NEW ZEALAND DATA SHEET

1. PURI-NETHOL Tablets (mercaptopurine 50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Purinethol 50 mg Tablets: Each tablet contains 50 mg mercaptopurine BP.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PURI-NETHOL is indicated for the treatment of acute leukaemia. It may be utilised in remission induction and is particularly indicated for maintenance therapy in:

acute lymphoblastic leukaemia;

acute myelogenous leukaemia.

PURI-NETHOL may be used in the treatment of chronic granulocytic leukaemia.

4.2 Dose and method of administration

Dosage in adults and children

PURI-NETHOL should be administered at least 1 hour before or 3 hours after food or milk (see section 5.2, Pharmacokinetic properties: Absorption).

For adults and children the usual dose is 2.5 mg/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 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 leukemia suggested that administration of mercaptopurine in the evening lowered the risk of relapse compared with morning administration.

Children considered to be overweight may require doses at the higher end of the dose range and therefore close monitoring of response to treatment is recommended (see section 5.2, Pharmacokinetic properties: Special patient populations; Overweight children).

Dosage in the elderly

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. (see section 5.2, Pharmacokinetic properties: Special Patient Populations; Renal impairment).

Dosage in hepatic impairment

Consideration should be given to reducing the dosage in patients with impaired hepatic function (see section 5.2, Pharmacokinetic properties: Special Patient Populations; Hepatic impairment).

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.

4.3 Contraindications

Hypersensitivity to any component of the preparation. In view of the seriousness of the indications there are no other absolute contra-indications.

4.4 Special warnings and precautions for use

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 in patients with leukaemia. In all cases, patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed.

Co-administration of ribavirin and PURI-NETHOL is not advised. Ribavirin may reduce efficacy and increase toxicity of 6-mercaptopurine (see section 4.5 Interaction with other medicines and other forms of interaction).

Safe handling of PURI-NETHOL Tablets

See section 6.6, Special precautions for disposal (and other use).

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 During maintenance therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and or hepatic disorder is present.

Haematological monitoring of the patient is advised when switching formulations.

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.

TPMT Testing

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of mercaptopurine monohydrate and prone to developing rapid bone marrow depression following the initiation of treatment with PURI-NETHOL. There have been fatal cases of myelosuppression in patients with low or absent TPMT activity treated with thiopurines. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. 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 section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Patients should be tested for TPMT activity before starting PURI-NETHOL. TPMT testing cannot substitute for complete blood count monitoring in patients receiving PURI-NETHOL. TPMT genotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity (homozygous for non-functional alleles) are at an increased risk of developing severe, life-threatening myelotoxicity from PURI-NETHOL if conventional doses are given. Alternative therapies may be considered for patients who have low or absent TPMT activity. PURI-NETHOL should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity.

TPMT testing is widely available through pathology laboratories and genetic testing services.

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. (see section 4.5, Interaction with other medicines and other forms of interaction: Myelosuppressive agents).

Hypersensitivity

Patients suspected to have previously presented with a hypersensitivity reaction to mercaptopurines should not be advised to use its pro-drug azathioprine, unless the patient has been confirmed as hypersensitive to mercaptopurine with allergological tets, and has tested negative for azathioprine. As azathioprine is a pro-drug of mercaptopurine, patients with a previous history of hypersensitivity to azathioprine must be assessed for hypersensitivity to mercaptopurine prior to initiating treatment

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 section 4.2, Dose and method of administration and section 5.2 Pharmacokinetic properties: Special Populations).

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.

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 single case has been reported where a patient was treated for pyoderma gangrenosum with 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 mercaptopurine played a causative role.

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.

Patients receiving immunosuppressive therapy are at an increased risk of developing non-Hodgkin’s lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi’s and non- Kaposi’s) and uterine cervical cancer in situ. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression

may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas.

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 (Undesirable effects).

Infections

Patients treated with mercaptopurine alone or in combination with other immnosuprresive agents, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection and viral reactivation. The infectious disease and complications may be more severe in these patients than in non-treated patients.

Serologic testing prior to starting treatment should be considered with respect to varicella zoster virus and hepatitis B. 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 measure should be taken, which may include antiviral therapy and supportive care.

Macrophage activation syndrome

Macrophage activation syndrome (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 mercaptopurine monohydrate. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with mercaptopurine monohydrate should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Lesch-Nyhan Syndrome

Limited evidence suggests that neither mercaptopurine nor its pro-drug azathioprine are effective in patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch – Nyhan syndrome). The use of mercaptopurine or azathioprine is not recommended in these patients.

Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level. As is usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited, and patients should wear protective clothing and use a sunscreen with a high protection factor.

4.5 Interaction with other medicines and other forms of interaction

When xanthine oxidase inhibitors, such as allopurinol, and PURI-NETHOL are administered concomitantly it is essential that only 25% of the usual dose of PURI-NETHOL is given since allopurinol decreases the rate of catabolism of 6 mercaptopurine (see section 4.5, Interaction with other medicines and other forms of interaction).

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe 6-mercaptopurine 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 (see section 4.4, Special warnings and precautions for use: Monitoring and section 5.2, Pharmacokinetic properties).

Most patients with heterozygous TPMT deficiency can tolerate recommended PURI-NETHOL doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see 4.4, Special warnings and precautions for use: Monitoring and section 5.2, Pharmacokinetic properties). Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see 4.4, Special warnings and precautions for use).

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 6-mercaptopurine and ribavirin; therefore concomitant administration of ribavirin and PURI-NETHOL is not advised (see 4.4, Special warnings and precautions for use and section 5.2, Pharmacokinetic properties: Metabolism).

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 4.4, Special warnings and precautions for use).

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

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 a quarter of the

usual dose of mercaptopurine is given (see section 4.2, Dose and method of administration and section 4.5, Interaction with other medicines and other forms of interaction) since allopurinol decreases the rate of catabolism of mercaptopurine.

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

Aminosalicylates

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 4.4, Special warnings and precautions for use).

Methotrexate

Methotrexate (20 mg/m2 orally) increased 6 mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m2 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.

Infliximab

Interactions have been observed between azathioprine, a pro-drug of mercaptopurine, and infliximab. Patients receiving ongoing azathioprine experienced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and decreases in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after 3 months.

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.

4.6 Fertility, pregnancy and lactation

Fertility

The effect of mercaptopurine therapy on human fertility is unknown.There are reports of successful father/motherhood after

receiving treatment during childhood or adolescence.Transient oligospermia has been reported following exposure to mercaptopurine.

Pregnancy

Substantial transplacental and transamniotic transmission of 6 mercaptopurine and its metabolites from the mother to the foetus have been shown to occur.

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' during treatment and for at least three months after receiving the last dose.

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 (see section 5.3, Preclinical safety data). The potential risk for humans is largely unknown. 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.

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. It is recommended that and thus mothers receiving PURI-NETHOL should not breast feed.

4.7 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.

4.8 Undesirable 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 and <1/10; uncommon ≥1/1000 and <1/100; rare ≥1/10,000 and <1/1000; very rare <1/10,000., not known (frequency cannot be estimated from the available data).

Neoplasms benign and malignant (including cysts and polyps)

Rare: Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia. (see 4.4, Special warnings and precautions for use).

Very rare: Hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease when used in combination with anti-TNF agents.

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, is increased in patients who receive immunosuppressive drugs, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself.

There have been rare reports of acute myeloid leukaemia and myelodysplasia (some in association with chromosomal abnormalities).

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.

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; pancreatitis (in the licensed indications)

Very rare: Intestinal ulceration

Hepato-biliary disorders

Common: Biliary stasis; hepatotoxicity

Rare: Hepatic necrosis

Frequency Unknown: Portal hypertension*, nodular regenerative hyperplasia*, sinusoidal obstruction syndrome*

*In patients with inflammatory bowel disease, an unlicensed indication.

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/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

General disorders and administration site conditions

Not known; Photosensitivity

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 professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 section 4.3, Interaction with other medicines and other forms of interaction).

Management

As there is no known antidote the blood picture 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 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

6-mercaptopurine is sulphydryl analogue of the purine bases adenine and 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 (TGNs) for cytotoxicity. The TGNs and other metabolites (e.g. 6-methyl-mecaptopurine ribonucleotides) inhibit de novo purine synthesis and purine nucleotide interconversions. The TGNs are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the drug.

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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of oral 6-mercaptopurine shows considerable inter-individual variability. When administered at a dosage of 75 mg/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.

After oral administration of PURI-NETHOL 75 mg/m2 to 14 children with acute lymphoblastic leukaemia, the mean Cmax was 0.89µM, with a range of 0.29 1.82µM and Tmax was 2.2 hours with a range of 0.5-4 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 5.2, Pharmacokinetic properties: Metabolism). PURI-NETHOL should be administered at least 1 hour before or 3 hours after food or milk (see section 4.2, Dose and method of administration).

Distribution

The mean (± SD) apparent volume of distribution of 6 mercaptopurine is 0.9 (±0.8) L/kg, although this may be an underestimate because 6-mercaptopurine is cleared throughout the body (and not just in the liver).

Concentrations of 6 mercaptopurine in cerebrospinal fluid (CSF) are low or negligible after IV or oral administration (CSF: plasma ratios of 0.05 to 0.27). Concentrations in the CSF are higher after intrathecal administration.

Metabolism

6 mercaptopurine is extensively metabolized by many multi-step pathways to active and inactive metabolites, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression. The predominant enzymes responsible for the metabolism of 6-mercaptopurine or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT) (see section 4.4, Special warnings and precautions for use: Monitoring and section 4.5, Interactions with other medicines and other forms of interaction: Aminosalicylates), xanthine oxidase (see section 4.5, Interactions with other medicines and other forms of interaction: Allopurinol/oxipurinol/thiopurinol and section 5.2, Pharmacokinetic properties: Absorption), inosine monophosphate dehydrogenase (IMPDH) (see section 4.5, Interaction with other medicines and other forms of interaction: Ribavirin), and hypoxanthine guanine

phosphribosyltransferase (HPRT). Additional enzymes involved in the formation of active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which form TGNs) and inosine triphosphate pyrophosphatase (ITPase). There are also multiple inactive metabolites formed via other pathways.

There is evidence that polymorphisms in the genes encoding the different enzyme systems involved with metabolism of 6 mercaptopurine may predict adverse drug reactions to 6 mercaptopurine therapy.

Thiopurine S Methyl Transferase (TPMT)

TPMT activity is inversely related to red blood cell 6 mercaptopurine derived thioguanine nucleotide concentration, with higher thioguanine nucleotide concentrations resulting in greater reductions in white blood cell and neutrophil counts. Individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations.

Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles—TPMT*2, TPMT*3A and TPMT*3C—account for about 95% of individuals with reduced levels of TPMT activity. Approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles. There may also be a group of approximately 2% who have very high TPMT activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells and can also be informative (see 4.4, Special warnings and precautions for use).

Elimination

In a study with 22 patients the mean 6 mercaptopurine clearance and half-life after IV infusion was 864 mL/min/m2 and 0.9 hours respectively. The mean renal clearance reported in 16 of these patients was 191 mL/min/m2. Only about 20% of the dose was excreted in the urine as intact drug after IV administration.

Special Patient Populations

Elderly

No specific studies have been carried out in the elderly (see section 4.2, Dose and method of administration).

Overweight children

In a US clinical study, 18 children (aged 3 to 14 years) were evenly divided into two groups; either a weight to height ratio above or below

the 75th percentile. Each child was on maintenance treatment of 6-mercaptopurine and the dosage was calculated based on their body surface area. The mean AUC (0-□) of 6-mercaptopurine in the group above the 75th percentile was 2.4 times lower than that for the group below the 75th percentile. Therefore, children considered to be overweight may require 6-mercaptopurine doses at the higher end of the dose range and close monitoring of response to treatment is recommended (see section 4.2, Dose and method of administration).

Renal impairment

Studies with a pro-drug of 6 mercaptopurine have shown no difference in 6 mercaptourine pharmacokinetics in uremic patients compared to renal transplant patients. Since little is known about the active metabolites of 6 mercaptopurine in renal impairment, consideration should be given to reducing the dosage in patients with impaired renal function (see section 4.2, Dose and method of administration).

6 mercaptopurine and/or its metabolites are eliminated by haemodialysis, with approximately 45% of radioactive metabolites eliminated during dialysis of 8 hours.

Hepatic impairment

A study with a pro-drug of 6 mercaptopurine was performed in three groups of renal transplant patients: those without liver disease, those with hepatic impairment (but no cirrhosis) and those with hepatic impairment and cirrhosis. The study demonstrated that 6-mercaptopurine exposure was 1.6 times higher in patients with hepatic impairment (but no cirrhosis) and 6 times higher in patients with hepatic impairment and cirrhosis, compared to patients without liver disease. Therefore, consideration should be given to reducing the dosage in patients with impaired hepatic function (see section 4.2, Dose and method of administration).

5.3 Preclinical safety data

Preclinical Safety Data

Mutagenicity and Carcinogenicity

6-mercaptopurine in common with other antimetabolites is potentially mutagenic in man and chromosome damage has been reported in mice and rats, and man.

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.

Patients receiving immunosuppressive therapy, including mercaptopurine are at an increased risk of developing lymphoproliferative disorders and other malignancies, 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.

Teratogenicity

6-mercaptopurine causes embryolethality 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, hydrolysed starch, stearic acid, magnesium stearate.

6.2 Incompatibilities

No data available.

6.3 Shelf-life

60 months from date of manufacture.

6.4 Special precautions for storage

Store at 25°C. Protect from light. Keep dry.

6.5 Nature and contents of container

Bottles, glass of 25 tablets.

6.6 Special precautions for disposal (and other handling)

Safe 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.

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.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pharmacy Retailing Pty Ltd
t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9. DATE OF FIRST APPROVAL

25 October 2004

10. DATE OF REVISION OF THE TEXT

30 November 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format
4.4	Safety related changes
4.4	Safety related changes
4.8	Safety related changes
5.3	Safety related changes