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, biconvex tablets, marked PT above the line and 50 below the line on one side and plain on the other.
Please note that the tablets should not be taken in divided doses.
Breaking the tablets across the score line is to enable swallowing only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute leukaemia in adults, adolescents and children. It may be utilised in:
Acute lymphoblastic leukaemia (ALL)
Acute promyelocytic leukaemia (APL)/Acute myeloid leukaemia M3 (AML M3).

4.2 Dose and method of 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/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 and in accordance with the employed treatment protocol. 6-mercaptopurine has been used in various combination therapy schedules for acute leukaemia and the literature and current treatment guidelines 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). Patients should be closely monitored for dose related adverse reactions (see section 4.4, 5.2).

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). Patients should be closely monitored for dose related adverse reactions (see section 4.4, 5.2).

Switching between tablet and oral suspension and vice versa

An oral suspension of 6-mercaptopurine is also available. The 6-mecaptopurine oral suspension and tablet are not bioequivalent with respect to peak plasma concentration, and therefore intensified haematological monitoring of the patient is advised on switching formulations (see section 5.2).

Drug interactions
When the xanthine oxidase inhibitors allopurinol, oxipurinol or thiopurinol and 6-mercaptopurine are administered concomitantly it is essential that only 25% of the usual dose of 6-mercaptopurine is given since these agents decrease the rate of catabolism of 6-mercaptopurine. 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 6-mercaptopurine toxicity from conventional doses of 6-mercaptopurine 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 6-mercaptopurine doses, but some may require dose reduction (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 5.2).

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.

PURI-NETHOL treatment should be supervised by a physician or other healthcare professional experienced in the management of patients with ALL and APL (AML M3).

Method of Administration
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 1 hour before or 2 hours after milk or dairy products.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.Vaccinations with live organism vaccines are contraindicated in immunocompromised individuals.

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
Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are contraindicated 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 medications used, the underlying disease, and other factors.

Ribavirin
Co-administration of ribavirin and 6-mercaptopurine is not advised. Ribavirin may reduce efficacy and increase toxicity of 6-mercaptopurine (see section 4.5).
Safe handling of 6-mercaptopurine tablets (see section 6.6).

Monitoring
Since 6-mercaptopurine is strongly myelosuppressive full blood counts must be taken daily during remission induction. Patients must be carefully monitored during therapy.

Bone marrow suppression
Treatment with 6-mercaptopurine causes 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 platelets, should be regularly monitored and more frequently if high dosage is used or if severe renal and/or hepatic disorder is present.
Increased haematological monitoring of the patient is advised when switching between different pharmaceutical formulations of 6-mercaptopurine.
The 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 immediately.
Bone marrow suppression is reversible if 6-mercaptopurine 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.
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).

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.

There have been case reports of cholestasis in pregnancy reported in association with thiopurine therapy. In most cases, patients had inflammatory bowel disease. Shifts in thiopurine metabolism may occur during pregnancy. Monitoring of 6-methyl mercaptopurine (6-MMP) should be considered in the presence of pruritis with elevated maternal total serum bile levels during pregnancy to establish early diagnosis and minimise impact on the foetus (see section 4.6). If cholestasis of pregnancy occurs, a case-by-case assessment is necessary considering the risks for mother and foetus. Medicine withdrawal or dose reduction may be necessary.

Tumour lysis syndrome
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 Deficiency
There are individuals with an inherited deficiency of the enzyme thiopurine S-methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of 6–mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with 6–mercaptopurine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. 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).
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 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 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 5.2).

Cross resistance
Cross resistance usually exists between 6-mercaptopurine and 6-thioguanine.

Hypersensitivity
Patients suspected to have previously presented with a hypersensitivity reaction to 6-mercaptopurine 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.

As azathioprine is a pro-drug of 6-mercaptopurine, patients with a previous history of hypersensitivity to azathioprine must be assessed for hypersensitivity to 6-mercapopurine prior to initiating treatment.

Renal and/or hepatic impairment
Caution is advised during the administration of 6-mercaptopurine in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored (see section 4.2).

Mutagenicity and carcinogenicity
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.
Increases in chromosomal aberrations were observed in the peripheral lymphocytes of leukaemic patients, in a hypernephroma patient who received an unstated dose of 6-mercaptopurine, and in patients with chronic renal disease treated at doses of 0.4 to 1.0 mg/kg/day.
Two cases have been documented of the occurrence of acute non-lymphatic leukaemia in patients who received 6-mercaptopurine, in combination with other drugs, for non-neoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with 6-mercaptopurine and later developed acute non-lymphatic leukaemia, but it is not clear whether this was part of the natural history of the disease or if 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.
Reports of hepatosplenic T-cell lymphoma in the Inflammatory Bowel Disease (IBD) population (unlicensed indication) have been received when 6-mercaptopurine is used in combination with anti-TNF agents (see section 4.8).

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) (unlicensed indication), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine.

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

Metabolism and nutrition disorders
Administration of purine analogues (azathioprine and mercaptopurine) may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency/pellagra. Few cases have been reported with the use of azathioprine, especially in patients with IBD (Crohn's disease, colitis ulcerative). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis); gastroenteritis (diarrhoea); and widespread neurologic deficits, including cognitive decline (dementia). Dose reduction or discontinuation of mercaptopurine treatment may not be required if appropriate medical care with niacin/nicotinamide supplementation is initiated. However, careful benefit-risk assessment is required on a case-by-case basis.

Paediatric population
Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving 6-mercaptopurine (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 6-mercaptopurine alone, or in combination with other immunosuppressive 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.
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. Serologic testing prior to starting treatment should be considered with respect to 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 measures should be taken, which may include antiviral therapy and supportive care.

Lesch-Nyhan syndrome
Limited evidence suggests that neither 6-mercaptopurine nor its pro-drug azathioprine are effective in patients with the rare inherited condition complete hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). The use of 6-mercaptopurine or azathioprine is not recommended in these patients.

Patients with rare hereditary problems of galactose intolerance, complete lactase deficiency or glucosegalactose malabsorption should not take this medicine.

UV exposure
Patients treated with 6-mercaptopurine are more sensitive to the sun.

Exposure to sunlight and UV light should be limited, and patients should be recommended to wear protective clothing and to use a sunscreen with a high protection factor.

Xanthine oxidase inhibitors
Patients treated with the xanthine oxidase inhibitors allopurinol, oxipurinol or thiopurinol, and 6-mercaptopurine should only receive 25% of the usual dose of 6-mercaptopurine since allopurinol decreases the rate of catabolism of 6-mercaptopurine (see section 4.2).

Anticoagulants
Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with 6-mercaptopurine; therefore, higher doses of the anticoagulant may be needed (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

The administration of 6–mercaptopurine with food may decrease systemic exposure slightly. 6-mercaptopruine may be taken with food or on an empty stomach, but patients should standardise the method of administration to avoid large variability in exposure. The dose should not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme which metabolises 6–mercaptopurine and might therefore lead to reduced plasma concentrations of mercaptopurine.

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.

Antiepileptics

Cytotoxic agents may decrease the intestinal absorption of phenytoin. Careful monitoring of the phenytoin serum levels is recommended. It is possible that the levels of other anti-epileptic medicinal products may also be altered. Serum antiepileptic levels should be closely monitored during treatment with 6-mercaptopurine, making dose adjustments as necessary.

4.6 Fertility, pregnancy and lactation

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 6-mercaptopurine 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 6-mercaptopurine tablets, during treatment and for at least three months after receiving the last dose.

Studies of 6-mercaptopurine in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is largely unknown.

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.

It is recommended that new-borns of women exposed to mercaptopurine during

pregnancy are monitored for haematological and immune system disorders.

Pregnancy may affect thiopurine metabolism, which may increase the risk of toxicity. Pregnant women on thiopurine therapy should be closely monitored. There have been case reports of cholestasis in pregnancy reported in association with thiopurine therapy (see section 4.4).

Breastfeeding

6-mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with a pro-drug of 6-mercaptopurine. It is recommended that mothers receiving 6-mercaptopurine should not breast feed.

Fertility

The effect of 6–mercaptopurine therapy on human fertility is unknown.

There are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence.

Transient oligospermia has been reported following exposure to 6–mercaptopurine.

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 frequency categories assigned to the adverse drug 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 agents. The main side effect of treatment with mercaptopurine monohydrate is bone marrow suppression leading to leucopenia and thrombocytopenia.

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.

Common: Anaemia

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

Not known: Hypoglycaemia*

* In the paediatric population

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
Not known:	Stomatitis

Hepato-biliary disorders

Common:	Biliary stasis; hepatotoxicity
Rare:	Hepatic necrosis
Not known:	Cholestasis of pregnancy

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
Unknown	erythema nodosum

Reproductive system and breast disorders

Very Rare:	Transient oligospermia

SOC 'Infections and infestations
Uncommon: Bacterial and viral infections, infections associated with neutropenia

Paediatric population
Hypoglycaemia has been reported in the paediatric population.

General disorders and administration site conditions

Not known; Photosensitivity
Not known: Mucosal inflammation

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://pophealth.my.site.com/carmreportnz/s/

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) 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).

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).

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 East 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. Therefore, genotypic analysis determining NUDT15 genotype should be determined for all patients, including paediatric patients, prior to initiating thiopurine treatment (see section 4.2). The prescribing physician 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

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.

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.

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.

6 MEDICINE SCHEDULE

Prescription medicine.

7 SPONSOR

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

8 DATE OF FIRST APPROVAL

25 October 2004

9 DATE OF REVISION OF THE TEXT

5 December 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format
4.4	Safety related changes
3	Tablet Appearance
4.2 & 6.6	Breaking of tablets
4.8	Inclusion of erythema nodosum
4.1, 4.2, 4.4, 4.5,4.8	
4.4, 4.6, 4.8	Cholestasis of Pregnancy, Stomatitis, Mucosal inflammation