1.3.1.1 Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PURI-NETHOL 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of PURI-NETHOL contains 50 mg of 6-mercaptopurine.

Contains sugar: Lactose monohydrate 59 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Pale, yellow, round tablets, biconvex, scored on one side, engraved PT above the score and 50 below the score and plain on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses (see section 4.2)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PURI-NETHOL is indicated in combination with other medicines for the treatment of acute leukaemia in adults, adolescents and children.

PURI-NETHOL is indicated for:

- Acute lymphoblastic leukaemia (ALL)
- Acute promyelocytic leukaemia (APL) / Acute myeloid leukaemia M3 (AML M3).

4.2 Posology and method of administration

Posology

PURI-NETHOL treatment should be supervised by a medical practitioner experienced in the management of patients with ALL and APL (AML M3) (see section 4.4).

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

PURI-NETHOL may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products (see section 4.5). PURI-NETHOL should be taken at least one hour before or two hours after milk or dairy products (see section 5.1).

Special populations

Adults and paediatric population

For adults and children the usual dose is 2,5 mg/kg bodyweight per day, or 50 to 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 medicines given in conjunction with PURI-NETHOL.

The dosage should be adjusted according to individual response and tolerance.

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

PURI-NETHOL should be administered to children with ALL in the evening to lower the risk of relapse.

Elderly population

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.

Renal impairment

Consideration should be given to reducing the dose in renal impairment.

Hepatic impairment

Consideration should be given to reducing the dose in hepatic impairment.

Medicine interactions

When the xanthine oxidase inhibitors, such as allopurinol and PURI-NETHOL are administered concomitantly it is essential that only a quarter (25 %) of the usual dose of PURI-NETHOL is given since these medicines decreases the rate of catabolism of PURI-

NETHOL. Concomitant administration of other xanthine oxidase inhibitors, such as febuxostat, should be avoided (see section 4.5).

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase TPMT activity are at increased risk for severe PURI-NETHOL toxicity from conventional doses of PURI-NETHOL and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established.

Most patients with heterozygous TPMT deficiency can tolerate recommended PURI-NETHOL doses, but some may require dose reduction.

The optimal starting dose for homozygous deficient patients has not been established (see section 4.4).

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and generally require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established.

Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk

of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations (see section 5.1).

Method of administration

For oral use

Instructions for use/handling

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.

Surplus PURI-NETHOL tablets should be destroyed in a manner appropriate to the prevailing local recommendations for the destruction of dangerous substances (see section 6.6)

4.3 Contraindications

PURI-NETHOL is contraindicated in:

- Patients with hypersensitivity to 6-mercaptopurine, azathioprine or to any of the excipients in PURI-NETHOL (see section 6.1).

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

4.4 Special warnings and precautions for use

PURI-NETHOL IS AN ACTIVE CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF MEDICAL PRACTITIONERS EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Monitoring

SINCE PURI-NETHOL IS STRONGLY MYELOSUPPRESSIVE FULL BLOOD COUNTS MUST BE TAKEN DAILY DURING REMISSION INDUCTION. PATIENTS MUST BE CAREFULLY MONITORED DURING THERAPY.

Hypersensitivity

Patients suspected to have previously presented with a hypersensitivity reaction to PURI-NETHOL should not be recommended to use its pro-drug azathioprine, unless the patient has been confirmed as hypersensitive to 6-mercaptopurine with allergological tests, and tested negative for azathioprine (see section 4.3).

Immunisation

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended in patients with ALL or APL (AML M3). In all cases, patients in remission should not receive live organism vaccines until the patient is deemed to be able to respond to the vaccine. The interval between discontinuation of chemotherapy and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medicines used , the underlying disease, and other factors. The interval between cessation of PURI-NETHOL and immunisation should be at least three months.

Ribavirin

Co-administration of ribavirin and PURI-NETHOL is not advised. Ribavirin may reduce efficacy and increase toxicity of PURI-NETHOL (see section 4.5).

Safe handling of PURI-NETHOL

For the safe handling of PURI-NETHOL tablets, refer to section 4.2.

It is advisable to take care when handling or halving these tablets not to contaminate hands or inhale the medicine.

Bone marrow suppression

The main side effect of treatment with PURI-NETHOL is bone marrow suppression leading to leukopenia and thrombocytopenia and, less frequently, to anaemia. Full blood counts must be taken frequently during remission induction. During maintenance therapy, complete blood counts, including platelet counts, should be regularly monitored and more frequently if high dosage is used or if severe renal and/or hepatic disorder is present.

Bone marrow suppression is usually reversible if PURI-NETHOL is withdrawn early enough.

During remission induction in APL (AML M3) the patient may frequently have to survive a period of relative bone marrow aplasia and it is important that adequate support facilities are available.

Leukocyte 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.

The dosage of PURI-NETHOL may need to be reduced when this medicine is combined with other medicines whose primary or secondary toxicity is myelosuppression (see sections 4.2 and 4.5).

Renal impairment

Caution is advised during the administration of PURI-NETHOL in patients with renal impairment. Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored.

Tumour lysis syndrome

During remission induction when rapid cell lysis occurs, uric acid levels in blood and urine should be monitored as hyperuricaemia and/or hyperuricosuria and acute gout may develop, with the risk of uric acid nephropathy.

Hepatotoxicity

PURI-NETHOL is hepatotoxic and liver function tests should be monitored weekly during treatment. Gamma glutamyl transferase (GGT) levels in plasma may be particularly predictive of withdrawal due to hepatotoxicity. 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. This may be reversible if 6-mercaptopurine therapy is stopped soon enough, but fatal liver damage has occurred.

Thiopurine methyltransferase (TPMT) deficiency

Individuals with an inherited deficiency of the enzyme TPMT may be unusually sensitive to the myelosuppressive effect of PURI-NETHOL and prone to developing rapid bone marrow depression following the initiation of PURI-NETHOL treatment. This problem could be exacerbated by co-administration with medicines that inhibit TPMT such as olsalazine, mesalazine or sulphasalazine.

There is an association between decreased TPMT activity and secondary leukaemias and myelodysplasia in individuals receiving PURI-NETHOL in combination with other cytotoxics (see section 4.8).

Approximately 0,3 % (1:300) of patients have little or no detectable enzyme activity. Approximately 10 % of patients have low or intermediate TPMT activity and almost 90 % of individuals have normal TPMT activity. There may also be a group of approximately 2 % who have very high TPMT activity.

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.

NUDT15 Mutation

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from thiopurine therapy and generally require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established. Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine

therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations (see section 5.1).

Cross resistance

Cross resistance usually exists between PURI-NETHOL, azathioprine and 6-thioguanine.

Mutagenicity and carcinogenicity

PURI-NETHOL is mutagenic and chromosome damage has been reported in mice, rats and man.

In view of its action on cellular deoxyribonucleic acid (DNA), 6-mercaptopurine is carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

Patients receiving immunosuppressive therapy, including mercaptopurine as in PURI-NETHOL are at an increased risk of developing lymphoproliferative disorders and other malignancies, including lymphoma, leukaemia and notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non- Kaposi's) and uterine cervical cancer *in situ*. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given

concomitantly increases the risk of Epstein- Barr virus (EBV)-associated lymphoproliferative disorders.

Macrophage activation syndrome (MAS)

MAS is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing the condition with the use of PURI-NETHOL. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with PURI-NETHOL should permanently be discontinued. Medical practitioners should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Paediatric population

Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving PURI-NETHOL (see section 4.8). The majority of reported cases were in children under the age of six or with a low body mass index.

Infections

Patients treated with PURI-NETHOL alone, or in combination with other immunosuppressive medicines, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe atypical infection, and viral reactivation. Examples of these infections are tuberculosis, atypical mycobacterial infections, herpes zoster, pneumocystis pneumonia and cytomegalovirus infections. The infectious disease and complications may be more severe in these patients than in non-treated patients.

Prior exposure to, or infection with varicella zoster virus should be taken into consideration prior to starting treatment. Local guidelines may be considered, including prophylactic therapy if necessary. PURI-NETHOL can induce hepatitis B virus (HBV) reactivation in patients carrying hepatitis B virus surface antigen (HBsAG) or anti-HBc.
Baseline HBV serology is recommended and HBsAG positive patients should receive anti-HBV prophylaxis therapy. Local guidelines may be considered, including prophylactic therapy for cases which have been confirmed positive by serologic testing. If the patient is infected during treatment appropriate measures should be taken, which may include antiviral therapy and supportive care.

Lesch-Nyhan syndrome

The use of PURI-NETHOL or azathioprine is not recommended in patients with Lesch-Nyhan syndrome (the rare inherited condition with complete hypoxanthine-guanine-phosphoribosyltransferase deficiency). Lymphoma cells lacking hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) are resistant to PURI-NETHOL.

UV exposure

Patients treated with PURI-NETHOL are more sensitive to the sun. Patients treated with PURI-NETHOL and with a history of high sun exposure may develop skin cancer. Azathioprine (a precursor of PURI-NETHOL) treatment has been reported to cause photosensitisation of skin to ultraviolet A (UVA) light which could contribute to the development of skin cancers. Limiting exposure to UV light and use of sunscreens and protective clothing is recommended during treatment (see section 4.8).

Xanthine oxidase inhibitors

Patients treated with the xanthine oxidase inhibitors such as allopurinol and PURI-NETHOL should only receive 25 % of the usual dose of PURI-NETHOL since allopurinol decreases the rate of catabolism of 6-mercaptopurine (see sections 4.2 and 4.5).

Anticoagulants

Inhibition of the anticoagulant effect of warfarin has been reported when co-administered with PURI-NETHOL; therefore higher doses of the anticoagulant may be needed (see section 4.5).

Porphyria

PURI-NETHOL may cause an acute attack of porphyria and should only be used if a safer alternative medicine is not available.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose -galactose malabsorption should not take PURI-NETHOL.

4.5 Interaction with other medicines and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).

The administration of PURI-NETHOL with food may decrease systemic exposure. PURI-NETHOL may be taken with food or on an empty stomach. However, patients should standardise the method of administration to avoid large variability in exposure. PURI-

NETHOL should not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme which metabolises PURI-NETHOL and might therefore lead to reduced plasma concentrations of PURI-NETHOL (see section 4.2).

Effect of concomitant medicines on PURI-NETHOL

Ribavirin

Ribavirin has an inhibitory effect on the enzyme inosine monophosphate dehydrogenase (IMPDH) and may reduce the efficacy and increase the toxicity of PURI-NETHOL (see section 4.4).

Myelosuppressive medicines

When PURI-NETHOL is combined with other myelosuppressive medicines caution should be used; dose reductions may be needed based on haematological monitoring (see section 4.4).

Allopurinol and other xanthine oxidase inhibitors

Xanthine oxidase activity is inhibited by allopurinol, which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol and PURI-NETHOL are administered concomitantly it is essential that only 25 % of the usual dose of PURI-NETHOL is given (see section 4.2).

Other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of PURI-NETHOL. Concomitant administration is not recommended as there is insufficient data to determine an adequate dose reduction.

Aminosalicylates

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 see section 4.4).

Methotrexate

Concomitant use of PURI-NETHOL with low dose oral methotrexate increased mean peak plasma concentrations of 6-mercaptopurine as in PURI-NETHOL by 26 % compared with the same dose of 6-mercaptopurine as in PURI-NETHOL alone in patients with ALL. The effect is due to inhibition of the first-pass metabolism of 6-mercaptopurine by methotrexate which is a potent inhibitor of xanthine oxidase. In another study high-dose intravenous methotrexate (2 or 5 g/m^2) increased the peak plasma concentrations of 6-mercaptopurine by 108 % and 121 % respectively. Therefore, when PURI-NETHOL is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

Infliximab

Interactions have been observed between azathioprine and infliximab in patients as represented by an increase in the intra-erythrocyte concentration of 6-thioguanine nucleotides, the active metabolites of azathioprine a pro-drug of 6-mecaptopurine as found in PURI-NETHOL, within 1 to 3 weeks after infliximab infusion. The increase in 6-thioguanine nucleotides was followed by a decrease in the leucocyte count and an increase in the mean corpuscular volume. These alterations usually returned to previous levels after three months.

Effect of PURI-NETHOL on other medicines

Anticoagulants

Inhibition of the anticoagulant effect of warfarin, when given with PURI-NETHOL. There have been reports that indicate a reduction in the anticoagulant activity of warfarin when 6-mercaptopurine, as in PURI-NETHOL, is used concurrently. Monitor international normalised ratio (INR) or prothrombin time if used concomitantly. Warfarin dose adjustments may be required to maintain desired levels of anticoagulation.

4.6 Fertility, pregnancy, lactation

The safety of PURI-NETHOL in pregnancy and lactation has not been established.

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.

Abortions and prematurity have been reported after maternal exposure. Multiple congenital abnormalities have been reported following maternal PURI-NETHOL treatment in combination with other chemotherapy medicines.

Substantial transplacental and transamniotic transmission of 6-mercaptopurine as found in PURI-NETHOL and its metabolites from the mother to the foetus have been shown to occur.

Adequate contraceptive precautions should be advised if either partner is receiving PURI-NETHOL tablets during treatment and for at least three months after receiving the last dose.

In utero exposure to thiopurines has not been associated with negative effects on long-term childhood development or susceptibility for infectious disease. Normal offspring with normal Apgar scores directly after birth in most cases, have been born after 6-mercaptopurine therapy administered during pregnancy.

Paternal exposure

Congenital abnormalities and spontaneous abortions have been reported after paternal exposure to PURI-NETHOL (see section 4.4).

Breastfeeding

PURI-NETHOL is excreted into breast milk. Mothers receiving PURI-NETHOL should not breastfeed.

Fertility

The effect of PURI-NETHOL therapy on human fertility is unknown.

Oligospermia has been reported following exposure to 6–mercaptopurine as found in PURI-NETHOL (see section 4.8).

4.7 Effects on ability to drive and use machines

PURI-NETHOL has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

For 6-mercaptopurine there is a lack of modern clinical documentation which can serve as support for accurately determining the frequency of undesirable effects. The frequency categories assigned to the adverse medicines reactions below are estimates: for most reactions, suitable data for calculating incidence are not available. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic medicines.

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

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Bacterial and viral infections, infections associated with neutropenia	
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ,* secondary leukaemia, myelodysplasia, hepatosplenic T-cell lymphoma in patients with IBD (when used in combination with anti-TNF medicines)	
Blood and the lymphatic system disorders	Bone marrow depression/failure, leukopenia, thrombocytopenia, anaemia		

Immune system disorders		Hypersensitivity, arthralgia, rash, pyrexia, facial oedema	
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia (In the paediatric population)
Gastrointestinal disorders	Pancreatitis, nausea, vomiting	Mouth ulceration, intestinal ulcer, mild diarrhoea, sprue-like symptoms	
Hepato-biliary disorders	Cholestasis, hepatotoxicity	Hepatic necrosis	
Skin and subcutaneous tissue disorders		Alopecia, photosensitivity reaction	
Reproductive system and breast disorder		Transient oligospermia	

c) Description of selected adverse reactions

The incidence of hepatoxicity varies considerably and can occur with any dose but more frequently when the recommended dose of 2,5 mg/kg bodyweight daily is exceeded.

d) Paediatric population

Hepatobiliary disorders

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. Gamma glutamyl transferase (GGT) levels in plasma may be particularly predictive of withdrawal

due to hepatotoxicity. This is usually reversible if 6-mercaptopurine therapy is stopped soon enough but fatal liver damage has occurred.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

Gastrointestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of an overdose.

The principal toxic effect is bone marrow suppression. Haematological toxicity is likely to be more profound with chronic overdosage than with a single ingestion of PURI-NETHOL. Liver dysfunction and gastro-enteritis may also occur.

The risk of overdosage is also increased when allopurinol is being given concomitantly with PURI-NETHOL (see section 4.5).

Treatment

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) may not be effective in the event of PURI-NETHOL overdose unless the procedure can be undertaken within 60 minutes of ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents

ATC code: L01BB

Mechanism of action

Mercaptopurine is an analogue of the nucleic acid constituent adenine and the purine base hypoxanthine.

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 effect.

The cytotoxic effects 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.

5.2. Pharmacokinetic properties

Absorption

The bioavailability of oral 6-mercaptopurine has high inter-individual variability. When administered at a dose 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.

After oral administration of 6-mercaptopurine 75 mg/m^2 to 14 children with acute lymphoblastic leukaemia, the mean C_{max} was 0,89 µM with a range of 0,29 to 1,82 µM and T_{max} was 2,2 hours with a range of 0,5 to 4 hours.

The mean relative bioavailability of 6-mercaptopurine was approximately 26 % lower following administration with food and milk compared to an overnight fast. 6-mercaptopurine is not stable in milk due to the presence of xanthine oxidase (30 % degradation within 30 minutes) see section 4.2.

Distribution

The mean volume of distribution of 6-mercaptopurine is 0,9 (± 0,8) litre per kilogram. There is low entry of 6-mercaptopurine into the cerebrospinal fluid.

One to four hours after an intravenous infusion of 6-mercaptopurine (100 mg/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 micromole/L).

Biotransformation

6-mercaptopurine is converted into 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 (TPMT) to form S-methylated nucleotides, which are also cytotoxic.

There is evidence that polymorphisms in the genes encoding the different enzyme systems involved with metabolism of 6-mercaptopurine may predict adverse medicine reactions to 6-mercaptopurine therapy. For example, individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations (see section 4.4).

NUDT15 R139C (NUDT15 c.415C>T) Variant

Recent studies indicate that a strong association exists between the NUDT15 variant NUDT15 c.415C > T (p.Arg139Cys) (also known as NUDT15 R139C (rs116855232)), which is thought to lead to a loss of function of the NUDT15 enzyme, and thiopurine-mediated toxicity such as leukopenia and alopecia. The frequency of NUDT15 c.415C >T has an ethnic variability of 9,8 % in Asians, 3,9 % in Hispanics, 0,2 % in Europeans and 0,0 % in Africans, indicating an increased risk for the Asian population. Patients who are

NUDT15 variant homozygotes (NUDT15 T risk alleles) are at an excessive risk of thiopurine toxicity compared with the C homozygotes.

Reduced thiopurine doses for patients who carry the NUDT15 variants may decrease their risk of toxicity. Genotypic analysis determining NUDT15 genotype should be determined for all patients, including paediatric patients, prior to initiating thiopurine treatment (see sections 4.2 and 4.4). The prescribing medical practitioner is advised to establish whether dose reduction is required based on patient response to treatment as well as their genetic profile.

Patients with variants in both the NUDT15 and TPMT enzymes are significantly less tolerant of thiopurines than those with risk alleles in only one of these two genes.
The precise mechanism of NUDT15-associated thiopurine-related toxicity is not understood.

Elimination

The elimination half-life of 6-mercaptopurine was 90 ± 30 minutes, but the active metabolites have a longer half-life. The total clearance is 719 ± 610 mL/min/m^2.
The main method of elimination for 6-mercaptopurine is by metabolic alteration. The kidneys eliminate approximately 7 % of 6-mercaptopurine unaltered within 12 hours of the medicine being administered. Xanthine oxidase catalyses the conversion of 6-mercaptopurine into the inactive metabolite, 6-thiouric acid. This is excreted in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, magnesium stearate, maize starch, modified maize starch, stearic acid

6.2 Incompatabilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep dry.

Keep in original packaging until required for use.

6.5 Nature and contents of the container

25 tablets are packed into an amber glass bottle. The bottle is closed with a child resistant closure with an induction heat seal liner. The bottle is placed in an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

6.6 Special precautions for disposal

Safe handling:

It is recommended that 6-mercaptopurine tablets should be handled following the prevailing local recommendations and/or regulations for the handling and disposal of cytotoxic medicines.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBER

H2751 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Date of registration: Old medicine

10. DATE OF REVISION OF TEXT

13 February 2022

Botswana: BOT1703040 S2

Namibia: NS2 14/26/0598

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.