# Summary of Product Characteristics

## 1 Name of the medicinal product

Puri-Nethol Tablets 50 mg

## 2 Qualitative and Quantitative composition

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.

Pale yellow, round tablets, biconvex, scored on one side, engraved GX above the score and EX2 below the score and plain on the other side.

The scoreline 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 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).

- **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 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 decreases 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 mercaptopurine or to any component of the preparation.
Lactation.
In view of the seriousness of the indications there are no other absolute contraindications.

## 4.4 Special warnings and precautions for use

*mercaptopurine is an active cytotoxic agent for use only under the direction of physicians experienced in the administration of such agents.*

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended in patients with ALL or AML. 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).

**Safe handling of Puri-Netol tablets**

See section 6.6 Instructions for disposal; Safe handling

**Monitoring**

*since 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 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 mercaptopurine.

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.

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 drugs 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.

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 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 sulfasalazine. 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.

**Renal and/or hepatic impairment**

Caution is advised during the administration of 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 Posology and method of administration and section 5.2 Pharmacokinetic properties: Special populations).

**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 hypernephroma patient who received an unstated dose of 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 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.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease (IBD) population have been received when mercaptopurine is used in combination with anti-TNF agents (see section 4.8 Undesirable Effects).

**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.

**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.

**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.

**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.

**Lactose**

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

**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**

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4 Special warnings and precautions for use).

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.

**Effect of concomitant medicinal products on mercaptopurine**

**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).

**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 mercaptopurine are administered concomitantly it is essential that only 25 % of the usual dose of mercaptopurine is given mercaptopurine(see section 4.2 Posology and method of administration: Medicinal product interactions).

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 sulfasalazine) 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 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 mercaptopurine on other medicinal products**

**Anticoagulants**

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with mercaptopurine; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with mercaptopurine

## 4.6 Fertility, pregnancy and lactation

**Fertility**

The effect of 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 mercaptopurine.

**Pregnancy**

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

The use of 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 mercaptopurine tablets, during treatment and for at least three months after receiving the last dose.

Studies of mercaptopurine in animals have shown reproductive toxicity (See section 5.3 Preclinical safety data). The potential risk for humans is largely unknown.

***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.

**Breast-feeding**

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

## 4.7 Effect 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 medical product.

## 4.8 Undesirable Effects

**Summary of the safety profile**

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 is bone marrow suppression leading to leucopenia and thrombocytopenia.

**Tabulated list of adverse reactions**

The following convention has been utilised for the classification of frequency:
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)

| 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 (see section 4.4 Special warnings and precautions for use); hepatosplenic T-cell lymphoma in patients with IBD (an unlicensed indication) when used in combination with anti-TNF agents (see section 4.4. Special warnings and precautions for use). |
| Blood and Lymphatic System Disorders | Very common | Bone marrow suppression; leucopenia and thrombocytopenia. |
| | Uncommon | Anaemia |
| Immune System Disorders | Rare | Hypersensitivity reactions with the following manifestations have been reported: Arthralgia; skin rash; drug fever. |
| | Very rare | Hypersensitivity reactions with the following manifestations have been reported: Facial oedema |
| Metabolism and nutrition disorders | Uncommon | Anorexia |
| | Not known | Hypoglycaemia# |
| 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 |
| Hepatobiliary Disorders | Common | Biliary stasis; hepatotoxicity |
| | Rare | Hepatic necrosis |
| Skin and Subcutaneous Tissue Disorders | Rare | Alopecia |
| | Not known | Photosensitivity |
| Reproductive system and breast disorders | Very 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 at http://sideeffects.health.gov.il
In addition, you can report to Perrigo via the following address: www.perrigo-pharma.co.il

## 4.9 Overdose

**Symptoms and signs**

Gastrointestinal 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 mercaptopurine. Liver dysfunction and gastroenteritis may also occur.

The risk of overdosage is also increased when allopurinol is being given concomitantly with mercaptopurine (see 4.5 Interaction with other medicinal products and other forms of interaction).

**Treatment**
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 (TGNs) for cytotoxicity. The

TGNs and other, metabolites (e.g. 6-methylmecaptopurine 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 medicinal product.

**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**

**Pharmacokinectics**

**Absorption**

The bioavailability of oral mercaptopurine shows considerable inter-individual variability. When administered 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%). The variable bioavailability probably results from the metabolism of a significant portion of mercaptopurine during first-pass hepatic metabolism.

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 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.

**Special patient populations**

**• Older population**
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 6-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

**• Carcinogenesis, mutagenesis**

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) mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

**• Teratogenicity**

Mercaptopurine causes embryolethality and severe teratogenic effects in the 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 are 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
Modified maize starch
Magnesium stearate
Stearic acid

### 6.2 Incompatibilities

None known

### 6.3 Shelf life

The expiry date is indicated on the packaging

### 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 Special precautions for disposal of a used medicinal product or waste material derived from such a medicinal products and other handling of the product**

**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 drugs.

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

**7. MANUFACTURER**:

**Ecxella GmbH, Feucht, Germany for Aspen**

**8. LICENSE HOLDER:**

**Perrigo Israel Agencies Ltd. 1 Rakefet st., Shoham, Israel**

**9. LICENSE NUMBER: 033-44-22532-00**

**REVEISED IN: November 2020**

18/11/2020