Puri-Nethol™

To the Medical and Pharmaceutical Professions.

Presentations

Each pale yellow, round biconvex tablet, scored on one side and coded GX/EX2, contains 50mg of Mercaptopurine PhEur.

Indications

Not all indications are registered in every country.

Puri-nethol is indicated for the 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.

Dosage and Administration

Dosage in adults and children:

For adults and children the usual dose is 2.5 mg/kg bodyweight per day, or 50-75 mg/m^2 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 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.

Studies carried out in children with acute lymphoblastic leukaemia 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 Puri-nethol 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.

Contra-indications

Hypersensitivity to any component of the preparation.

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

Precautions and Warnings

PURI-NETHOL IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

Safe handling of Puri-nethol Tablets:

It is recommended that the handling of Puri-nethol tablets follows the "Guidelines for the Handling of Cytotoxic Drugs" according to prevailing local recommendations and/or regulations.

If halving of a tablet is required, care should be taken not to contaminate the hands or inhale the drug.

Disposal:

Puri-nethol tablets surplus to requirements should be destroyed in a manner appropriate to the prevailing local regulations for the destruction of dangerous substances.

Monitoring:

SINCE PURI-NETHOL 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 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 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. Cross resistance usually exists between 6-mercaptopurine and 6-thioguanine (LANVIS).

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 0.4-1.0 mg/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.

Drug Interactions

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 (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent Puri-nethol therapy (see Precautions and Warnings).

Pregnancy and Lactation

Pregnancy:

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.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving Puri-nethol 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. Abortions and prematurity have been reported after maternal exposure. 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 after paternal exposure to 6-mercaptopurine.

Studies of 6-mercaptopurine in animals have shown reproductive toxicity (see Precautions and Warnings). 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 Puri-nethol should not breast feed.

Effects on Ability to Drive and Use Machines

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 drug.

Adverse Reactions

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.

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.

Metabolism and nutrition disorders

Uncommon - Anorexia

Gastrointestinal disorders

Common - Nausea; vomiting; pancreatitis in the IBD population

Rare - Oral ulceration

Very rare - Intestinal ulceration

Pancreatitis has been reported in association with the unlicensed use of 6-mercaptopurine in the treatment of inflammatory bowel disease.

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 2.5 mg/kg bodyweight daily or 75 mg/m^2 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 - Skin rash; alopecia

Reproductive system and breast disorders

Very Rare - Transient oligospermia

General disorders and administration site conditions

Rare - Drug fever

Overdosage

Symptoms and signs:

Gastro-intestinal 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 Puri-nethol. Liver dysfunction and gastroenteritis may also occur.

The risk of overdosage is also increased when allopurinol is being given concomitantly with Puri-nethol (see Drug Interactions).

Management:

As there is no known antidote the blood picture 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 or gastric lavage) may not be effective in the event of 6-mercaptopurine overdose unless the procedure can be undertaken within 60 minutes of ingestion.

Pharmacodynamic Properties

Pharmacotherapeutic group:

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

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.

Pharmacokinetic Properties

The bioavailability of oral 6-mercaptopurine shows considerable inter-individual variability. When administered at a dosage of 75 mg/m^2 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 paediatric 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/m^2. One to four hours after an intravenous infusion of 6-mercaptopurine (100mg/m^2/h) cerebrospinal fluid levels are between 10 and 25% of the corresponding plasma levels. After oral administration of between 50 and 165 mg/m^2 levels in the cerebrospinal fluid were not detectable (<0.18 micromol/L). 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 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.

Pharmaceutical Precautions and Recommendations

List of Excipients

Lactose Monohydrate
Maize starch
Hydrolysed starch
Stearic acid
Magnesium stearate

Instructions for Use/Handling

Do not store above 25°C. Protect from light. Keep dry.

Shelf Life

The expiry date is indicated on the packaging

Nature and Contents of Container

Amber glass bottle with cap containing 25 tablets.

Manufactured by
EXCELLA GmbH,
Nürnberger Strasse 12,
90537 Feucht,
Germany
Marketing Authorization Holder
Aspen Pharma Trading Limited
12/13 Exchange Place
I.F.S.C, Dublin 1,
Ireland
Service tel: +800 00404142

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

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