# Leukin

Mercaptopurine 50 mg

**COMPOSITION**
Leukin tablet: Each film coated tablet contains Mercaptopurine USP 50 mg.

**DESCRIPTION**
6-Mercaptopurine is sulphydryl analogue of the purine base hypoxanthine and acts as a cytotoxic antimetabolite.

**CLINICAL PHARMACOLOGY**
**Mode of Action**
6-Mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides for cytotoxicity. The 6-Mercaptopurine metabolites inhibit de novo purine synthesis and purine nucleotide interconversions. The thioguanine nucleotides are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the drug.

6-Mercaptopurine is converted into the active thioguanine nucleotides by the enzyme hypoxanthineguanine phosphoribosyltransferase. The conversion of 6-Mercaptopurine into its active thioguanine nucleotides is a stepwise process, via thioinosinic acid. 6-Mercaptopurine can also undergo methylation by the enzyme thiopurine methyltransferase to form S-methylated nucleotides, which are also cytotoxic.

**Pharmacodynamics/Kinetics:**
The bioavailability of oral 6-mercaptopurine shows considerable inter-individual variability. When administered at a dosage of 75mg/m2 to 7 paediatric patients, the bioavailability averaged 16% of the administered dose, with a range of 5 to 37%. The variable bioavailability probably results from the metabolism of a significant portion of 6-mercaptopurine during first-pass hepatic metabolism.

The mean time to peak plasma concentration in 14 pediatric patients was 2.2 hours with a range of 0.5 to 4 hours. In 7 paediatric patients the elimination half-life of 6-mercaptopurine was 90 ± 30 minutes, but the active metabolites have a longer half life (approximately 5 hours), and the total clearance is 719 ± 610 mL/min/m2. One to four hours after an intravenous infusion of 6-mercaptopurine (100mg/m2/h) cerebrospinal fluid levels are between 10 and 25% of the corresponding plasma levels. After oral administration of between 50 and 165mg/m2 levels in the cerebrospinal fluid were not detectable ((0.18 micromol/L). There is a low entry of 6-mercaptopurine into the cerebrospinal fluid. There is low entry of 6-mercaptopurine into the cerebrospinal fluid.

The cytotoxic effect of 6-mercaptopurine can be related to the levels of red blood cell 6-mercaptopurine derived thioguanine nucleotides, but not to the plasma 6-mercaptopurine concentration.

The main method of elimination for 6-mercaptopurine is by metabolic alteration (see also Pharmacodynamic Properties). The kidneys eliminate approximately 7% of 6-mercaptopurine unaltered within 12 hours of the drug being administered. Xanthine oxidase catalyses the conversion of 6-mercaptopurine into the inactive metabolite, 6-thiouric acid. This is excreted in the urine.

**Preclinical Safety Data**

**INDICATIONS**
6-Mercaptopurine is indicated for the treatment of acute leukaemia. It may be utilised in remission induction and particularly indicated for maintenance therapy in:
acute lymphoblastic leukaemia;
acute myelogenous leukaemia.
6-Mercaptopurine may be used in the treatment of chronic granulocytic leukaemia.

**DOSAGE AND ADMINISTRATION**
**Dosage in adults and children**
For adults and children the usual dose is 2.5mg/kg bodyweight per day, or 50-75 mg/m2 body surface area per day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with 6-Mercaptopurine.

The dosage should be carefully adjusted to suit the individual patient.
6-Mercaptopurinehas been used in various combination therapy schedules for acute leukaemia and the literature should be consulted for details.

Studies carried out in children with acute lymphoblastic leukemia suggested that administration of mercaptopurine in the evening lowered the risk of relapse compared with morning administration.
**Dosage in the elderly**
No specific studies have been carried out in the elderly. However, it is advisable to monitor renal and hepatic function in these patients, and if there is any impairment, consideration should be given to reducing the 6-Mercaptopurine dosage.
**Dosage in renal impairment**
Consideration should be given to reducing the dosage in patients with impaired renal function.
**Dosage in hepatic impairment**
Consideration should be given to reducing the dosage in patients with impaired hepatic function.
**In general**
When allopurinol and 6-Mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of 6-Mercaptopurine is given since allopurinol decreases the rate of catabolism of 6-Mercaptopurine.
**Pregnancy**
The use of 6-Mercaptopurineshould be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving 6-Mercaptopurine tablets.
**Maternal exposure**
Normal offspring have been born after 6-Mercaptopurine therapy administered as a single chemotherapy agent during human pregnancy, particularly when given prior to conception or after the first trimester. Multiple congenital abnormalities have been reported following maternal 6-Mercaptopurine treatment in combination with other chemotherapy agents.

**Paternal exposure** Congenital abnormalities and spontaneous abortions have been reported exposure to 6-Mercaptopurine.

Studies of 6-Mercaptopurine in animals have shown reproductive toxicity. The potential risk for humans is largely unknown.
**Lactation**
6-Mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with azathioprine, a pro-drug of 6-Mercaptopurine and thus mothers receiving 6-Mercaptopurineshould not breast feed.
**CONTRAINDICATIONS**
Hypersensitivity to any component of the preparation. In view of the seriousness of the indications there are no other absolute contra-indications.
**PRECAUTIONS**
6-Mercaptopurine is an active cytotoxic agent for use only under the direction of physicians experienced in the administration of such agents.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.
**Monitoring**
Since 6-Mercaptopurine is strongly myelosuppressive full blood counts must be taken daily during remission induction. Patients must be carefully monitored during therapy.Treatment with 6-Mercaptopurine causes bone marrow suppression leading to leucopenia and thrombocytopenia and, less frequently, to anaemia. Full blood counts must be taken daily during remission induction and careful monitoring of haematological parameters should be conducted during maintenance therapy.

The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in the counts, treatment should be interrupted immediately.

Bone marrow suppression is reversible if 6-Mercaptopurineis withdrawn early enough.

During remission induction in acute myelogenous leukaemia the patient may frequently have to survive a period of relative bone marrow aplasia and it is important that adequate supportive facilities are available. 6-Mercaptopurine is hepatotoxic and liver function tests should be monitored weekly during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. The patient should be instructed to discontinue 6-Mercaptopurineimmediately if jaundice becomes apparent.
During remission induction when rapid cell lysis is occurring, uric acid levels in blood and urine should be monitored as hyperuricaemia and/or hyperuricosuria may develop, with the risk of uric acid nephropathy.
There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of 6-Mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with PURI-NETHOL. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-Mercaptopurine in combination with other cytotoxics (see Undesirable Effects). Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.
Cross resistance usually exists between 6-Mercaptopurine and 6-thioguanine. The dosage of 6-Mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression.
**Mutagenicity and carcinogenicity**
Increases in chromosomal aberrations were observed in the peripheral lymphocytes of leukaemic patients, in a hypernephroma patient who received an unstated dose of 6-Mercaptopurine and in patients with chronic renal disease treated at doses of 0.4-1.0mg/kg/day.

Two cases have been documented of the occurrence of acute nonlymphatic leukaemia in patients who received 6-Mercaptopurine, in combination with other drugs, for non-neoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with 6-Mercaptopurine and later developed acute nonlymphatic leukaemia, but it is not clear whether this was part of the natural history of the disease or if the 6-Mercaptopurine played a causative role.

A patient with Hodgkin's disease treated with 6-Mercaptopurine and multiple additional cytotoxic agents developed acute myelogenous leukaemia.

Twelve and a half years after 6-Mercaptopurine treatment for myasthenia gravis a female patient developed chronic myeloid leukaemia.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease population have been received when 6-Mercaptopurine is used in combination with anti-TNF agents .
**OVERDOSE**
The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience using dialysis as a treatment for Capecitabine overdose has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low-molecular-weight metabolite of the parent compound.

Single doses of Capecitabine were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m2 basis).
**ADVERSE EFFECTS**
For mercaptopurine there is a lack of modern clinical documentation which can serve as support for accurately determining the frequency of undesirable effects.

The following convention has been utilised for the classification of undesirable effects:- Very common ≥1/10, common ≥ 1/100, <1/10, uncommon ≥ 1/1000 and <1/100, rare ≥ 1/10,000 and <1/1000, very rare <1/10,000.
**Neoplasms benign, malignant and unspecified (including cysts and polyps)**
Very rare: Secondary Leukaemia and myelodysplasia
**Blood and lymphatic system disorders**
Very common: Bone marrow suppression; leucopenia and thrombocytopenia.

The main side effect of treatment with 6-Mercaptopurine is bone marrow suppression leading to leucopenia and thrombocytopenia.

Secondary leukaemia and myelodysplasia; hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease (an unlicenced indication) when used in combination with anti-TNF agents has been reported very rarely .
**Immune system disorders**
**Hypersensitivity reactions with the following manifestations have been reported**
Rare : Arthralgia; skin rash; drug fever
Very rare : Facial oedema

**Metabolism and nutrition disorders**
Uncommon : Anorexia

**Gastrointestinal disorders**
Common : Nausea; vomiting; pancreatitis in the IBD population
Rare : Oral ulceration; pancreatitis
Very rare : Intestinal ulceration
**Hepato-biliary disorders**
Common : Biliary stasis; hepatotoxicity
Rare : Hepatic necrosis

6-Mercaptopurine is hepatotoxic in animals and man. The histological findings in man have shown hepatic necrosis and biliary stasis

The incidence of hepatotoxicity varies considerably and can occur with any dose but more frequently when the recommended dose of 2.5mg/kg bodyweight daily or 75mg/m2 body surface area per day is exceeded.

Monitoring of liver function tests may allow early detection of hepatotoxicity. This is usually reversible if 6-Mercaptopurine therapy is stopped soon enough but fatal liver damage has occurred.

**Skin and subcutaneous tissue disorders**
Rare : Alopecia

**Reproductive system and breast disorders**
Very rare : Transient oligospermia

**DRUG INTERACTIONS**
Vaccinations with live organism vaccines are not recommended in immunocompromised individuals .
When allopurinol and 6-Mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of mercaptopurine is given since allopurinol decreases the rate of catabolism of mercaptopurine.

Inhibition of the anticoagulant effect of warfarin, when given with 6-Mercaptopurine, has been reported. As there is in vitro evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent 6-Mercaptopurinetherapy.

**PHARMACEUTICAL INFORMATION**
**Storage condition**
Store in a cool and dry place, away from light. Keep out of the reach of children.

**Packaging**
Leukin Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By
BEACON
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Mymensingh, Bangladesh

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