

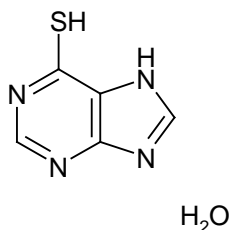
## PRODUCT INFORMATION

### PURI-NETHOL<sup>®</sup> TABLETS

#### NAME OF THE MEDICINE:

PURI-NETHOL tablets contain 50 mg mercaptopurine.

The chemical name (CAS) of mercaptopurine is 6*H*-Purine-6-thione, 1,7-dihydro-, monohydrate, it has a relative molecular mass of 170.2, its molecular formula is C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>S·H<sub>2</sub>O, CAS No.: 6112-76-1 (monohydrate) and the chemical structure is:



#### DESCRIPTION:

Mercaptopurine is odourless or practically odourless, yellow crystalline powder, with a solubility of 0.26 mg/mL in water at 37°C. Each PURI-NETHOL tablet also contains lactose, starch-maize, starch-hydrolysed maize, magnesium stearate and stearic acid.

#### PHARMACOLOGY:

Mercaptopurine is an analogue of adenine, one of the bases required for nucleic acid biosynthesis, and of the purine base hypoxanthine. Hence PURI-NETHOL acts as an antimetabolite and interferes with the synthesis of nucleic acids in proliferating cells. Its metabolites are also pharmacologically active.

#### Pharmacokinetics:

Absorption of an oral dose of PURI-NETHOL is incomplete and variable averaging about 50% of the administered dose. The half-life of mercaptopurine in the circulation is of the order of 90 minutes. It is extensively metabolised and excreted via the kidneys and the active metabolites have a longer half-life than the parent drug. Mercaptopurine has pKa's of 7.7 and 11.

#### INDICATIONS:

Treatment of acute leukaemia. It is of value in remission induction and is particularly indicated for maintenance therapy in acute lymphoblastic leukaemia and acute myelogenous leukaemia.

PURI-NETHOL is also used in the treatment of chronic granulocytic leukaemia.

## **CONTRAINDICATIONS:**

Hypersensitivity to any component of the preparation.

In view of the seriousness of the indications there are no other absolute contraindications.

## **PRECAUTIONS:**

PURI-NETHOL 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.

Co-administration of ribavirin and PURI-NETHOL is not advised. Ribavirin may reduce efficacy and increase toxicity of mercaptopurine (see INTERACTIONS).

The handling of PURI-NETHOL tablets should follow standard guidelines for the handling and disposal of cytotoxic drugs.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving PURI-NETHOL tablets.

**Monitoring:** Since PURI-NETHOL is strongly myelosuppressive, full blood counts must be monitored daily during remission induction. Patients must be carefully monitored during therapy.

Treatment with mercaptopurine causes bone marrow suppression leading to leucopenia and thrombocytopenia, and less frequently 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 abnormally large fall in the counts, treatment should be interrupted immediately.

Bone marrow suppression is reversible if PURI-NETHOL is 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.

PURI-NETHOL 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 PURI-NETHOL immediately 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 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 PURI-NETHOL in combination with other cytotoxics (see ADVERSE 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 mercaptopurine and 6-thioguanine (Lanvis).

The dosage of mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression (see INTERACTIONS: Myelosuppressive agents).

### **Renal and/or hepatic impairment**

Caution is advised during the administration of PURI-NETHOL 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 (see DOSAGE AND ADMINISTRATION).

### **Carcinogenesis, mutagenesis, impairment of fertility**

PURI-NETHOL in common with other anti-metabolites is potentially mutagenic and chromosome damage has been reported in rats and humans.

Mercaptopurine causes embryoletality and severe teratogenic effects in mice, rats, hamsters and rabbits at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and type of malformations is dependent on the dose and the stage of gestation at the time of administration.

Increases in chromosomal aberrations were observed in the peripheral lymphocytes of leukaemic patients and in a hyper nephroma patient who received an unstated dose of mercaptopurine and in patients with chronic renal disease treated at doses of 0.4-1.0 mg/kg/day.

In view of its action on cellular deoxyribonucleic acid (DNA), mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment. Three cases have been documented of the occurrence of acute nonlymphatic leukaemia in patients who received mercaptopurine for non-neoplastic disorders.

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

Twelve and a half years after 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 mercaptopurine is used in combination with anti-TNF agents (see ADVERSE EFFECTS).

### **Use in Pregnancy: (Category D)**

Substantial transplacental and transamniotic transmission of mercaptopurine and its metabolites from the mother to the foetus have been shown to occur.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving PURI-NETHOL tablets.

PURI-NETHOL has been shown to be embryotoxic in rats at doses that are not toxic to the mother. It has also been proven to be embryoletal when administered at higher doses in the first half of the gestation period. The potential risk for humans is largely unknown.

**Maternal exposure:** Normal offspring have been born after 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 mercaptopurine treatment in combination with other chemotherapy agents.

**Paternal exposure:** Congenital abnormalities and spontaneous abortions have been reported after paternal exposure to mercaptopurine.

A leukaemia patient treated with mercaptopurine 100 mg/day (plus splenic irradiation) throughout pregnancy gave birth to a normal, premature baby. A second baby, born to the same mother who was treated as before, together with busulfan 4 mg/day, had multiple severe abnormalities, including corneal opacities, microphthalmia, cleft palate and hypoplasia of the thyroid and ovaries. The use of PURI-NETHOL 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.

Transient profound oligospermia was observed in a young man who received mercaptopurine 150 mg/day plus prednisone 80 mg/day for acute leukaemia. Two years after cessation of the chemotherapy he had a normal sperm count and fathered a normal child.

**Use in Lactation:** Mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with azathioprine, a pro-drug of mercaptopurine and thus mothers receiving PURI-NETHOL should not breast feed.

## **INTERACTIONS:**

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (See PRECAUTIONS).

### **Effect of concomitant drugs on PURI-NETHOL**

#### **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 mercaptopurine and ribavirin; therefore concomitant administration of ribavirin and PURI-NETHOL is not advised (see PRECAUTIONS).

#### **Myelosuppressive agents**

When PURI-NETHOL is combined with other myelosuppressive agents, caution should be used; dose reductions may be needed based on haematological monitoring (see PRECAUTIONS).

#### **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 mercaptopurine are administered concomitantly it is essential that only a 25% of the usual dose of mercaptopurine is given (see DOSAGE AND ADMINISTRATION) since allopurinol decreases the rate of catabolism of mercaptopurine.

## **Aminosalicylates**

Inhibition of the anticoagulant effect of warfarin when given with mercaptopurine, has been reported.

There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme. Therefore, lower doses of PURI-NETHOL may need to be considered when administered concomitantly with aminosalicylate derivatives (see PRECAUTIONS).

Following unregulated consumption of salicylates, sulphonamides or undefined tranquillisers by patients receiving mercaptopurine therapy, a slower onset of pancytopenia has been documented.

## **Effect of PURI-NETHOL on other drugs**

### **Anticoagulants**

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with PURI-NETHOL; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with PURI-NETHOL.

## **ADVERSE EFFECTS:**

The following convention has been utilised for the classification of undesirable effects: *very common* ( $\geq 1/10$ ), *common* ( $\geq 1/100$  and  $< 1/10$ ), *uncommon* ( $\geq 1/1000$  and  $< 1/100$ ), *rare* ( $\geq 1/10,000$  and  $< 1/1000$ ), *very rare* ( $< 1/10,000$ ).

### **Neoplasms benign, malignant and unspecified (including cysts and polyps)**

*Very rare:* secondary leukaemia and myelodysplasia; hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease (an unlicensed indication) when used in combination with anti-TNF agents has been reported very rarely (see PRECAUTIONS).

### **Blood and lymphatic system disorders**

*Very common:* bone marrow suppression; leucopenia and thrombocytopenia.

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

### **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 (an unlicensed indication)

*Rare:* oral ulceration; intestinal ulceration; pancreatitis (in the licensed indication)

### **Hepatobiliary disorders**

*Common:* biliary stasis; hepatotoxicity

*Rare:* hepatic necrosis

Mercaptopurine is hepatotoxic in animals and humans. The histological findings in humans 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 2.5 mg/kg bodyweight daily is exceeded.

Monitoring of liver function tests may allow early detection of liver toxicity. This is usually reversible if mercaptopurine therapy is stopped soon enough. However, irreversible liver damage leading to a fatal outcome has occurred.

#### **Skin and subcutaneous tissue disorders**

*Rare:* alopecia

#### **Reproductive system and breast disorders**

*Very rare:* transient oligospermia.

### **DOSAGE AND ADMINISTRATION:**

#### **Adults and children**

For adults and children the usual dose is 2.5 mg/kg bodyweight/day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with PURI-NETHOL.

The dosage should be carefully adjusted to suit the individual patient.

PURI-NETHOL has been used in various combination therapy schedules for acute leukaemia and the literature should be consulted for details.

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.

#### **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 reduce the PURI-NETHOL dosage.

#### **Renal or hepatic impairment**

Consideration should be given to reducing the dosage in patients with impaired hepatic or renal function.

### **OVERDOSAGE:**

Gastro-intestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of overdose having occurred. The principal toxic effect is on the bone marrow and haematological toxicity is likely to be more profound with chronic overdose than with a single ingestion of PURI-NETHOL.

The risk of overdose is also increased when allopurinol is being given concomitantly with PURI-NETHOL. Liver dysfunction and gastroenteritis may also occur.

**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 mercaptopurine overdose unless the procedure can be undertaken within 60 minutes of ingestion.

Further management should be as clinically indicated. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

**PRESENTATION AND STORAGE CONDITIONS:**

**Presentation:** PURI-NETHOL tablets are pale yellow, round tablets, biconvex, scored on one side, engraved GX above the score and EX2 below the score and plain on the other side. They each contain 50 mg mercaptopurine and are supplied in amber glass bottles with cap.

Each bottle contains 25 tablets.

**Storage:** Store below 25°C, keep dry and protect from light.

**NAME AND ADDRESS OF THE SPONSOR:**

Aspen Pharmacare Australia Pty Ltd  
34-36 Chandos Street  
St Leonards NSW 2065

**POISON SCHEDULE OF THE MEDICINE:**

S4

**DATE OF MOST RECENT AMENDMENT:**

9 January 2012.

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