin
Floxuridine	Tobramycin sulfate
Gentamicin sulfate	Vinorelbine tartrate
Haloperidol lactate	

3 DOSAGE FORMS AND STRENGTHS

For Injection: 500 mg of allopurinol as a sterile, white lyophilized powder or cake in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

Allopurinol Sodium for Injection is contraindicated in patients with a history of severe reaction to any formulation of allopurinol.

5 WARNINGS AND PRECAUTIONS

5.1 Skin Rash and Hypersensitivity

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking allopurinol [see *Adverse Reactions (6.1)*]. These reactions occur in approximately 5 in 10,000 (0.05%) patients taking allopurinol. Other serious hypersensitivity reactions that have been reported include exfoliative, urticarial and purpuric lesions; generalized vasculitis; and irreversible hepatotoxicity. Discontinue Allopurinol Sodium for Injection at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction.

The HLA-B*58:01 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol. Patients who carry the HLA-B*58:01 allele are at a higher

risk of allopurinol hypersensitivity syndrome (AHS), but hypersensitivity reactions have been reported in patients who do not carry this allele. The frequency of this allele is higher in individuals of African, Asian (e.g., Han Chinese, Korean, Thai), and Native Hawaiian/Pacific Islander ancestry [see *Clinical Pharmacology (12.5)*]. The use of Allopurinol Sodium for Injection is not recommended in HLA-B*58:01 positive patients unless the benefits clearly outweigh the risks.

Prior to starting Allopurinol Sodium for Injection, consider testing for the HLA-B*58:01 allele in genetically at-risk populations. Screening is generally not recommended in patients from populations in which the prevalence of HLA-B*58:01 is low, or in current allopurinol users, as the risk of SJS/TEN/DRESS is largely confined to the first few months of therapy, regardless of HLA-B*58:01 status.

Hypersensitivity reactions to Allopurinol Sodium for Injection may be increased in patients with decreased renal function receiving thiazide diuretics and Allopurinol Sodium for Injection concurrently. In addition, concomitant use of the following drugs may increase the risk of skin rash, which may be severe: bendamustine, thiazide diuretics, ampicillin and amoxicillin [see *Drug Interactions (7.1)*]. Patients should stop Allopurinol Sodium for Injection and seek medical attention if they develop a rash.

5.2 Renal Function Impairment

Treatment with Allopurinol Sodium for Injection may result in renal impairment due to formation of xanthine calculi or due to precipitation of urates in patients receiving concomitant uricosuric agents. Patients with pre-existing renal disease, including renal impairment or history of kidney stones, may be at increased risk for worsening renal impairment due to xanthine calculi or precipitation of urates while receiving treatment with Allopurinol Sodium for Injection.

Monitor serum creatinine at least daily during the early stages of allopurinol administration. Maintain fluid intake sufficient to yield a urinary output of at least 2 liters per day in adults. In patients with severely impaired renal function or increase in uric acid concentration associated with decreased urate clearance, reduce the dosage of Allopurinol Sodium for Injection [see *Use In Specific Populations (8.6)* and *Dosage and Administration (2.1, 2.2)*].

5.3 Hepatotoxicity

Cases of reversible clinical hepatotoxicity have been noted in patients taking oral allopurinol. 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, evaluate liver enzymes. In patients with pre-existing liver disease, monitor liver enzymes periodically during the early stages of therapy. Discontinue Allopurinol Sodium for Injection in patients with elevated liver enzymes.

5.4 Myelosuppression

Myelosuppression, manifested by anemia, leukopenia or thrombocytopenia, has been reported in patients receiving allopurinol [see *Adverse Reactions (6.1)*]. The cytopenias have occurred from as early as 6 weeks to as late as 6 years after the initiation of allopurinol therapy. Discontinue use of Allopurinol Sodium for Injection in patients with unexplained cytopenias. Concomitant use with allopurinol with cytotoxic drugs associated with myelosuppression may increase the risk of myelosuppression. Monitor

blood counts more frequently [see *Drug Interactions (7)*].

Concomitant use with allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of myelosuppression. Reduce the dosage of mercaptopurine or azathioprine as recommended in the respective prescribing information when used concomitantly with Allopurinol Sodium for Injection. [see *Drug Interactions (7)*].

5.5 Drowsiness

Drowsiness has been reported in patients taking Allopurinol Sodium for Injection [see *Adverse Reactions (6.1)*]. Advise patients to avoid operation of automobiles or other dangerous machinery and activities made hazardous by decreased alertness when starting Allopurinol Sodium for Injection or increasing the dose until they know how the drug affects them. Advise patients that the central nervous system depressant effects of Allopurinol Sodium for Injection may be additive to those of alcohol and other CNS depressants.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Skin Rash and Hypersensitivity [see *Warnings and Precautions (5.1)*]
- Renal Function Impairment [see *Warnings and Precautions (5.2)*]
- Hepatotoxicity [see *Warnings and Precautions (5.3)*]
- Myelosuppression [see *Warnings and Precautions (5.4)*]
- Drowsiness [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Allopurinol Sodium for Injection was evaluated in an uncontrolled compassionate use study of 1,378 patients with advanced malignancies requiring treatment with cytotoxic chemotherapy and in patients with other serious conditions.

Adverse reactions were reported in 9% (125/1378) of the patients treated with Allopurinol Sodium for Injection.

The most common adverse reaction was skin rash. Two patients experience serious adverse reactions (decreased renal function and generalized seizure) and one patient experienced severe diarrhea. Approximately 1.1% of patients experienced allergic adverse reactions (including rash, eosinophilia, local injection site reaction).

A listing of the adverse reactions reported from clinical trials follows:

Incidence Greater Than 1%:

Cutaneous/Dermatologic: rash (1.5%)

Genitourinary: renal failure/insufficiency (1.2%)

Gastrointestinal: nausea (1.3%), vomiting (1.2%)

Incidence Less Than 1%:

Body as a Whole: fever, pain, chills, alopecia, infection, sepsis, enlarged abdomen, mucositis/pharyngitis, blast crisis, cellulitis, hypervolemia

Cardiovascular: heart failure, cardiorespiratory arrest, hypertension, pulmonary embolus, hypotension, decreased venous pressure, flushing, headache, stroke, septic shock, cardiovascular disorder, ECG abnormality, hemorrhage, bradycardia, thrombophlebitis, ventricular fibrillation

Cutaneous/Dermatologic: urticaria, pruritus, local injection site reaction

Gastrointestinal: diarrhea, gastrointestinal bleeding, hyperbilirubinemia, splenomegaly, hepatomegaly, intestinal obstruction, jaundice, flatulence, constipation, liver failure, proctitis

Genitourinary: hematuria, increased creatinine, oliguria, kidney function abnormality, urinary tract infection

Hematologic: leukopenia, marrow aplasia, thrombocytopenia, eosinophilia, neutropenia, anemia, pancytopenia, ecchymosis, bone marrow suppression, disseminated intravascular coagulation

Metabolic: hypocalcemia, hyperphosphatemia, hypokalemia, hyperuricemia, electrolyte abnormality, hypercalcemia, hyperglycemia, hyponatremia, hyponatremia, metabolic acidosis, edema, glycosuria, hyperkalemia, lactic acidosis, water intoxication, hypomagnesemia

Neurologic: seizure, status epilepticus, myoclonus, twitching, agitation, mental status changes, cerebral infarction, coma, dystonia, paralysis, tremor

Pulmonary: respiratory failure/insufficiency, ARDS, increased respiration rate, apnea

Musculoskeletal: arthralgia

Other: hypotonia, diaphoresis, tumor lysis syndrome

7 DRUG INTERACTIONS

Clinically important interactions with the drugs listed below were observed in patients undergoing treatment with an oral allopurinol formulation.

7.1 Drugs Known to Affect the Occurrence of Skin Rash and Hypersensitivity

Concomitant use of the following drugs may increase the risk of skin rash, which may be severe: bendamustine, thiazide diuretics, ampicillin and amoxicillin. Renal impairment may further increase risk with concomitant use of thiazide diuretics [*see Warnings and Precautions (5.1) (5.2) and Clinical Pharmacology (12.2)*].

Monitor renal function and reduce the dose of Allopurinol Sodium for Injection in patients with concomitant thiazide diuretic use and impaired renal function [*see Dosage and Administration (2.2)*].

Discontinue Allopurinol Sodium for Injection at the first appearance of skin rash or other signs which may indicate a hypersensitivity reaction when use concomitantly with these drugs.

7.2 Other Drugs Known to Have Clinically Important Drug Interactions with Allopurinol Sodium for Injection

Table 4: Interventions for Clinically Important Drug Interactions with Allopurinol Sodium for Injection

Capecitabine	
<i>Clinical Impact</i>	Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease capecitabine efficacy.
<i>Intervention</i>	Avoid the use of Allopurinol Sodium for Injection during treatment with capecitabine.
Cyclosporine	
<i>Clinical Impact</i>	Concomitant use of allopurinol increases cyclosporine concentrations which may increase the risk of adverse reactions.
<i>Intervention</i>	Increase frequency of monitoring cyclosporine concentrations as reflected in the prescribing information when used concomitantly with Allopurinol Sodium for Injection.
Cytotoxic Agents	
<i>Clinical Impact</i>	Concomitant use of allopurinol with cytotoxic agents increases bone marrow suppression among patients with neoplastic disease, except leukemia [see <i>Warnings and Precautions (5.4) and Clinical Pharmacology (12.2)</i>].
<i>Intervention</i>	Blood count monitoring and regular physician follow-up recommended.
Fluorouracil	
<i>Clinical Impact</i>	Based on non-clinical data, allopurinol may decrease anti-tumor activity due to suppression of phosphorylation of 5-fluorouracil.
<i>Intervention</i>	Concomitant administration with fluorouracil should be avoided.
Mercaptopurine or Azathioprine	
<i>Clinical Impact</i>	Allopurinol inhibits xanthine oxidase mediated metabolism of mercaptopurine and azathioprine. Concomitant use of allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of their adverse reactions including myelosuppression [see <i>Warnings and Precautions (5.4)</i>].
<i>Intervention</i>	Reduce the dosage of mercaptopurine or azathioprine as recommended in the respective prescribing information.
Pegloticase	
<i>Clinical Impact</i>	Concomitant use of Allopurinol Sodium for Injection and pegloticase may potentially blunt the rise of serum uric acid levels and increase the risk of pegloticase related anaphylaxis in patients whose uric acid level increase to above 6 mg/dL.
<i>Intervention</i>	Discontinue and do not institute Allopurinol Sodium for Injection therapy during treatment with pegloticase.
Theophylline	
<i>Clinical Impact</i>	Concomitant use of allopurinol doses greater than or equal to 600 mg/day may decrease the clearance of theophylline.

<i>Intervention</i>	Monitor and adjust theophylline doses as reflected in the prescribing information.
Uricosuric Agents	
<i>Clinical Impact</i>	Uricosuric agents increase the excretion of the active allopurinol metabolite oxypurinol. Concomitant use with uricosuric agents decreases oxypurinol exposure which may reduce the inhibition of xanthine oxidase by oxypurinol and increases the urinary excretion of uric acid.
<i>Intervention</i>	Monitor uric acid levels due to the increased chance of hypouricemic effects.
Warfarin	
<i>Clinical Impact</i>	Allopurinol may inhibit the metabolism of warfarin, possibly enhancing its anticoagulant effect.
<i>Intervention</i>	Patients on concomitant therapy should be monitored for excessive anticoagulation. The INR should be checked frequently and warfarin dosage adjusted accordingly when allopurinol is added to warfarin therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, Allopurinol Sodium for Injection may cause fetal harm when administered to a pregnant woman. Adverse developmental outcomes have been described in exposed animals (*see Data*). Allopurinol and its metabolite oxypurinol have been shown to cross the placenta following administration of maternal allopurinol.

Available limited published data on allopurinol use in pregnant women do not demonstrate a clear pattern or increase in frequency of adverse developmental outcomes. Among approximately 50 pregnancies described in published literature, 2 infants with major congenital malformations have been reported with following maternal allopurinol exposure. Advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

There was no evidence of fetotoxicity or teratogenicity in rats or rabbits treated during the period of organogenesis with oral allopurinol at doses up to 200 mg/kg/day and up to 100 mg/kg/day, respectively (about three times the human dose on a mg/m² basis). However, there is a published report in pregnant mice that single intraperitoneal doses of 50 or 100 mg/kg (about 1/3 or 3/4 the human dose on a mg/m² basis) of allopurinol on gestation days 10 or 13 produced significant increases in fetal deaths and teratogenic effects (cleft palate, harelip, and digital defects). It is uncertain whether

these findings represented a fetal effect or an effect secondary to maternal toxicity. In another published study with no reported maternal toxicity, allopurinol administered orally at 15 or 45 mg/kg to pregnant rats during organogenesis caused embryonic resorptions, growth retardation, decreased fetal weight, and skeletal, liver, kidney, and brain abnormalities. In rats, maternal treatment with allopurinol in normoxic pregnancy has been shown to increase the cardiac protein levels of sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2a) in the adult male offspring. The mechanism underlying this effect is not understood. However, this effect was not matched by an increase in left ventricular end diastolic pressure or sympathetic dominance in hearts of adult male offspring of normoxic pregnancy treated with allopurinol.

8.2 Lactation

Risk Summary

Allopurinol and oxypurinol are present in human milk. Based on information from a single case report, allopurinol and its active metabolite, oxypurinol, were detected in the milk of a mother at five weeks postpartum at an estimated relative infant dose of 0.14 and 0.2 mg/kg of allopurinol and between 7.2 to 8 mg/kg of oxypurinol daily. There was no report of effects of allopurinol on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatments with Allopurinol Sodium for Injection and for one week after the last dose.

8.4 Pediatric Use

The safety and effectiveness of Allopurinol Sodium for Injection have been established in approximately 200 pediatric patients. The efficacy and safety profile observed in this patient population were similar to that observed in adults.

8.5 Geriatric Use

Clinical studies of Allopurinol Sodium for Injection did not include sufficient numbers of patients 65 years and older to determine whether they respond differently than younger patients.

8.6 Renal Impairment

Allopurinol and its primary active metabolite, oxypurinol, are eliminated by the kidneys [see *Clinical Pharmacology* (12.3)]. Therefore, changes in renal function will likely increase allopurinol and oxypurinol exposure. In patients with decreased renal function, or who have concurrent illnesses that can affect renal function such as hypertension and diabetes mellitus, perform periodic laboratory parameters of renal function, particularly BUN and serum creatinine or creatinine clearance, should be performed.

In patients with severely impaired renal function or decreased urate clearance, the half-life of oxypurinol in the plasma is greatly prolonged. Reduce the dose of Allopurinol Sodium for Injection in patients with creatinine clearance ≤ 20 mL/min [see *Dosage and Administration* (2.2)]. Patients should be treated with the lowest effective dose, in order to minimize possible side effects.

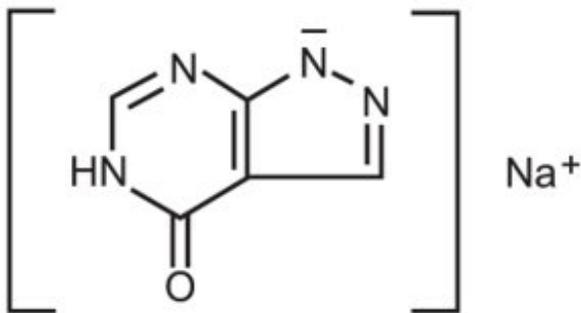
10 OVERDOSAGE

In the management of overdose, there is no specific antidote for Allopurinol Sodium for Injection. Both allopurinol and oxypurinol are dialyzable; however, the usefulness of hemodialysis or peritoneal dialysis in the management of an overdose of Allopurinol Sodium for Injection is unknown.

11 DESCRIPTION

Allopurinol Sodium for Injection, a xanthine oxidase inhibitor, is a sterile, white, lyophilized powder or cake, in a single-dose vial for reconstitution. Each vial contains 500 mg of allopurinol equivalent to 580.7 mg of allopurinol sodium and 162.5 mg of sodium hydroxide as a solubilizer. Sodium hydroxide is also used as a pH adjuster. Allopurinol Sodium for Injection contains no preservatives.

Allopurinol is a xanthine oxidase inhibitor. The chemical name for allopurinol sodium is 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one monosodium salt. It is a white amorphous mass with a molecular weight of 158.09 and molecular formula $C_5H_3N_4NaO$. The structural formula is:



The pKa of allopurinol sodium is 9.31.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Allopurinol is a structural analogue of the natural purine base, hypoxanthine. Allopurinol and its oxypurinol metabolite inhibit xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, the end product of purine metabolism in humans. Allopurinol does not disrupt the biosynthesis of purines.

The action of oral allopurinol differs from that of uricosuric agents, which lower the serum uric acid level by increasing urinary excretion of uric acid. Allopurinol reduces both the serum and urinary uric acid levels by inhibiting the formation of uric acid. The use of allopurinol to block the formation of urates avoids the hazard of increased renal excretion of uric acid posed by uricosuric drugs.

12.2 Pharmacodynamics

Allopurinol reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation in a dose dependent manner. The pharmacological

action of allopurinol is generally believed to be mediated by its oxypurinol metabolite.

Effect on Hypoxanthine and Xanthine

Reutilization of both hypoxanthine and xanthine for nucleotide and nucleic acid synthesis is markedly enhanced when their oxidations are inhibited by allopurinol and oxypurinol. This reutilization does not disrupt normal nucleic acid anabolism because feedback inhibition is an integral part of purine biosynthesis. As a result of xanthine oxidase inhibition, the serum concentration of hypoxanthine plus xanthine in patients receiving allopurinol for treatment of hyperuricemia is usually in the range of 0.3 to 0.4 mg/dL compared to a normal level of approximately 0.15 mg/dL. A maximum of 0.9 mg/dL of these oxypurines has been reported when the serum urate was lowered to less than 2 mg/dL by high doses of allopurinol. These values are far below the saturation levels, at which point their precipitation would be expected to occur (above 7 mg/dL). The increased xanthine and hypoxanthine in the urine in patients who were treated with oral allopurinol have not been accompanied by problems of nephrolithiasis; however, there are isolated case reports of xanthine crystalluria.

Drug Interaction Studies

Fluorouracil

Based on non-clinical data, allopurinol may decrease anti-tumor activity due to suppression of phosphorylation of 5-fluorouracil.

Pegloticase

Concomitant use of Allopurinol Sodium for Injection and pegloticase may potentially blunt the rise of serum uric acid levels required for monitoring the safe use of pegloticase.

Cytotoxic Agents

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease, except leukemia, in the presence of allopurinol.

Thiazide Diuretics

Reports that the concomitant administration of allopurinol and thiazide diuretics contributed to increased allopurinol toxicity were reviewed; however, a causal mechanism or cause-and-effect relationship was not found.

12.3 Pharmacokinetics

Following single 100 mg and 300 mg intravenous and oral administration of Allopurinol Sodium for Injection, the relative intravenous C_{max} was approximately 3-fold and 3.8-fold and AUC_{0-inf} was approximately 1.9-fold higher for allopurinol at both dosages, respectively. The relative intravenous oxypurinol C_{max} and AUC_{0-inf} was approximately 1 compared to oral administration at both dosages.

The C_{max} and AUC_{0-inf} for both allopurinol and oxypurinol following intravenous administration of Allopurinol Sodium for Injection were dose proportional in the dose range of 100 to 300 mg.

Distribution

The steady-state allopurinol volume of distribution (mean \pm S.D.) is approximately 0.87 ± 0.13 L/Kg following intravenous administration.

Elimination

The half-life (mean \pm S.D.) of allopurinol and oxypurinol are approximately 1.21 ± 0.33 and 23.5 ± 4.5 hours following intravenous administration, respectively. The net renal clearance of oxypurinol about 30 mL/min.

Metabolism

Allopurinol is a weak CYP1A2 inhibitor. Allopurinol is rapidly eliminated from the systemic circulation primarily via oxidative metabolism to oxypurinol.

The oxypurinol (alloxanthine) metabolite is also a xanthine oxidase inhibitor and is present in systemic circulation in much higher concentrations and for a much longer period than allopurinol. In general, the ratio of the area under the plasma concentration vs time curve ($AUC_{0-\infty}$) between oxypurinol and allopurinol was in the magnitude of 30 to 40.

Excretion

Approximately 12% of an allopurinol intravenous dose was excreted unchanged, 76% excreted as oxypurinol, and the remaining dose excreted as riboside conjugates in the urine. Oxypurinol was primarily eliminated unchanged in urine by glomerular filtration and tubular reabsorption.

Drug Interaction Studies

Capecitabine

Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease capecitabine efficacy.

Cyclosporine

Concomitant use of allopurinol increases cyclosporine concentrations which may increase the risk of adverse reactions.

Mercaptopurine or Azathioprine

Allopurinol inhibits xanthine oxidase mediated metabolism of mercaptopurine and azathioprine. Concomitant use of allopurinol increases the exposure of either mercaptopurine or azathioprine which may increase the risk of their adverse reactions including myelosuppression.

Theophylline

Concomitant use of allopurinol doses greater than or equal to 600 mg/day may decrease the clearance of theophylline.

Uricosuric Agents

Uricosuric agents increase the excretion of the active allopurinol metabolite oxypurinol. Concomitant use with uricosuric agents decreases oxypurinol exposure which may reduce the inhibition of xanthine oxidase by oxypurinol and increases the urinary excretion of uric acid.

Warfarin

Allopurinol may inhibit the metabolism of warfarin, possibly enhancing its anticoagulant effect.

12.5 Pharmacogenomics

The HLA-B*58:01 allele is a genetic marker for severe skin reactions indicative of hypersensitivity to allopurinol [see *Warnings and Precautions (5.1)*]. The frequency of the HLA-B*58:01 allele ranges from 8 to 10% in Han Chinese populations, about 8% in Thai populations, and about 6% in Korean populations based upon published literature and available databases. The frequency of the HLA-B*58:01 allele is about 4% in Blacks, about 1-2 % in indigenous peoples of the Americas and Hispanic populations, and <1% in people from European descent and Japanese.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Allopurinol was administered at doses up to 20 mg/kg/day to mice and rats for the majority of their life span. No evidence of carcinogenicity was seen in either mice or rats (at doses about 1/6 or 1/3 the recommended human dose on a mg/m² basis, respectively).

Allopurinol administered intravenously to rats (50 mg/kg) was not incorporated into rapidly replicating intestinal DNA. No evidence of clastogenicity was observed in an in vivo micronucleus test in rats, or in lymphocytes taken from patients treated with allopurinol (mean duration of treatment 40 months), or in an in vitro assay with human lymphocytes.

Allopurinol oral doses of 20 mg/kg/day had no effect on male or female fertility in rats or rabbits (about 1/3 or 1/2 the human dose on a mg/m² basis, respectively).

14 CLINICAL STUDIES

A compassionate use trial of Allopurinol Sodium for Injection conducted in the United States from 1977 through 1989 included 718 evaluable patients with malignancies requiring treatment with cytotoxic chemotherapy who were unable to ingest or retain oral medication. Of these patients, 411 had established hyperuricemia and 307 had normal serum urate levels at the time that treatment was initiated. Normal serum uric acid levels were achieved in 68% of the former (reduction of serum uric acid was documented in 93%), and were maintained throughout chemotherapy in 97% of the latter. Because of the study design, it was not possible to assess the impact of the treatment with Allopurinol Sodium for Injection on the clinical outcome of the patient groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

STERILE SINGLE DOSE VIAL FOR INTRAVENOUS INFUSION.

Allopurinol Sodium for Injection, 50 mL flint glass vials with rubber stoppers each containing allopurinol sodium equivalent to 500 mg of allopurinol (white lyophilized powder), individually boxed, (**NDC 0143-9533-01**).

Store unreconstituted powder at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Skin Rash and Hypersensitivity

Inform patients that Allopurinol Sodium for Injection may increase the risk of serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS). Instruct the patient to be alert for skin rash, blisters, fever or other signs and symptoms of these hypersensitivity reactions. Advise patients to stop the Allopurinol Sodium for Injection immediately if they develop any type of rash and seek medical attention [see *Warnings and Precautions (5.1)*].

Renal Function Impairment

Advise patients to stay well hydrated (e.g., 2 liters of liquid per day) while taking Allopurinol Sodium for Injection [see *Warnings and Precautions (5.2)*].

Hepatotoxicity

Advise patients of the risk of hepatotoxicity and to report any signs and symptoms of liver failure, including jaundice, pruritus, bleeding, bruising, or anorexia to their healthcare provider [see *Warnings and Precautions (5.3)*].

Myelosuppression

Advise patients of the risk of myelosuppression and to report any signs and symptoms of infection, fever, bleeding, shortness of breath, or significant fatigue to their healthcare provider [see *Warnings and Precautions (5.4)*].

Drowsiness

Inform patients that drowsiness has been reported in patients taking Allopurinol Sodium for Injection and to be cautious when engaging in activities where alertness is mandatory [see *Warnings and Precautions (5.5)*].

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with Allopurinol Sodium for Injection [see *Use in Specific Populations (8.1)*].

Lactation

Advise women not to breastfeed during treatment with Allopurinol Sodium for Injection for one week after the last dose. [see *Use in Specific Populations (8.2)*].

For Product Inquiry call 1-877-845-0689.

Manufactured by

HIKMA FARMACÊUTICA (PORTUGAL), S.A.

Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem SNT, PORTUGAL

Distributed by

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

Revised March 2022

PIN408-WES/4

PRINCIPAL DISPLAY PANEL - 500 mg/vial

NDC 0143-9533-01 Rx only

Allopurinol Sodium

for Injection

500 mg per vial

For Intravenous Infusion

Sterile Single Use Vial

NDC 0143-9533-01 Rx only

**Allopurinol Sodium
for Injection**

500 mg per vial

**For Intravenous
Infusion**

Sterile Single Use Vial

Preparation of Solution: Inject 25 mL Sterile Water for Injection into vial. Swirl vial until solution results. The solution should be stored at 20° to 25°C (68° to 77°F) and administration should begin within 10 hours after reconstitution. Further dilution is required before intravenous administration. See Package insert for additional reconstitution instructions and for Dosage and Administration. **Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].** Each vial contains allopurinol sodium equivalent to 500 mg of allopurinol.

Mfd by: HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Distr. by: Hikma, Berkeley Heights, NJ 07922

(01)00301439533016
PLB927-WES/2

Lot:
Exp:

NDC 0143-9533-01 Rx only

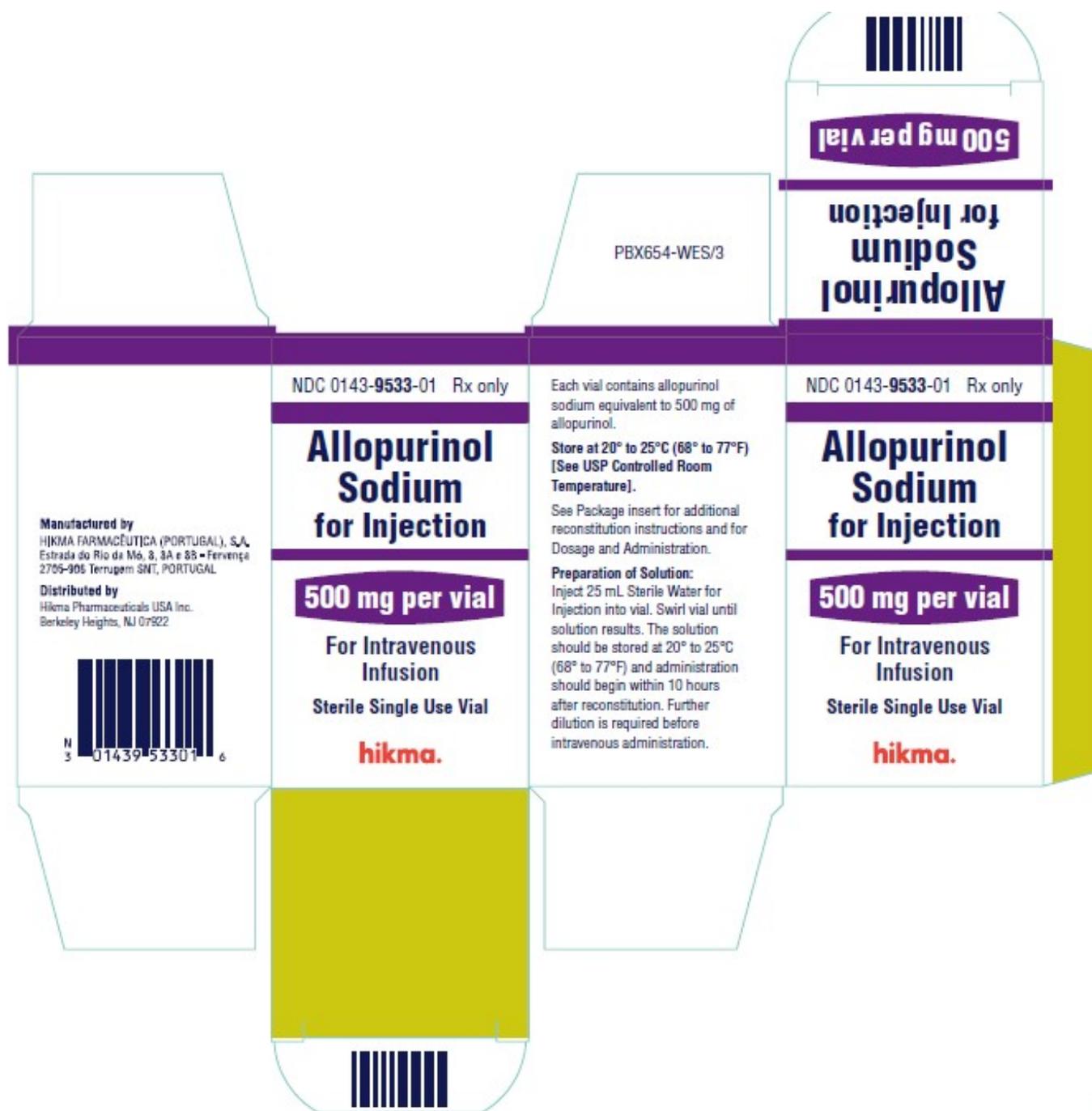
Allopurinol Sodium

for Injection

500 mg per vial

For Intravenous Infusion

Sterile Single Use Vial



ALLOPURINOL SODIUM

allopurinol sodium injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0143-9533
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ALLOPURINOL SODIUM (UNII: 428673RC2Z) (ALLOPURINOL - UNII:63CZ7GJN5I)	ALLOPURINOL	500 mg in 25 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9533-01	1 in 1 BOX, UNIT-DOSE	09/01/2004	
1		25 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076870	09/01/2004	

Labeler - Hikma Pharmaceuticals USA Inc. (001230762)

Revised: 3/2022

Hikma Pharmaceuticals USA Inc.