PURINETONE Tablet

Mercaptopurine 50 mg

COMPOSITION
Each tablet contains
Mercaptopurine ..... 50 mg

List of Excipients: Lactose monohydrate, Corn starch, Carboxymethyl cellulose calcium, Hydroxypropyl cellulose, Silicon dioxide and Magnesium stearate

DESCRIPTION
Pale yellow to yellow, round tablet

INDICATIONS
Mercaptopurine is indicated for treatment or maintenance therapy in acute leukemia, acute lymphoblastic leukemia, and acute myelogenous leukemia.
Mercaptopurine is also used in the treatment of chronic granulocytic leukemia.

DOSAGE AND ADMINISTRATIONS
For adults and children the usual dose is 2.5 mg/kg bodyweight per day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with Mercaptopurine. The dosage should be carefully adjusted to suit the individual patient. Mercaptopurine has been used in various combination therapy schedules for acute leukemia and the literature should be consulted for details. Consideration should be given to reducing the dosage in patients with impaired hepatic or renal function. When allopurinol and 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.

CONTRAINDICATIONS
1) Purinetone should not be used in patients who have a hypersensitivity to mercaptopurine or any component of the formulation.
2) Purinetone contains lactose and should not be taken by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

ADVERSE REACTIONS
There is no recent clinical data that can support to the onset frequency of adverse reactions.
The onset frequency: Very frequently (≧1/10), frequently (≧1/100, <1/10), occasionally (≧1/1000, <1/1000), rarely (≧1/10,000, <1/10,000), very rarely (<1/10,000)
1) Unspecific tumor including cystoma and sarcoma may occur. Secondary leukemia and myelodysplasia may appear very rarely.
2) *Hematologic system*: Myelosuppression is very frequent adverse reaction to Purinetone. The induction of complete remission of acute lymphatic leukemia frequently is associated with marrow hypoplasia. Maintenance of remission generally involves multiple-drug regimens whose component agents cause myelosuppression. Anemia, leukopenia, and thrombocytopenia are frequently observed. Dosages and schedules are adjusted to prevent life-threatening cytopenias.
3) *Hepatic system:* Frequently hepatotoxicity may occur. Cholestasis and hepatic gangrene may be observed rarely. Mercaptopurine is hepatotoxic in animals and man. The incidence of hepatotoxicity may occur with any dose but more frequently when dosage is exceeds 2.5 mg/kg bodyweight or 75mg/m^2 (body surface area) daily. Hepatic function must be carefully monitored in patients receiving mercaptopurine. Gamma glutamyl transferase (GGT) levels in plasma may be predictive of withdrawal due to hepatotoxicity. This is reversible if 6-mercaptopurine therapy is stopped soon enough but fatal liver damage has occurred.
4) *Gastrointestinal system:* Intestinal ulceration has been reported. Nausea, vomiting, and anorexia are uncommon during initial administration. Mild diarrhea and sprue-like symptoms have been noted occasionally, but it is difficult at present to attribute these to the medication. Oral lesions are rarely seen, and when they occur they resemble thrush rather than antifolic ulcerations. An increased risk of pancreatitis may be associated with the investigational use of Purinetone in inflammatory bowel disease.
5) *Immune system:* Arthralgia and drug fever has been reported rarely with Purinetone. Very rarely facial swelling may be observed.
6) *Dermatologic and subcutaneous system:* While dermatologic reactions can occur as a consequence of disease, the administration of Purinetone has been associated with skin rashes and hyperpigmentation. Rarely alopecia has been reported.
7) *Reproductive system:* Oligospermia has been reported very rarely.

PRECAUTIONS
1) Purinetone is an active cytotoxic agent for use only under the direction of physician experienced in the administation of such agents.
2) Treatment with 6-mercaptopurine cause 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.
3) 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-mercaptopurine is withdrawn early enough.
4) 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-mercaptopurine immediately if jaundice becomes apparent.
5) During remission induction in acute myelogenous leukemia 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) During remission induction when rapid cell lysis is occurring, uric acid levels in blood and urine should be monitored as hyperuricemia and/or hyperuricosuria may develop, with the risk of uric acid nephropathy.
7) In view of its action on cellular deoxyribonucleic acid (DNA) 6-mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment
8) 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 6-mercaptopurine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfazalazine. 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. 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.
9) There are no data on the effect of 6-mercaptopurine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the medicinal product.
10) Renal and/or hepatic impairment :
Caution is advised during the administration of 6-mercaptopurine in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored.

DRUG INTERACTIONS
1) Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.
2) There is usually complete cross-resistance between mercaptopurine and thioguanine.
3) 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.
4) Effect of concomitant medicinal products on 6-mercaptopurine
① Ribavirin
Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of a pro-drug of 6-mercaptopurine and ribavirin; therefore concomitant administration of ribavirin and 6-mercaptopurine is not advised.
② Myelosuppressive agents
When 6-mercaptopurine is combined with other myelosuppressive agents caution should be used; dose reductions may be needed based on haematological monitoring.
③ Allopurinol/oxipurinol/thiopurinol
Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol, which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxipurinol and/or thiopurinol and 6-mercaptopurine are administered concomitantly it is essential that only 25 % of the usual dose of 6-mercaptopurine is given.
④ Aminosalicylates
There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulfazalazine) inhibit the TPMT enzyme. Therefore, lower doses of 6-mercaptopurine may need to be considered when administered concomitantly with aminosalicylate derivatives.
⑤ Methotrexate
Methotrexate (20 mg/m^2 orally) increased 6-mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m^2 intravenously) increased 6-mercaptopurine AUC by 69 and 93%, respectively. Therefore, when 6-mercaptopurine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.
5) Effect of 6-mercaptopurine on other medicinal products
① Anticoagulants
Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with 6-mercaptopurine; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with 6-mercaptopurine.

PREGNANCY AND LACTATION
1) Substantial transplacental and transamniotic transmission of 6-mercaptopurine and its metabolites from the mother to the foetus have been shown to occur.
2) As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving 6-mercaptopurine tablets.
3) 6-mercaptopurine is potentially teratogenic. The use of 6-ercaptopurine should 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.
4) 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. Abortions and prematurity have been reported after maternal exposure. Multiple congenital abnormalities have been reported following maternal 6-mercatopurine treatment in combination with other chemotherapy agents.
5) Paternal exposure: Congenital abnormalities and spontaneous abortion have been reported after paternal exposure to 6-mercaptopurine.
6) 6-mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with a pro-drug of 6-mercaptopurine. It is recommended that mothers receiving 6-mercaptopurine should not breast-feed.

OVERDOSAGE
1) Symptoms and signs
Gastrointestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of overdosage having occurred. The principal toxic effect is on the bone marrow, resulting in myelosuppression. Haematological toxicity is likely to be more profound with chronic overdosage than with a single ingestion of 6-mercaptopurine. Liver dysfunction and gastroenteritis may also occur. The risk of overdosage is also increased when allopurinol is being given concomitantly with 6-mercaptopurine.
2) Treatment
As there is no known antidote, blood counts should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of 6-mercaptopurine overdose unless the procedure can be undertaken within 60 minutes of ingestion. Further management should be as clinically indicated or as recommended by the national poisons centre.

OTHERS
1) 6-Mercaptopurine causes embryolethality and severe teratogenic effects in the mouse, rat, hamster and rabbit at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and the type of malformations are dependent on the dose and stage of the gestation at the time of administration.
2) 6-Mercaptopurine, in common with other antimetabolites, is potentially mutagenic in man and chromosome damage has been reported in mice, rats and man.

3) 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 to 1.0 mg/kg/day.
4) Two cases have been documented of the occurrence of acute non-lymphatic 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 non-lymphatic 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.
5) A patient with Hodgkin's disease treated with 6-mercaptopurine and multiple additional cytotoxic agents developed acute myelogenous leukaemia.
6) Twelve and a half years after 6-mercaptopurine treatment for myasthenia gravis, a female patient developed chronic myeloid leukaemia.

STORAGE
Preserve in tight containers.
Store at room temperature not exceeding 30°C.

PACKAGE
100 Tablets/Box (10 Tablets/Blister × 10 Blisters/Box)
100 Tablets/Bottle

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KOREA UNITED PHARM. INC.
107, Gongdan-ro, Yeonseo-myeon, Sejong-si, Korea