Allopurinol
Llanol®
100 mg & 300 mg Tablet
Antigout

℞

FORMULATION
Each tablet contains:
Allopurinol……100 mg or 300 mg

PRODUCT DESCRIPTION
Allopurinol (Llanol®) 100 mg Tablet: Round, light yellow tablet, with a small letter "t" embossed on one side, and flat, plain, bevel-edged on the other side
Allopurinol (Llanol®) 300 mg Tablet: Round, dark yellow tablet, with a small letter "t" embossed on one side, and flat, plain, bevel-edged on the other side

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Allopurinol is a structural analogue of hypoxanthine, the natural purine base. Allopurinol and its active metabolite oxipurinol (alloxanthine), lower uric acid levels in plasma and urine by inhibiting xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and from xanthine to uric acid, the end product of purine metabolism. Inhibition of this enzyme accounts for the major pharmacological effects of allopurinol.
In addition, allopurinol increases reutilization of oxypurine precursors such as hypoxanthine and xanthine for nucleotide and nucleic acid synthesis via an action involving the enzyme hypoxanthine- guanine phosphorbosyl-transferase (HGPRTase). The increase in nucleotide concentration leads to feedback inhibition of *de novo* purine synthesis. In this way, allopurinol decreases uric acid concentrations in both serum and urine.
Thus, allopurinol reduces the plasma concentration and urinary excretion of uric acid and increases the plasma concentration and renal excretion of the more soluble oxypurine precursors.

PHARMACOKINETICS
Allopurinol is rapidly absorbed from the upper gastrointestinal tract after oral administration. Its mean bioavailability varies from 67% to 90%. The peak serum levels of allopurinol occur approximately 1.5 hours after oral administration, but fall rapidly and are barely detectable after six hours. The peak serum levels of oxipurinol occur within 3 to 5 hours after oral dosing and are more sustained.
Allopurinol is negligibly bound to plasma proteins and, therefore, variations in protein binding do not significantly alter clearance. Allopurinol's apparent volume of distribution is approximately 1.6 L/kg, which suggests its relatively extensive uptake by tissues. Tissue concentrations of allopurinol have not been reported in humans, but it is likely that allopurinol and oxipurinol will be present in the highest concentrations in the liver and intestinal mucosa where xanthine oxidase activity is high. There is gradual accumulation of oxipurinol with continued administration of allopurinol in patients with normal renal function. Serum oxipurinol levels in such patients are in the range of 5 to 10 mg/L on a daily dose of allopurinol 300 mg. At steady state, comparable peak allopurinol levels are between 1.5 and 2 mg/L. The area under the curve (AUC) determination for oxipurinol is approximately 20-fold greater than that of allopurinol over a 24-hour period. Allopurinol and its metabolites have been detected in human milk.
Approximately 20% of a dose of allopurinol is excreted in the feces in 48 to 72 hours. Elimination of allopurinol is mainly by metabolic conversion to oxipurinol (in the liver and probably also in the intestines) by xanthine oxidase and aldehyde oxidase, with less than 10% of unchanged drug excreted in the urine. Allopurinol has a plasma half-life of about 1 to 2 hours, and is cleared primarily by glomerular filtration. Oxipurinol is eliminated unchanged in the urine but has a long elimination half-life (13.6 to 29 hours) because it is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

Special Populations:
Renal Insufficiency: Elimination of both allopurinol and oxipurinol is delayed in patients with kidney impairment resulting in higher plasma levels with chronic therapy.
A reduction in dose is required (see **Dosage and Administration**).
Hepatic Insufficiency: The clearance of allopurinol may be reduced in patients with liver disease. A reduction in dose is required (see **Dosage and Administration**).
Elderly: The kinetics of allopurinol in elderly patients is not likely to be altered other than due to deteriorating renal function (see **Warnings and Precautions**).

INDICATIONS
- For the management of patients with signs and symptoms of primary and secondary gout (recurrent acute attacks, arthropathy, tophi, radiographic changes of gout, or associated uric acid nephrolithiasis);
- For the management of patients with leukemia, lymphoma and solid tumor malignancies who are undergoing chemotherapy expected to result in tumor lysis and subsequent elevations of serum and urinary uric acid concentrations. Allopurinol therapy should be discontinued when the potential for hyperuricemia is no longer present;
- For the management of patients with recurrent calcium oxalate renal calculi in males whose urinary urate excretion exceeds 800 mg daily and in females whose urinary urate excretion exceeds 750 mg daily. The use of allopurinol for this condition must be carefully evaluated initially and reevaluated periodically to determine that therapy with the drug is beneficial and outweighs the risks.

DOSAGE AND MODE OF ADMINISTRATION
Dosage of allopurinol varies with the severity of the disease and should be adjusted according to the response and tolerance of the patient.
Dosage of allopurinol may also be adjusted according to results of serum uric acid concentration, which should be maintained within the normal range.
In all patients receiving allopurinol, fluid intake should be sufficient to yield a daily urine output of at least two liters and maintenance of a neutral or, preferably, alkaline urine is desirable to: (1) avoid the possibility of formation of xanthine calculi under the influence of allopurinol therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Management of Gout
Allopurinol is indicated in patients with frequent disabling attacks of gout. Because therapy with allopurinol is not without some serious risks, the drug is not recommended for the management of asymptomatic hyperuricemia.

Optimal treatment of gout requires both nonpharmacological (e.g., weight loss if obese, low purine diet, reduced alcohol intake especially beer) and pharmacological modalities and should be tailored according to:
- Specific risk factors (levels of serum urate, previous attacks, radiographic signs);
- Clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout);
- General risk factors (age, sex, obesity, alcohol consumption, urate elevating drugs, drug interactions, and comorbidity).

Associated comorbidity and risk factors such as hyperlipidemia, hypertension, hyperglycemia, obesity, and smoking should be addressed as an important part of the management of gout.

If shifting a patient from a uricosuric agent to allopurinol, the dose of the uricosuric agent should be gradually reduced over a period of several weeks and the dose of allopurinol gradually increased to the required dose needed to maintain a normal serum uric acid level.

Recommended Allopurinol Adult Oral Dose for the Management of Intercritical Gout and Chronic Tophaceous Gout:

Starting Dose: 100 mg/day two weeks after the pain and swelling of acute gouty arthritis have subsided.
- Dose should be titrated by 50 to 100 mg/day every 2 to 4 weeks to achieve serum uric acid < 6 mg/dL (0.36 mmol/L).
- **Maximum dose of allopurinol is 300 mg/day.**
- Referral to a rheumatologist is recommended if serum uric acid persistently remains > 6 mg/dL despite maximum dose of allopurinol.
- Serum uric acid and serum creatinine should be periodically monitored.

Management of Leukemia, Lymphoma, and Solid Tumor Malignancies

Recommended Adult Dose: 600 to 800 mg/day for 2 to 3 days
It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinization of urine to increase solubility of urinary urate/uric acid. The dose of allopurinol should be in the lower range.
It is advisable to correct existing hyperuricemia and/or hyperuricosuria with allopurinol before commencing cytotoxic therapy.

Management of Recurrent Calcium Oxalate Renal Calculi
Initial Dose: 200 to 300 mg/day in divided doses or as a single dose
Subsequent dosage may be increased or decreased, depending on control of hyperuricosuria assessed by 24-hour urinary urate excretion determination.
Clinical experience shows that patients with recurrent calcium oxalate stones may also benefit from dietary changes such as reduction of animal protein, sodium, refined sugars, oxalate-rich foods, and excessive calcium intake, as well as an increase in oral fluids and dietary fiber.

Recommended Oral Doage in Renal Impairment
Allopurinol and its metabolites are excreted by the kidneys, therefore impairment of renal function may lead to retention of the drug and/or its metabolites. The plasma half-lives of allopurinol and/or its metabolites may, as a consequence, be prolonged.
Dosage should be reduced in patients with impaired renal function to avoid accumulation of allopurinol and its metabolite, oxipurinol.
Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two to three times a week, an alternative dosage schedule of 300 to 400 mg allopurinol immediately after each dialysis with none in the interim should be considered.

• Initial Dose in Renal Impairment:

Creatinine Clearance (mL/minute)	Initial Dose in Patients with Renal Impairment
Less than 10	Not more than 100 mg daily
10 to 20	Not more than 200 mg daily
	Or, as prescribed by a physician.

In patients with severely impaired renal function, 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.

• Maintenance Dose in Renal Impairment:

Creatinine Clearance (mL/minute)	Maintenance Dose in Patients with Renal Impairment
0	100 mg every 3 days
10	100 mg every 2 days
20	100 mg daily
40	150 mg daily
60	200 mg daily
80	250 mg daily
	Or, as prescribed by a physician.

The correct dose and frequency of dosage for maintaining the serum uric acid just within the normal range is best determined by using the serum uric acid level as an index.

CONTRAINDICATIONS
Hypersensitivity to allopurinol or to any component in the product

WARNINGS AND PRECAUTIONS

ALLOPURINOL HYPERSENSITIVITY SYNDROME

Allopurinol should be withdrawn immediately at the first sign of a skin rash or if other evidence of allergic reaction or hypersensitivity occurs. It should be withdrawn immediately and permanently at the first sign of intolerance.
Allopurinol may cause a rare but potentially life-threatening allopurinol hypersensitivity syndrome (AHS) which consists of an erythematous maculopapular rash with desquamation, fever, nephritis, eosinophilia, and worsening of renal function.
Severe hypersensitivity reactions (e.g., exfoliative, urticarial and purpuric lesions) as well as severe cutaneous adverse reactions [e.g., Stevens-Johnson Syndrome (SJS) or erythema multiforme exudativum, Toxic Epidermal Necrolysis (TEN) or Lyell's Syndrome, and/or generalized vasculitis], which may be fatal (deaths associated with allopurinol have been rare and almost always as a result of generalized hypersensitivity), have been reported following the appearance of skin rash. Very rarely, acute anaphylactic shock has been reported. If such reactions occur, which may be at any time during treatment, allopurinol should be withdrawn immediately and permanently. When generalized hypersensitivity reactions occur and a renal and/or hepatic disorder is present, the outcome could be fatal.

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, about 12% in the Korean population and 1 to 2% in individuals of Japanese or European origin. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the patient is a known carrier of HLA-B*5801, the use of allopurinol may be considered if the benefits are thought to exceed risks. Close monitoring 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.

Skin and Subcutaneous Reactions
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. Allopurinol should be withdrawn immediately should such reactions occur.
Angioedema has been reported to occur with and without signs and symptoms of a more generalized hypersensitivity reaction.

Asymptomatic hyperuricemia
Allopurinol is not indicated for the treatment of asymptomatic hyperuricemia. Adequate fluid intake (two liters per day), dietary modification, and management of the underlying cause may treat the condition.
In the general population, asymptomatic hyperuricemia should not be routinely treated with allopurinol. Well-known associated risk factors of hyperuricemia such as dyslipidemia, obesity, metabolic syndrome, psoriasis, malignancies and congestive heart failure should be addressed.
Lifestyle changes are recommended which include appropriate diet and exercise.

Acute gouty attacks
Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated.
As with other uricosuric agents, acute gouty attacks may be precipitated during the first six to 12 months of allopurinol treatment in new patients, and these may persist even when normal or subnormal serum uric acid levels have been attained. The mobilization of urates from tissue deposits, which cause fluctuations in the serum uric acid levels, is thought to be the mechanism of these episodes.

In the absence of contraindications (i.e., gastrointestinal ulcers or renal impairment), colchicine or a suitable anti-inflammatory agent (e.g., nonsteroidal anti-inflammatory drugs or selective cyclooxygenase-2 inhibitors) may be used as prophylaxis for the first three to six months, especially in new patients and in those who had high previous attack rate. Although acute attacks may still occur, these are reported to be shorter in duration and less severe after several months of treatment. Acute gouty attacks may also be prevented by slowly introducing allopurinol treatment (See ***Dosage and Administration***). If acute gouty attacks develop in patients currently taking allopurinol, treatment should proceed with the same dosage while the acute attack is treated with an appropriate anti-inflammatory agent. Ice compress may also be given in combination with pharmacologic agents for relief of joint pain and swelling of acute gouty arthritis.

Xanthine deposition
In conditions where the rate of urate formation is greatly increased (e.g., neoplastic disease and its treatment; Lesch-Nyhan Syndrome), the absolute concentration of xanthine in urine may rise sufficiently in rare cases and allow deposition of xanthine stones in the urinary tract. This risk may be minimized by adequate hydration to achieve optimal urine dilution.

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

Bone marrow depression
There have been reports of bone marrow depression, particularly in patients receiving concomitant drugs which have the potential to cause the reaction (see ***Interactions with Other Medicaments)***. This may occur as early as six weeks to as long as six years after initiation of allopurinol therapy. In patients receiving allopurinol alone, varying degrees of bone marrow depression, affecting one or more cell lines may be observed rarely.

Hepatic Insufficiency
There have been a few cases of reversible clinical hepatotoxicity and asymptomatic increase in serum alkaline phosphatase or serum transaminase observed in patients receiving allopurinol. If patients receiving allopurinol develop anorexia, weight loss, or pruritus, assessment of liver function should be included in the diagnostic evaluation. Periodic liver function tests and complete blood counts are recommended during the early stages of therapy in patients with pre-existing liver disease.

Renal Insufficiency
Since allopurinol and its metabolites are excreted by the kidneys, impaired renal function may lead to retention of the drug and/or its metabolites with consequent prolongation of their plasma half-lives.
Some patients with pre-existing renal disease or poor urate clearance have shown a rise in blood urea nitrogen (BUN) during allopurinol administration. Patients with impaired renal function must be carefully observed while taking allopurinol (particularly during the early stages of therapy) and the dosage decreased or the drug discontinued if evidence of deterioration in renal function occurs and persists.
Renal failure associated with allopurinol use has been reported in patients with hyperuricemia secondary to neoplastic diseases. Concomitant illnesses such as multiple myeloma and congestive myocardial disease were seen in patients whose renal dysfunction increased after allopurinol was started. Renal failure is also frequently associated with gouty nephropathy and rarely with hypersensitivity reactions associated with allopurinol. Albuminuria has been reported in patients who developed clinical gout following chronic glomerulonephritis and chronic pyelonephritis.
Particular care should also be taken in the elderly where renal function may be reduced thus leading to retention of the drug and its metabolites with consequent prolongation of action. Renal function tests should be performed before starting allopurinol therapy. Renal function tests, particularly BUN, serum creatinine, or creatinine clearance, should be periodically assessed in patients with decreased renal function or those with co-morbidities that may affect renal function (e.g., hypertension, diabetes). Dosage should be reassessed in these patients.

Cardiovascular Disorders
Allopurinol should be used with caution in patients under treatment for hypertension or cardiac insufficiency, such as with diuretics or angiotensin-converting-enzyme (ACE) inhibitors, since such patients may have some concomitant impairment of kidney function.

Thyroid disorders
In a long-term open-label extension study, increases in thyroid-stimulating hormones (TSH) levels have been observed in patients during allopurinol therapy. Thus, allopurinol should be used with caution in patients with impaired thyroid function.

Hemochromatosis
A study revealed that reversible rises in serum iron levels and reduction in total iron binding capacity occurred in patients receiving 500 to 600 mg of allopurinol daily. These effects returned to normal when dosage was reduced to 300 mg daily.
Caution should be exercised in the administration of allopurinol to patients with abnormal iron storage, including hemochromatosis.

Information to Patients
Patients undergoing allopurinol treatment should be informed of the following:
- Allopurinol should be discontinued immediately at the first sign of a skin rash, painful urination, blood in the urine, irritation of the eyes or swelling of the lips or mouth. Patients should also be advised to consult their physician immediately if such reactions occur.
- Fluid intake (2 liters/day) during therapy is recommended to prevent renal stones;
- If a single dose of allopurinol is occasionally missed, there is no need to double the dose at the next scheduled time;
- Patients should be reminded that there may be certain risks associated with the concomitant use of allopurinol and dicumarol, sulfinpyrazone, mercaptopurine, azathioprine, ampicillin, amoxicillin, or thiazide diuretics.
- Allopurinol can cause drowsiness and can affect coordination. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are sure that allopurinol does not adversely affect performance;
- In order to minimize gastric irritation, patients should take allopurinol after a meal.
- Patients should not take allopurinol without the advice of a physician. Regular follow-up with a physician is recommended.

Effects on Ability to Drive or Use Machines
Allopurinol may cause somnolence, dizziness, ataxia, and vertigo. Since allopurinol has the potential to impair their ability to perform activities requiring mental alertness, patients should be cautioned about operating hazardous machinery and during motor vehicles.

INTERACTIONS WITH OTHER MEDICAMENTS
- **Ampicillin/Amoxicillin:** Increased frequency of skin rash occurred among patients concurrently taking allopurinol with ampicillin or amoxicillin compared to those taking allopurinol, amoxicillin, or ampicillin alone. The cause of the interaction is not yet established.
  It is recommended that the combination be avoided, and alternative antibiotics be administered in patients receiving allopurinol.
- **Angiotensin-converting-enzyme (ACE) inhibitors (e.g., captopril):** Concomitant use of captopril and allopurinol may predispose to hypersensitivity reactions such as Stevens-Johnson syndrome. Patients on the combination should be monitored and if a reaction occurs, the use of these drugs should be discontinued.
- **Antacids:** Antacids (e.g., aluminum hydroxide) may decrease the blood levels and reduce the therapeutic effects of allopurinol when taken concomitantly.
- **Anticoagulants (e.g., warfarin and other coumarin derivatives):** Allopurinol may prolong the elimination half-life of coumarin, but there is no evidence that this has any clinical significance. However, careful monitoring is advised for all patients taking anticoagulants.
- **Chlorpropamide:** Allopurinol or its metabolites may compete with chlorpropamide for excretion in the renal tubule. Concomitant administration of these drugs in patients with poor renal function may increase the risk of prolonged hypoglycemic effect of chlorpropamide.
- **Cyclophosphamide and other cytotoxic agents (e.g., doxorubicin, bleomycin, procarbazine, mechloroethamine, bendamustine):** In the presence of allopurinol, enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease other than leukemia. However, allopurinol did not appear to increase the toxic reaction of these cytotoxic agents in a well-controlled study of patients treated with cyclophosphamide, doxorubicin, bleomycin, procarbazine, and/or mechloroethamine (mustine hydrochloride).
- **Ciclosporin:** Allopurinol may increase the plasma concentration of ciclosporin. The risk of enhanced ciclosporin toxicity should be considered during the coadministration of these drugs. If these drugs are coadministered, ciclosporin blood levels should be monitored, and possible adjustments of cyclosporin dosage should be considered.
- **Didanosine:** The mean peak plasma concentrations (Cmax) and AUC values of didanosine were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting its terminal half-life in healthy volunteers and in patients with human immunodeficiency virus (HIV). Concomitant use of these drugs is generally not recommended. If concomitant use is unavoidable, a dose reduction of didanosine may be required, and patients should be closely monitored.
- **Diuretics:** Thiazide diuretics and ethacrynic acid may elevate serum oxipurinol concentrations, resulting to increased risk of serious allopurinol toxicity, including hypersensitivity, particularly in patients with renal impairment. Renal function of patients concurrently taking these medications should be monitored, even in the absence of renal failure. If reduced renal function is detected in these patients, dosage levels should be adjusted conservatively. There have been reports of increased serum urate and plasma oxipurinol following the co-administration of allopurinol and furosemide.
- **Drugs that increase serum urate concentrations (e.g., pyrazinamide, diazoxide, alcohol, mecylamine):** If drugs that increase the serum urate concentrations are coadministered, increase in allopurinol dosage may be required.
- **Mercaptopurine or azathioprine:** Allopurinol inhibits the oxidative metabolism of azathioprine and mercaptopurine by xanthine oxidase, resulting to the prolonged activity of these drugs. If allopurinol is used concomitantly, only one-third or one-fourth of the usual doses of azathioprine or mercaptopurine should be initially administered; doses of azathioprine or mercaptopurine should be adjusted according to the patient's response and toxic effects.
- **Phenytoin:** Hepatic oxidation of phenytoin may be inhibited by allopurinol, but the clinical significance of this interaction has not been determined.
- **Theophylline:** Inhibition of theophylline metabolism has been reported with relatively high doses of allopurinol (i.e., 300 mg twice a day). The mechanism of the interaction may be explained by xanthine oxidase being involved in the biotransformation of theophylline in man. Theophylline levels should be monitored in patients starting or increasing allopurinol therapy.
- **Uricosurics and Salicylates:** Drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxipurinol; this may result in decreased therapeutic activity of allopurinol.
- **Vidarabine (Adenine Arabinoside):** The plasma half-life of vidarabine is increased in the presence of allopurinol. If used concomitantly, extra caution is necessary to determine enhanced toxic effects.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy
Pregnancy Category C. There is no adequate evidence on the safety of allopurinol in pregnant women. Allopurinol should be used only if there is no safer alternative, when the disease itself carries risk for the mother or fetus, and if the potential benefits outweigh the possible risk to the fetus.
Lactation
Since allopurinol and oxypurinol are distributed into milk, the drug should not be used by breastfeeding women.

Pediatric Use
It is generally recommended that the use of allopurinol be restricted to children with hyperuricemia secondary to neoplastic disease, cancer chemotherapy, or genetic disorders of purine metabolism (i.e., Lesch-Nyhan syndrome).
Use in Elderly
Appropriate dosage of allopurinol in geriatric patients should be selected with caution because of the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease and drug therapy in these patients.

Renal Impairment
Since allopurinol and its metabolites are excreted by the kidneys, impaired renal function may lead to retention of the drug and/or its metabolites.
Patients with chronic renal impairment may be at a higher risk of developing hypersensitivity reactions such as SJS/TEN. Close monitoring should be practiced to detect signs of hypersensitivity syndrome or SJS/TEN. Patients should also be instructed of the need to stop treatment immediately and permanently at the first manifestations of symptoms.
Increases in blood urea nitrogen (BUN) have been observed in some patients with pre-existing renal disease or with poor urate clearance. Allopurinol should be used with caution in patients with impaired renal function and they should be carefully monitored, particularly during the initial phases of allopurinol therapy. The dosage of allopurinol should be reduced in patients with renal impairment (see **Dosage and Administration**).

Hepatic Impairment
The dosage of allopurinol should be reduced in patients with hepatic impairment (See **Dosage and Administration**). Liver function tests should be conducted in patients with pre-existing liver disease before and periodically during allopurinol therapy, especially during the early stages of therapy.

UNDESIRABLE EFFECTS
The most common adverse effects of allopurinol are rashes, which are generally maculopapular or pruritic, and may be purpuric. The incidence of skin rashes may be increased in patients with renal insufficiency. More serious hypersensitivity reactions, including exfoliative rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) may occur. Acute attacks of gout were also reported. Gastrointestinal adverse effects, such as diarrhea and nausea, are common, especially if allopurinol is taken before meals or on an empty stomach. Increases in liver enzymes and serum alkaline phosphatase were also observed.
Infections and infestations: Cellulitis, furunculosis, furunculosis of the nose, infections, sepsis, septic shock, urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps): Angioimmunoblastic lymphadenopathy, tumor lysis syndrome
Blood and lymphatic system disorders: Agranulocytosis, anemia, aplastic anemia, blast crisis, bone marrow aplasia, bone marrow suppression, clotting abnormalities, disseminated intravascular coagulation, ecchymosis, eosinophilia, eosinophilia hepato-splenomegaly, eosinophilic fibrohistiocytic bone marrow lesion, granulocytopenia, hemolytic anemia, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, neutropenia, pancytopenia, pseudolymphoma, reticulocytosis, splenomegaly, thrombocytopenia
Immune system disorders: Anaphylactic shock, angioedema, bronchospasm, erythema multiforme, hypersensitivity, pure red cell aplasia
Metabolism and nutrition disorders: Anorexia, diabetes mellitus, edema, electrolyte imbalance, hypercalcemia, hyperglycemia, hyperkalemia, hyperlipidemia, hypernatremia, hyperphosphatemia, hyperuricemia, hypervolemia, hypokalemia, hypomagnesemia, hyponatremia, hypovolemia, lactic acidosis, metabolic acidosis, water intoxication
Psychiatric disorders: Confusion, depression, drowsiness, insomnia, somnolence
Nervous system disorders: Agitation, amnesia, ataxia, cerebral infarction, cerebrovascular accident, changes in mental status, coma, dizziness, dystonia, epilepsy, foot drop, generalized seizure, headache, myoclonus, neuritis (including peripheral), neuropathy (including peripheral), paralysis, paresthesia, seizures, status epilepticus, tremor, twitching, vertigo
Eye disorders: Amblyopia, cataract, conjunctivitis, iritis, macular changes, macular retinitis, maculopathy, optic neuritis, visual disturbance, visual impairment
Ear and labyrinth disorders: Deafness, tinnitus
Cardiac disorders: Angina (pectoris), bradycardia, cardiac failure, cardiorespiratory arrest, congestive heart failure, pericarditis, ventricular fibrillation
Vascular disorders: Flushing, hemorrhage, hypersensitivity vasculitis, hypertension, hypotension, necrotizing angiitis, peripheral vascular disease, thrombophlebitis, vasculitis, vasodilation
Respiratory, thoracic, and mediastinal disorders: Acute respiratory distress syndrome, apnea, asthma, epistaxis, pharyngitis, pulmonary embolism, respiratory failure, respiratory insufficiency, rhinitis
Gastrointestinal disorders: Abdominal distention, [intermittent] abdominal pain, ageusia, change in bowel habit, constipation, dysgeusia, dyspepsia, flatulence, gastritis, gastrointestinal hemorrhage, hematemesis, hemorrhagic pancreatitis, intestinal obstruction, pancreatitis, proctitis, salivary gland swelling, steatorrhea, stomatitis, tongue edema, vomiting
Hepatic and hepatobiliary disorder: Cholestatic jaundice, granulomatous hepatitis, hepatic dysfunction, hepatic necrosis, hepatitis, hepatocellular damage, hepatocellular necrosis, hepatomegaly, hepatotoxicity, hyperbilirubinemia, jaundice, liver failure, vanishing bile duct syndrome
Skin and subcutaneous tissue disorders: Alopecia, dermatitis (eczematoid, erythematous, exfoliative, hemorrhagic, purpuric, vesicobullous), drug eruption, eczema, hair color changes, hair discolored, ichthyosis, lichen planus, onycholysis, pruritus, purpura, rash (erythematous, scaly), skin edema, skin exfoliation, skin granuloma, toxic pustuloderma, urticaria
Musculoskeletal and connective tissue disorders: Arthralgia, gouty arthritis, hypotonia, myalgia, myopathy
Renal and urinary disorders: Albuminuria, arterial nephrosclerosis, azotemia, bilateral ureteral obstruction, decreased renal function, dysuria, glycosuria, hematuria, impaction of partly dissolved renal uric acid stones in the ureter, interstitial nephritis, nephritis, oliguria, oxipurinol stones, pyelonephritis, renal colic, renal failure, renal impairment, uremia, xanthine stone deposition
Reproductive system and breast disorders: Erectile dysfunction, gynecomastia (male), impotence, infertility (male), libido decreased, nocturnal emission
General disorders and administration site conditions: Asthenia, chills, death, diaphoresis, face edema, fever, hyperhidrosis, malaise, mucositis
Investigations: Abnormal electrocardiogram (ECG), abnormal liver function test results, decreased blood urea nitrogen, decreased prothrombin levels, decreased sulfobromophthalein excretion, decreased venous pressure, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood urea nitrogen, increased creatinine, increased respiratory rate, increased urinary urobilinogen, liver biopsy findings of eosinophilia and noncaseating granulomas

OVERDOSE AND TREATMENT
Ingestion of 20 g allopurinol resulted in nausea, vomiting, diarrhea, and dizziness in one patient who eventually recovered following general supportive measures. However, ingestion of larger doses of allopurinol (i.e., up to 22.5 g) without adverse effects has also been reported.
Massive absorption of allopurinol may result to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine and/or azathioprine are being concomitantly administered.
There is no specific antidote for allopurinol in the management of overdosage. The drug should be withdrawn, and patients should be monitored. Normal supportive measures should be provided. Adequate hydration should be guaranteed to maintain optimum diuresis to facilitate urinary excretion of allopurinol and its metabolites. If other forms of acute distress occurred, gastric lavage should be considered; otherwise, symptomatic treatment should be provided.
Hemodialysis may be used if necessary.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Allopurinol (Llanol®) 100 mg Tablet, flex foil pack of 4's (box of 100 tablets)
Allopurinol (Llanol®) 300 mg Tablet, flex foil pack of 4's (box of 100 tablets)

Store at temperatures not exceeding 30°C.
Keep the product out of reach and sight of children.

Date of First Authorization: May 1972
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Registration Numbers:
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