hovid-Allopurinol Tablet 100mg

VIALLxx-0 (FEO)2

DESCRIPTION
Round, white uncoated tablet, bevel-edged, flat faces, "HD" and break-bar embossed on the same face.

COMPOSITION
Allopurinol Tablet B.P. 100mg

PHARMACODYNAMICS
Allopurinol is a structural isomer of hypoxanthine. The affinity of allopurinol for xanthine oxidase is much greater than that of xanthine. Allopurinol is of value in the treatment of gout because it is an inhibitor of xanthine oxidase, the enzyme responsible for converting xanthine and hypoxanthine to uric acid.

Both Allopurinol and its major metabolite alloxanthine (oxypurinol) inhibit xanthine oxidase. Xanthine and hypoxanthine are more easily excreted than uric acid. Allopurinol decreases the rate of formation and the blood levels of uric acid considerably but does not appreciably affect that of the more water soluble xanthine. Body uric acid is therefore decreased by reducing uric acid formation. By lowering the serum concentration of uric acid below its solubility limits, allopurinol promotes the resolution of tophi and uric acid crystals.

PHARMACOKINETICS
Absorption: Allopurinol is rapidly absorbed from the upper gastrointestinal tract and appears to be about
80% to 90% absorbed.

Blood concentration: 100 mg of Allopurinol administered thrice daily produced plasma concentrations of alloxanthine (oxipurinol), the major metabolite of allopurinol, of 5 to 15 microgram/ml, after one week.

Half-life: Plasma half-life is about 1 to 3 hours for allopurinol and 12 to 30 hours for alloxanthine (oxipurinol).

Protein Binding: Neither allopurinol nor its metabolite, oxipurinol, is bound to plasma proteins.

Distribution: Allopurinol is well distributed throughout the body water. Both allopurinol and alloxanthine (oxipurinol) are not bound to serum proteins and are excreted mainly in urine. Alloxanthine (oxipurinol) may accumulate in renal function impairment.

Metabolism: Allopurinol is rapidly oxidized the liver to its active metabolite, alloxanthine (oxipurinol).

Excretion: About 30% of a dose is excreted unchanged in the urine, whilst 45 to 65% is excreted as alloxanthine (oxipurinol).

INDICATIONS
Allopurinol is indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition has already occurred (e.g. gouty arthritis, skin tophi, nephrolithiasis) or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy).

The main clinical conditions where urate/uric acid deposition may occur are: idiopathic gout; uric acid lithiasis; acute uric acid nephropathy; neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously, or after cytotoxic therapy; certain enzyme disorders which lead to overproduction of urate, for glucose-6-phosphatase including glycogen storage disease; phosphoribosylpyrophosphate synthetase, phosphoribosylpyrophosphate amidotransferase; adenine phosphoribosyltransferase.

Allopurinol is indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyltransferase.
Allopurinol is indicated for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary and similar measures have failed.

CONTRAINDICATIONS
Allopurinol should not be administered to individuals known to be hypersensitive to allopurinol or to any of the components of formulation.

WARNINGS AND PRECAUTIONS
Allopurinol hypersensitivity reactions can manifest in many different ways, including maculopapular exanthema, hypersensitivity syndrome (also known as DRESS) and SJS/TEN. These reactions are clinical diagnoses, and their clinical presentations remain the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately. Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions.

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

SJS/TEN can still occur in patients who are found to be negative for HLA-B*5801 irrespective of their ethnic origin.

Chronic renal impairment
Patients with chronic renal impairment and concomitant diuretic use, in particular thiazides, may be at increased risk of developing hypersensitivity reactions including SJS/TEN associated with allopurinol. Extra vigilance for the signs of hypersensitivity syndrome or SJS/TEN is required and the patient should be informed of the need to stop treatment immediately and permanently at the first appearance of symptoms.

Hepatic or renal impairment
Reduced doses should be used in patients with hepatic or renal impairment. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in this group.

Asymptomatic hyperuricaemia
Asymptomatic hyperuricaemia per se is generally not considered an indication for use of Allopurinol. Fluid and dietary modification with management of the underlying cause may correct the condition.

Acute gouty attacks
Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated.

In the early stages of treatment with Allopurinol, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine for at least one month. The literature should be consulted for details of appropriate dosage and precautions and warnings.

If acute attacks develop in patients receiving allopurinol, treatment should continue at the same dosage while the acute attack is treated with a suitable anti-inflammatory agent.

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

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.

Thyroid disorders
Increased TSH values (>5.5 µIU/mL) were observed in patients on long-term treatment with allopurinol (5.8%) in a long term open label extension study. Caution is required when allopurinol is used in patients with alteration of thyroid function.

Lactose
Allopurinol tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Warning
Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction.
Hypersensitivity to allopurinol usually appears after some weeks of therapy, and more rarely immediately after beginning treatment.

In some instances, a skin rash may be followed by severe reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity and even death.

Symptoms of Overdose and Treatments:
Ingestion of up to 22.5 g allopurinol without adverse effect has been reported. Symptoms and signs including nausea, vomiting, diarrhea and dizziness have been reported in a patient who ingested 20 g allopurinol. Recovery followed general supportive measures. Massive absorption of Allopurinol may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless affecting concomitant medication, especially with 6-mercaptopurine and/or azathioprine. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary haemodialysis may be used.

Interactions with Other Medicaments
6-mercaptopurine and azathioprine
Azathioprine is metabolised to 6-mercaptopurine which is inactivated by the action of xanthine oxidase. When 6-mercaptopurine or azathioprine is given concurrently with Allopurinol, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.

Vidarabine (Adenine Arabinoside)
Evidence suggests that the plasma half-life of vidarabine is increased in the presence of allopurinol. When the two products are used concomitantly extra vigilance is necessary, to recognise enhanced toxic effects.

Salicylates and uricosuric agents
Oxipurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of Allopurinol, but the significance needs to be assessed in each case.

Chlorpropamide
If Allopurinol is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity because allopurinol and chlorpropamide may compete for excretion in the renal tubule.

Coumarin anticoagulants
There have been rare reports of increased effect of warfarin and other coumarin anticoagulants when co-administered with allopurinol, therefore, all patients receiving anticoagulants must be carefully monitored.

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

Theophylline
Inhibition of the metabolism of theophylline has been reported. 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.

Ampicillin/Amoxicillin
An increase in frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the reported association has not been established. However, it is recommended that in patients receiving allopurinol an alternative to ampicillin or amoxicillin is used where available.

Cytostatics
With administration of allopurinol and cytostatics (e.g. cyclophosphamide, doxorubicin, bleomycin, procarbazine, alkyl

halogenides), blood dyscrasias occur more frequently than when these active substances are administered alone.
Blood count monitoring should therefore be performed at regular intervals.

Ciclosporin
Reports suggest that the plasma concentration of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered if the drugs are co-administered.

Didanosine
In healthy volunteers and HIV patients receiving didanosine, plasma didanosine Cmax and AUC values were approximately doubled with concomitant allopurinol treatment (300 mg daily) without affecting terminal half-life. Co-administration of these 2 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
An interaction between allopurinol and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported.

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

Angiotensin-converting-enzyme (ACE) inhibitors
An increased risk of hypersensitivity has been reported when allopurinol is given with ACE inhibitors especially in renal impairment.

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

PREGNANCY AND LACTATION
Pregnancy
There is inadequate evidence of safety of Allopurinol in human pregnancy, although it has been in wide use for many years without apparent ill consequence.
Use in pregnancy only when there is no safer alternative and when the disease itself carries risks for the mother or unborn child.

Lactation
Allopurinol and its metabolite oxipurinol is excreted in the human breast milk. Concentrations of 1.4 mg/litre allopurinol and 53.7 mg/litre oxipurinol have been demonstrated in breast milk from a woman taking Allopurinol 300 mg/day. However, there are no data concerning the effects of allopurinol or its metabolites on the breast-fed baby. Allopurinol during breastfeeding is not recommended.

DRUG INTERACTIONS
- Dosage adjustments may be necessary when used concurrently with alcohol, chlorthalidone, ethacrynic acid, frusemide, metolazone, pyrazinamide, quinethazone, thiazide diuretics, mercaptopurine, azathioprine, anticoagulants, coumarin or indandione derivative.
- Co-administration of ampicillin or cyclophosphamide may increase the potential for toxicity.
- Effects of urinary acidifiers may increase the possibility of kidney stone formation during concurrent therapy with allopurinol.

MAIN SIDE/ADVERSE EFFECTS
Side Effects
Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

Adverse reactions in association with Allopurinol are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder.

1. Very rare reports have been received of thrombocytopenia, agranulocytosis and aplastic anaemia, particularly in individuals with impaired renal and/or hepatic function, reinforcing the need for particular care in this group of patients.
2. A delayed multi-organ hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) with fever, rashes, vasculitis,lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia hepato-splenomegaly, abnormal liver function tests, and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, and colon). If such reactions do occur, it may be at any time during treatment, allopurinol should be withdrawn IMMEDIATELY AND PERMANENTLY.

   Rechallenge should not be undertaken in patients with hypersensitivity syndrome and SJS/TEN. Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present particularly when the outcome has been fatal.
3. Angioimmunoblastic T-cell lymphoma has been described very rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of Allopurinol.
4. Hepatic dysfunction has been reported without overt evidence of more generalised hypersensitivity.
5. Skin reactions are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). The highest risk for SJS and TEN, or other serious hypersensitivity reactions, is within the first weeks of treatment. The best results in managing such reactions come from early diagnosis and immediate discontinuation of any suspect drug. Allopurinol should be withdrawn immediately should such reactions occur. After recovery from mild reactions, Allopurinol may, if desired, be re-introduced at a small dose (e.g. 50 mg/day) and gradually increased. The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The use of genotyping as a screening tool to make decisions about treatment with allopurinol has not been established. If the rash recurs, Allopurinol should be permanently withdrawn as more severe hypersensitivity may occur. If SJS/TEN, or other serious hypersensitivity reactions cannot be ruled out, DO NOT re-introduce allopurinol due to the potential for a severe or even fatal reaction. The clinical diagnosis of SJS/TEN remains the basis for decision making. If such reactions occur at any time during treatment, allopurinol should be withdrawn immediately and permanently.
6. Angioedema has been reported to occur with and without signs and symptoms of a more generalised hypersensitivity reaction.
7. Fever has been reported to occur with and without signs and symptoms of a more generalised Allopurinol hypersensitivity reaction.
8. The occurrence of increased thyroid stimulating hormone (TSH) in the relevant studies did not report any impact on free T4 levels or had TSH levels indicative of subclinical hypothyroidism.

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OVERDOSE AND TREATMENT
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EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Since adverse reactions such as somnolence, vertigo and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that allopurinol does not adversely affect performance.

DOSAGE AND ADMINISTRATION
Adults
Allopurinol should be introduced at low dosage e.g. 100 mg/day to reduce the risk of adverse reactions and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor. The following dosage schedules are suggested:
- 100 to 200 mg daily in mild conditions,
- 300 to 600 mg daily in moderately severe conditions,
- 700 to 900 mg daily in severe conditions.

If dosage on an mg/kg bodyweight basis is required, 2 to 10 mg/kg bodyweight/day should be used.

Paediatric population
Children under 15 years: 10 to 20 mg/kg bodyweight/day up to a maximum of 400 mg daily. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Older people
In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used. Particular attention should be paid to advice in Renal impairment.

Renal impairment
Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the drug and/or its metabolites with consequent prolongation of plasma half-lives. In severe renal insufficiency, it may be advisable to use less than 100 mg per day or to use single doses of 100 mg at longer intervals than one day. If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 micromol/litre (15.2 mg/litre). Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two to three times a week consideration should be given to an alternative dosage schedule of 300-400 mg Allopurinol immediately after each dialysis with none in the interim.

Hepatic impairment
Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Treatment of high urate turnover conditions, e.g. neoplasia, Lesch-Nyhan syndrome
It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with Allopurinol before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinisation of urine to increase solubility of urinary urate/uric acid. Dosage of Allopurinol should be at the lower end of the recommended dosage schedule.

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

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation.

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

Method of administration
Allopurinol may be taken orally once a day after a meal. It is well tolerated, especially after food. Should the daily dosage exceed 300 mg and gastrointestinal intolerance be manifested, a divided doses regimen may be appropriate.

Storage: Store below 30˚C.

Packaging Particulars:
100's tablets and 1000's tablets per plastic bottle.
Blister of 10 x 10's

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