SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Puri-Nethol Tablets 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mercaptopurine.

Each tablet contains 50 mg of the active substance mercaptopurine.

Excipients with known effect:

Lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

A pale yellow, round, biconvex tablet, marked PT above the score line and 50 below the score line on one side and plain on the other.

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of acute leukaemia and also in cases of chronic myelogenous leukemia.

4.2 Posology and Method of Administration

Posology

Mercaptopurine should be administered at least 1 hour before or 3 hours after food or milk (see sections 5.2 Pharmacokinetic properties: Absorption).

Populations

- **Adults and children**

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

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

mercaptopurine has been used in various combination therapy schedules for acute leukaemia and the literature should be consulted for details.

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

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).

- **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 mercaptopurine dosage.

- **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).

- **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).

Medicinal product interaction:

When the xanthine oxidase inhibitors, such as allopurinol, oxipurinol or thiopurinol and mercaptopurine are administered concomitantly it is essential that only 25 % of the usual dose of mercaptopurine is given since these agents decrease the rate of catabolism of mercaptopurine. 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

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe mercaptopurine toxicity from conventional doses of mercaptopurine 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 mercaptopurine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see section 4.4 Special warnings and precautions for use: Monitoring and section 5.2 Pharmacokinetic properties).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Monitoring

Since mercaptopurine 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 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 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 and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine. 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 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 is not advised. Ribavirin may reduce efficacy and increase toxicity of mercaptopurine (see Section 4.5 Interaction with other medicinal products and other forms of interactions).

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 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 Interaction with other medicinal products and other forms of interactions: Myelosuppressive agents).

Hepatotoxicity
Mercaptopurine 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 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 in patients with renal impairment and/or hepatic impairment (see section 4.2 and section 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 Puri-Nethol, 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 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.

Two cases have been documented of the occurrence of acute non-lymphatic leukaemia in patients who received mercaptopurine, 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 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 played a causative role.

A patient with Hodgkin’s disease treated with mercaptopurine and multiple additional cytotoxic agents developed acute myelogenous leukaemia.
Twelve and a half years after mercaptopurine 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) or mercaptopurine , 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. 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.

Infections

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

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

Paediatric population

Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving mercaptopurine (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 should only receive 25% of the usual dose of mercaptopurine since allopurinol decreases the rate of catabolism of mercaptopurine (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, 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 and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine. This problem could be exacerbated by co-administration with medicinal products that inhibit TPMT, such as olsalazine, mesalazine or sulfazalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving mercaptopurine 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 and 6-thioguanine.

Hypersensitivity

Patients suspected to have previously presented with a hypersensitivity reaction to mercaptopurine should not be recommended to use its pro-drug azathioprine, unless the patient has been confirmed as hypersensitive to mercaptopurine with allergological tests, and 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 mercapopurine prior to initiating treatment.

Lesch-Nyhan syndrome

Limited evidence suggests that neither 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 mercaptopurine or azathioprine is not recommended in these patients.

UV exposure

Patients treated with 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.

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 tablets-See section 6.6

4.5 Interactions with other medicinal products and other forms of interaction

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

Effects of mercaptopurine 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 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, making dose adjustments as necessary.

Effects of other medicinal products on mercaptopurine

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 are administered concomitantly it is essential that only a quarter of the usual dose of mercaptopurine is given since allopurinol decreases the rate of metabolism of mercaptopurine via xanthine oxidase. Also other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of mercaptopurine 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 sulfazalazine) inhibit the TPMT enzyme. Therefore, lower doses of mercaptopurine 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 AUC by approximately 31% and methotrexate (2 or 5 g/m^2 intravenously) increased mercaptopurine AUC by 69 and 93%, respectively. Therefore, when mercaptopurine is administered concomitantly with high dose methotrexate, the dose should be adjusted and white blood cell counts should be very closely monitored.

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. Therefore, close monitoring of haematological parameters is necessary if mercaptopurine is administered with concomitant Infliximab therapy.

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 and ribavirin; therefore concomitant administration of ribavirin and mercaptopurine is not advised (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties: metabolism).

Myelosuppressive agents

When mercaptopurine 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 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 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 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. 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 mercatopurine 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 during pregnancy.

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

Breast-feeding

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

Fertility

The effect of mercaptopurine 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 in combination with corticosteroids.

Maternal exposure:

Normal offspring have been born after 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 mercaptopurine treatment in combination with other chemotherapy agents.

Paternal exposure

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

4.7 Effects on ability to drive and use machines

There are no data on the effect of mercaptopurine 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 is bone marrow suppression leading to leucopenia and thrombocytopenia.

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.

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;
	Unknown	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#
Gastrointestinal Disorders	Common	Nausea; vomiting; pancreatitis in the IBD population (an unlicensed indication), stomatitis.
	Rare	Oral ulceration; pancreatitis (in the licensed indications)
	Very rare	Intestinal ulceration
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

In the paediatric population

Description of selected adverse reactions:

Hepatobiliary disorders

Mercaptopurine is hepatotoxic in animals and man. The histological findings in man have shown hepatic necrosis and biliary stasis.

The incidence of hepatotoxicity varies considerably and can occur with any dose but more frequently when the recommended dose of 2.5 mg/kg bodyweight daily or 75 mg/m^2 body surface area per day is exceeded.

Monitoring of liver function tests may allow early detection of hepatotoxicity. Gamma glutamyl transferase (GGT) levels in plasma may be particularly predictive of withdrawal due to hepatotoxicity. This is usually reversible if mercaptopurine therapy is stopped soon enough but fatal liver damage has occurred.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
In addition, you may also report to: Padagis.co.il

4.9 Overdose

Symptoms and signs

Gastrointestinal 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. Liver dysfunction and gastroenteritis may also occur.

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

Management

As there is no known antidote, blood 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 mercaptopurine 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 is sulphydryl analogue of the purine bases, adenine and hypoxanthine and acts as a cytotoxic antimetabolite.

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

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

Pharmacodynamic effects

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

5.2-Pharmacokinetic properties

Absorption

The bioavailability of oral mercaptopurine 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 75 mg/m^2 to 14 children with acute lymphoblastic leukaemia, the mean C_{max} was 0.89µM, with a range of 0.29 - 1.82µM and T_{max} was 2.2 hours with a range of 0.5 - 4 hours.

The mean relative bioavailability of mercaptopurine was approximately 26 % lower following administration with food and milk compared to an overnight fast. Mercaptopurine 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 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 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 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 may predict adverse drug reactions to mercaptopurine 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 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 clearance and half-life after IV infusion was 719 (+/-610) ml/min/m^2 and 0.9 (+/-0.3) hours respectively.

<u>Special patient populations</u>

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

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 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 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 (see Section 4.2 Posology and method of administration).

5.3 Preclinical safety data

Genotoxicity
Mercaptopurine, 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 is potentially carcinogenic.

Teratogenicity
Mercaptopurine 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
Magnesium stearate
Stearic acid

6.2 Incompatibilities

None known

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.
Keep dry. Keep the bottle tightly closed.

6.5 Nature and Contents of Container

Amber glass bottle with a child resistant high density polyethylene closures with induction heat seal liners.
Pack size: 25 tablets

6.6 Instructions for Use/Handling

Safe handling:

It is recommended that Puri-Nethol 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. MANUFACTURER:

Aspen Pharma Trading Ltd., Dublin, Ireland

8. REGISTRATION HOLDER:

Padagis Israel Agencies Ltd., 1 Rakefet st., Shoham, Israel

9. REGISTRATION NUMBER: 033-44-22532-00

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