Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Puri-Nethol 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of the active substance mercaptopurine monohydrate.

Excipients with known effect:
Each tablet contains 59mg of the excipient lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pale yellow, round tablets, biconvex, scored on one side, engraved PT and 50 on either side of the scoreline and plain on the other side.

The scoreline is only to facilitate breaking of the tablets for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mercaptopurine monohydrate is indicated for the 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 Posology and method of administration

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

Posology
The dose is governed by cautiously monitored haematotoxicity and the dose should be carefully adjusted to suit the individual patient in accordance with the employed treatment protocol.
Depending on phase of treatment, starting or target doses should be lower in patients with reduced or absent Thiopurine Methyl Transferase (TPMT) enzyme activity (see section 4.4).

For adults and children, the usual dose is 2.5 mg/kg bodyweight per day, or 50 to 75mg/m^2 body surface area per day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with mercaptopurine monohydrate.
The dosage should be carefully adjusted to suit the individual patient.

Mercaptopurine monohydrate has been used in various combination therapy schedules for acute leukaemia and the literature and current treatment guidelinesshould be consulted for details.

Studies carried out in children with acute lymphoblastic leukaemia suggested that administration of mercaptopurine monohydrate in the evening lowered the risk of relapse compared with morning administration.

Special populations

Elderly

It is advisable to monitor renal and hepatic function in these patients, and if there is impairment, consideration should be given to reducing the mercaptopurine monohydrate dosage.

- ***Renal impairment***

Since mercaptopurine monohydrate pharmacokinetics has not been formally studied in renal impairment, no specific dose recommendations can be given. Since impaired renal function may result in slower elimination of mercaptopurine monohydrate and its metabolites and therefore a greater cumulative effect, consideration should be given to reduced starting doses in patients with impaired renal function. Patients should be closely monitored for dose related adverse reactions.

- ***Hepatic impairment***

Since mercaptopurine monohydrate pharmacokinetics has not been formally studied in hepatic impairment, no specific dose recommendations can be given. Since there is a potential for reduced elimination of mercaptopurine monohydrate, consideration should be given to reduced starting doses in patients with impaired hepatic function. Patients should be closely monitored for dose related adverse reactions (see sections 4.4 and 5.2).

Switching between tablet and oral suspension and vice versa

An oral suspension of mercaptopurine monohydrate is also available. The mecaptopurine monohydrate 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).

Combination with xanthine oxidase inhibitors

When the xanthine oxidase inhibitors allopurinol oxipurinol or thiopurinol and mercaptopurine monohydrate are administered concomitantly it is essential that only 25 % of the usual dose of mercaptopurine monohydrate is given since these agents decrease the rate of catabolism of mercaptopurine monohydrate. Concomitant administration of other xanthine oxidase inhibitors, such as febuxostat, should be avoided (see Section 4.5 Interaction with other medicinal products and other forms of interactions).

- ***TPMT-deficient patients***

Mercaptopurine monohydrate is metabolised by the polymorphic TPMT enzyme. Patients with little or no inherited thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe mercaptopurine monohydrate toxicity from conventional doses of mercaptopurine monohydrate and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established. TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. TPMT testing cannot substitute for haematological monitoring in patients receiving mercaptopurine monohydrate (see Section 4.4, 5.2).

- ***Patients with NUDT15 variant***

Patients with inherited mutated NUDT15 gene are at increased risk for severe mercaptopurine monohydrate toxicity (see 4.4). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes (see 4.4). Genotypic testing of NUDT15 variants may be considered before initiating mercaptopurine monohydrate therapy. In any case, close monitoring of blood counts is necessary.

Method of administration

Mercaptopurine monohydrate 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). Mercaptopurine monohydrate should be taken at least 1 hour before or 2 hours after milk or dairy products.

Mercaptopurine monohydrate displays diurnal variation in pharmacokinetics and efficacy. Administration in the evening compared to morning administration may lower the risk of relapse. Therefore the daily dose of mercaptopurine should be taken in the evening.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Mercaptopurine monohydrate is an active cytotoxic agent and should be used only under the direction of physicians experienced in the administration of such agents.

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

Cytotoxicity and haematological monitoring
Treatment with mercaptopurine monohydrate causes bone marrow suppression leading to leucopenia and thrombocytopenia and, less frequently, to anaemia. Careful monitoring of haematological parameters should be conducted during therapy. The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in the counts, treatment should be interrupted immediately. Bone marrow suppression is reversible if mercaptopurine monohydrate is withdrawn early enough.

There are individuals with an inherited deficiency of the TPMT enzyme activity who are very sensitive to the myelosuppressive effect of mercaptopurine monohydrate and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine monohydrate. This problem could be exacerbated by coadministration with active substances that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. 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 necessary. Substantial dose reductions are generally required for homozygous-TPMT deficiency patients to avoid the development of life-threatening bone marrow suppression.
A possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving mercaptopurine monohydrate in combination with other cytotoxics (see Section 4.8).
Increased haematological monitoring of the patient is advised when switching between different pharmaceutical formulations of mercaptopurine.

Immunosuppression
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 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. Co-administration of ribavirin and mercaptopurine monohydrate is not advised. Ribavirin may reduce efficacy and increase toxicity of mercaptopurine monohydrate (see Section 4.5).
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 mercaptopurine monohydrate may need to be reduced when this agent is combined with other medicinal products whose primary or secondary toxicity is myelosuppression (see Section 4.5).

Hepatotoxicity
Mercaptopurine monohydrate 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 mercaptopurine monohydrate immediately if jaundice becomes apparent (see Section 4.8).

Renal toxicity
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. Hydration and urine alkalinisation may minimize potential renal complications.

Renal and/or hepatic impairment

Caution is advised during the administration of mercaptopurine monohydrate in patients with renal impairment and/or hepatic impairment (see Section 4.2 and 5.2).

Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored.

Pancreatitis in off-label treatment of patients with inflammatory bowel disease

Pancreatitis has been reported to occur at a frequency of ≥ 1/100 to < 1/10 ("common") in patients treated for the unlicensed indication inflammatory bowel disease.

Mutagenicity and carcinogenicity

Patients receiving immunosuppressive therapy, including mercaptopurine monohydrate, 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 renal cell carcinoma patient who received an unstated dose of mercaptopurine monohydrate 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 monohydrate is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

Two cases have been documented of the occurrence of acute non-lymphatic leukaemia in patients who received mercaptopurine monohydrate, in combination with other medicinal products, for non-neoplastic disorders.

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

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

Twelve and a half years after mercaptopurine monohydrate treatment for myasthenia gravis, a female patient developed chronic myeloid leukaemia.

Hepatosplenic T-cell lymphoma has been reported in patients with inflammatory bowel disease* treated with azathioprine (the prodrug to mercaptopurine monohydrate) or mercaptopurine monohydrate, either with or without concomitant treatment with anti-TNF alpha antibody. This rare type of T cell lymphoma has an aggressive disease course and is usually fatal (see also Section 4.8).

*inflammatory bowel disease (IBD) is an unlicensed indication.

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 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.

Metabolic and nutritional disorders

Purine analogues (azathioprine and mercaptopurine) may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Cases of pellagra have been reported with the use of purine analogues, particularly in patients with chronic inflammatory bowel disease. The diagnosis of pellagra should be considered in patients with a localised pigmented rash (dermatitis), gastroenteritis, or neurological deficits including cognitive deterioration. Appropriate medical care with niacin/nicotinamide supplementation must be initiated.

Infections

Patients treated with mercaptopurine monohydrate 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. Cases of neutropenic sepsis have been reported in patients receiving mercaptopurine monohydrate for ALL.

If the patient is infected during treatment appropriate measures should be taken, which may include appropriate antimicrobial therapy and supportive care.

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe mercaptopurine monohydrate toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being NUDT15 variant homozygotes (see Section 4.2). The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans. In any case, close monitoring of blood counts is necessary.

Paediatric population

Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving mercaptopurine monohydrate (see Section 4.8 Undesirable Effects). The majority of reported cases were in children under the age of six or with a low body mass index.

Interactions

Xanthine oxidase inhibitors

Patients treated with the xanthine oxidase inhibitors allopurinol, oxipurinol or thiopurinol, and mercaptopurine monohydrate should only receive 25 % of the usual dose of mercaptopurine monohydrate since allopurinol decreases the rate of catabolism of mercaptopurine monohydrate (see Section 4.2 Posology and method of administration and Section 4.5 Interaction with other medicinal products and other forms of interaction).

Anticoagulants

When oral anticoagulants are co-administered with mercaptopurine monohydrate, a reinforced monitoring of INR (International Normalised Ratio) is recommended (see Section 4.5).

TPMT Deficiency

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 mercaptopurine monohydrate. This problem could be exacerbated by co-administration with medicinal products 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 mercaptopurine monohydrate in combination with other cytotoxics (see Section 4.8 Undesirable effects). 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.

Cross Resistance

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

Hypersensitivity

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

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

UV exposure
Patients treated with mercaptopurine monohydrate 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.

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

Safe handling of mercaptopurine monohydrate tablets – see Section 6.6

4.5 Interaction with other medicinal products and other forms of interaction

The administration of mercaptopurine monohydrate with food may decrease systemic exposure slightly. Mercaptopurine monohydrate 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 mercaptopurine monohydrate and might therefore lead to reduced plasma concentrations of mercaptopurine monohydrate.

Effects of mercaptopurine monohydrate on other medicinal products
Concomitant administration of yellow fever vaccine is contraindicated, due to the risk of fatal disease in immunocompromised patients (see section 4.3).

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

Anticoagulants
Inhibition of the anticoagulant effect of warfarin, when given with mercaptopurine monohydrate has been reported. Monitoring of the INR (International Normalised Ratio) value is recommended during concomitant administration with oral anticoagulants.

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 mercaptopurine monohydrate, making dose adjustments as necessary.

Effects of other medicinal products on mercaptopurine monohydrate
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 and mercaptopurine monohydrate are administered concomitantly it is essential that only a quarter of the usual dose of mercaptopurine monohydrate is given since allopurinol decreases the rate of metabolism of mercaptopurine monohydrate via xanthine oxidase. Also other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of mercaptopurine monohydrate and 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 mercaptopurine monohydrate may need to be considered when administered concomitantly with aminosalicylate derivatives (see Section 4.4 Special warnings and precautions for use).

Methotrexate

Methotrexate (20 mg/m^2 orally) increased mercaptopurine exposure (area under curve, AUC) by approximately 31% and methotrexate (2 or 5 g/m^2 intravenously) increased mercaptopurine AUC by 69% and 93%, respectively. When administered concomitantly with high dose methotrexate, the mercaptopurine dose may need adjustment.

Infliximab
Interactions have been observed between azathioprine, a pro-drug of 6-mercaptopurine, and infliximab. Patients receiving 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.

Ribavirin
Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of a pro-drug of mercaptopurine monohydrate and ribavirin; therefore concomitant administration of ribavirin and mercaptopurine monohydrate is not advised (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties: metabolism).

Myelosuppressive agents
When mercaptopurine monohydrate is combined with other myelosuppressive agents caution should be used; dose reductions may be needed based on haematological monitoring (see Section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Evidence of the teratogenicity of mercaptopurine monohydrate in humans is equivocal. Both sexually active men and women should use effective methods of contraception during treatment and for at least three months after receiving the last dose. Animal studies indicate embryotoxic and embryolethal effects (see section 5.3).

Pregnancy
Mercaptopurine monohydrate should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.

Substantial transplacental and transamniotic transmission of mercaptopurine monohydrate and its metabolites from the mother to the foetus have been shown to occur.
There have been reports of premature birth and low birth weight following maternal exposure to mercaptopurine monohydrate. There have also been reports of congenital abnormalities and spontaneous abortion following either maternal or paternal exposure. Multiple congenital abnormalities have been reported following maternal mercaptopurine monohydrate treatment in combination with other chemotherapy agents.

A more recent epidemiological report suggests that there is no increased risk of preterm births, low birth weight at term, or congenital abnormalities in women exposed to mercaptopurine monohydrate during pregnancy.

It is recommended that newborns of women exposed to mercaptopurine monohydrate during pregnancy are monitored for haematological and immune system disturbances.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine (a prodrug of 6-mercaptopurine) therapy. A careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed.

Breast-feeding
Mercaptopurine monohydrate has been identified in the colostrum and breast milk of women receiving azathioprine treatment and thus women receiving mercaptopurine monohydrate should not breast-feed.

Fertility
The effect of mercaptopurine monohydrate therapy on human fertility is unknown but there are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence.

Transient profound oligospermia has been reported following exposure to mercaptopurine monohydrate in combination with corticosteroids.

Maternal exposure:
Normal offspring have been born after mercaptopurine monohydrate therapy administered as a single chemotherapy agent during human pregnancy, particularly when given prior to conception or after the first trimester.
Abortions and prematurity have been reported after maternal exposure. Multiple congenital abnormalities have been reported following maternal mercaptopurine monohydrate treatment in combination with other chemotherapy agents.

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

4.7 Effects on ability to drive and use machines

There are no data on the effect of mercaptopurine monohydrate on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the medicinal product.

4.8 Undesirable effects

Summary of the safety profile
The main side effect of treatment with mercaptopurine monohydrate is bone marrow suppression leading to leucopenia and thrombocytopenia.

For mercaptopurine monohydrate, 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.

Tabulated list of adverse reactions

The following events have been identified as adverse reactions. The adverse reactions are displayed by system organ class and frequency:
very common (≥1/10),
common (≥1/100 to < 1/10),
uncommon (≥1/1000 to < 1/100),
rare (≥1/10,000 to < 1/1000)
very rare (< 1/10,000) and
Not known (frequency cannot be estimated from the available data)
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body System		Side effects
Infections and Infestations	Uncommon	Bacterial and viral infections, infections associated with neutropenia
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ* (see Section 4.4).
	Very rare	Secondary leukaemia and myelodysplasia
	Not known	Hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease (IBD) (an unlicensed indication) when used in combination with anti TNF agents (see Section 4.4.).
Blood and Lymphatic System Disorders	Very common	Bone marrow suppression; leucopenia and thrombocytopenia.
	Common	Anaemia
Immune System Disorders	Uncommon	Hypersensitivity reactions with the following manifestations have been reported: Arthralgia; skin rash; drug fever.

	Rare	Hypersensitivity reactions with the following manifestations have been reported: Facial oedema
Metabolism and nutrition Disorders	Common	Anorexia
	Not known	Hypoglycaemia# Pellagra (see section 4.4)
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,Cheilitis
Hepatobiliary Disorders	Common	Biliary stasis; hepatotoxicity
	Uncommon	Hepatic necrosis
Skin and Subcutaneous Tissue Disorders	Rare	Alopecia
	Not known	Photosensitivity; erythema nodosum
Reproductive System and Breast Disorders	Rare	Transient oligospermia
General disorders and administration site conditions	Not known	Mucosalinflammation
Investigations	Not known	Coagulationfactors decreased

In the paediatric population

Description of selected adverse reactions

Hepatobiliary disorders

Mercaptopurine monohydrate 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. Hepatotoxicity is usually reversible if mercaptopurine monohydrate therapy is stopped soon enough but fatal liver damage has occurred.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: http://www.hpra.ie.

4.9 Overdose

Symptoms and signs

Gastro-intestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of overdose having occurred. The principal toxic effect is on the bone marrow, resulting in myelosuppression. Haematological toxicity is likely to be more profound with chronic overdose than with a single ingestion of mercaptopurine monohydrate. Liver dysfunction and gastroenteritis may also occur.

The risk of overdose is also increased when xanthine oxidase inhibitors are being given concomitantly with mercaptopurine monohydrate (see Section 4.5).

Management

As there is no known antidote, blood countsshould be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of mercaptopurine monohydrate overdose unless the procedure can be undertaken within 60 minutes of ingestion.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, purine analogues, ATC code: L01BB02

Mechanism of action
Mercaptopurine monohydrate is sulphydryl analogue of the purine bases adenine and hypoxanthine and acts as a cytotoxic anti-metabolite.

Mercaptopurine monohydrate is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides for cytotoxicity. The mercaptopurine monohydrate metabolites inhibit de novo purine synthesis and purine nucleotide interconversions. The thioguanine nucleotides are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the active substance. Cross-resistance usually exists between mercaptopurine monohydrate and 6-thioguanine.

Pharmacodynamic effects
The cytotoxic effect of mercaptopurine monohydrate can be related to the levels of red blood cell mercaptopurine monohydrate derived thioguanine nucleotides, but not to the plasma mercaptopurine monohydrate concentration.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of oral mercaptopurine monohydrate shows considerable inter-individual variability, which probably results from its first-pass metabolism. When administered orally at a dosage of 75 mg/m^2 to seven paediatric patients, the bioavailability averaged 16 % of the administered dose, with a range of 5 to 37 %.
After oral administration of mercaptopurine monohydrate 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 - 1.82 µM and T_{max} was 2.2 hours with a range of 0.5 - 4 hours.

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

Distribution
Concentrations of mercaptopurine monohydrate 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.

Biotransformation
Mercaptopurine monohydrate is extensively metabolized by many multi-step pathways to active and inactive metabolites. 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 mercaptopurine monohydrate or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT), xanthine oxidase, inosine monophosphate dehydrogenase (IMPDH) 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 mercaptopurine monohydrate may predict adverse drug reactions to mercaptopurine monohydrate therapy. For example, individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations (see Section 4.4)**.**

Elimination
In a study with 22 adult patients the mean mercaptopurine monohydrate clearance and half-life after IV infusion was 864 mL/min/m^2 and 0.9 hours respectively. The mean renal clearance reported in 16 of these patients was 191 mL/min/m^2. Only about 20 % of the dose was excreted in the urine as intact drug medicinal product after IV administration. In a study with 7 children patients the mean mercaptopurine monohydrate clearance and half-life after IV infusion was 719 (+/-610) ml/min/m^2 and 0.9 (+/-0.3) hours respectively.

Special patient populations

- ***Elderly***

No specific studies have been carried out in the elderly (see Section 4.2 Posology and method of administration).

- ***Renal impairment***

Studies with a pro-drug of mercaptopurine monohydrate have shown no difference in mercaptopurine monohydrate pharmacokinetics in uremic patients compared to renal transplant patients. Since little is known about the active metabolites of mercaptopurine monohydrate in renal impairment (see Section 4.2 Posology and method of administration).

Mercaptopurine monohydrate 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 mercaptopurine monohydrate 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 mercaptopurine monohydrate 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 (see Section 4.2 Posology and method of administration).

5.3 Preclinical safety data

Genotoxicity
Mercaptopurine monohydrate, in common with other antimetabolites, is mutagenic and causes chromosomal aberrations in vitro and in vivo in mice and rats.

Carcinogenicity
Given its genotoxic potential, mercaptopurine monohydrate is potentially carcinogenic.

Teratogenicity
Mercaptopurine monohydrate causes embryolethality and severe teratogenic effects in the mouse, rat, hamster and rabbit at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and the type of malformations are dependent on the dose and stage of the gestation at the time of administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Modified maize starch
Stearic acid
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container in order to protect from light.
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Amber glass bottle containing 25 tablets with a child resistant high density polyethylene/polypropylene closure with induction heat seal liners (IHS).

6.6 Special precautions for disposal

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

Anyone handling Puri-Nethol should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling Puri-Nethol.

Puri-Nethol contact with skin or mucous membrane must be avoided. If Puri-Nethol comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Women who are pregnant, planning to be or breast-feeding should not handle Puri-Nethol. (See Section 4.6).

Parents / care givers and patients should be advised to keep Puri-Nethol out of the reach and sight of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Disposal
Puri-Nethol is cytotoxic. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1979

Date of last renewal: 1st April 2009

10 DATE OF REVISION OF THE TEXT

November 2024