SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Purimmun 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of mercaptopurine monohydrate.

Excipient with known effect:
Lactose: 59 mg per tablet
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round 6 mm yellowish tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Purimmun is indicated for the treatment of acute promyelocytic leukemia (APL) / acute myeloid leukemia M3 (AML M3) in adults, adolescents and children.

4.2 Posology and method of administration

Treatment with Purimmun must be under the supervision of a physician or other healthcare professional experienced in the treatment of patients with acute promyelocytic leukemia (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).

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 leukemia and the literature should be consulted for details.

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
Since mercaptopurine 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 and its metabolites and therefore a greater cumulative effect, consideration should be given to reduced starting doses in patients with impaired renal function (see section 5.2). Patients should be closely monitored for dose-related adverse reactions.

Hepatic impairment
Since mercaptopurine pharmacokinetics has not been formally studied in hepatic impairment, no specific dose recommendations can be given. Since there is a risk for reduced elimination of mercaptopurine, 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
Mercaptopurine is also available in oral suspension form. The mercaptopurine 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 are administered concomitantly, it is essential that only 25% of the recommended 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).

TPMT deficient patients
Mercaptopurine is metabolised by the polymorphic TPMT enzyme. 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. 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 (see sections 4.4 and 5.2).

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

<u>Method of administration</u>
Mercaptopurine may be taken with food or on an empty stomach, but patients should standardise the method of administration. Mercaptopurine should not be taken with milk or dairy products (see section 4.5). Mercaptopurine should be taken at least 1 hour before or 2 hours after ingestion of milk or dairy products.

Mercaptopurine 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 is an active cytotoxic agent for use only under the direction of physicians 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 anemia. 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 serious 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 hematological monitoring of the patient is recommended when switching between different medication forms 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 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 immunosuppressants 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).

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).

Hepatotoxicity
Mercaptopurine is hepatotoxic and liver function tests should be monitored weekly during treatment. The level of gamma glutamyl transferase (GT) in plasma can be especially predictive of discontinuation due to hepatotoxicity. More frequent monitoring may be advisable in those with preexisting 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. Consideration should be given to reducing the dosage in these patients and hematological response should be carefully monitored (see sections 4.2 and section 5.2).

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 are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and nonmelanoma), 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 leukemic 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.

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 leukemia in patients who received mercaptopurine, in combination with other drugs, for nonneoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with mercaptopurine and later developed acute non-lymphatic leukemia, 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 leukemia.

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

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease*population have been received when they have been treated with treated with azathioprine (pro-drug of mercaptopurine) or mercaptopurine is used in combination with or without anti-TNF-alpha agents. This rare type of T cell lymphoma has an aggressive disease course and is usually fatal (see 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.

Metabolism and nutrition disorders
Administration of purine analogues, azathioprine and mercaptopurine, may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Few cases have been reported with the use of azathioprine and mercaptopurine, especially in patients with IBD (Crohn’s disease, colitis ulcerative). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis), gastroenteritis (diarrhoea), or neurologic deficits, including cognitive decline (dementia). Appropriate medical care with niacin/nicotinamide supplementation must be initiated, and dose reduction or discontinuation of azathioprine must be considered.

Infections
Patients treated with mercaptopurine monotherapy or in combination with other immunosuppressive drugs, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection and reactivation of the virus. Infectious disease and complications can be more serious in these patients than in patients who did not undergo treatment.

Prior exposure to or infection with the varicella zoster should be considered prior to initiation of therapy. Local guidelines may be taken into account, including prophylactic treatment if necessary. Serological tests before starting treatment should be considered for hepatitis B. Local guidelines may be taken into account, including prophylactic treatment in cases where serological tests gave positive affirmation. Cases of infections associated with neutropenia have been reported in patients receiving mercaptopurine. If patients experience infection during treatment, appropriate measures, which may include antiviral therapy and supportive care.

Patients with NUDT15 variant
Patients with inherited mutated NUDT15 gene are at increased risk for severe mercaptopurine 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 (see section 4.8). The majority of reported cases were in children under the age of six or with a low body mass index.

Interactions

Xanthine oxidase inhibitors
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 allopurinol decreases the rate of catabolism of mercaptopurine (see sections 4.2 and 4.5)

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 coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfazalazine. Also, a possible association between decreased TPMT activity and secondary leukemias and myelodysplasia has been reported in individuals receiving 6–mercaptopurine in combination with other cytotoxics (see section 4.8).

About 0.3% (1: 300) of patients have low or no detectable enzyme activity. Approximately 10% of patients with low or intermediate TPMT activity, and 90% of patients have normal TPMT activity. There may also be a group of around 2% with a 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-tioguanine.

Hypersensitivity
Patients suspected of having suffered a hypersensitivity reaction to mercaptopurine should not be recommended to use its pro-drug azathioprine, unless the patient has been confirmed to be hypersensitive to mercaptopurine by 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 the mercaptopurine nor its pro-drug azathioprine are effective in patients with the rare inherited disease total hypoxanthine-deficient (Lesch-Nyhan syndrome). The use of mercaptopurine or azathioprine is not recommended in these patients.

UV exposure
Patients treated with Purimmun is more sensitive to sunlight. Exposure to sunlight and UV light should be limited, and patients should be advised to wear protective clothing and use sunscreen with a high protection factor.

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

Safe handling of Purimmun
See section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Taking mercaptopurine with food may decrease systemic exposure slightly. mercaptopurine can be taken with food or on an empty stomach, but patients should keep to a route of administration to avoid large variations in exposure. The dose must not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme that metabolizes mercaptopurine and therefore may lead to reduced plasma concentrations of mercaptopurine.

Effect of concomitant medicinal products on mercaptopurine
Concomitant administration of yellow fever vaccine is contraindicated, due to the risk of fatal disease in immune compromised patients (see section 4.3).
Vaccinations with other live organism vaccines are not recommended in patients with impaired immune response (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, 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 monohydrate 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 (see section 4.2).

Also other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of mercaptopurine. Co-administration is not recommended, because 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).

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 and infliximab. Patients treated with azathioprine were hit by transient increases in the levels of 6-TGN (6-tioguaninnukleotid, an active metabolite of azathioprine) and decreases in the average number of leukocytes in the first weeks after infusion of infliximab, 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 sections 4.4 and 5.2).

Myelosuppressive agents
When mercaptopurine is combined with other myelosuppressive agents caution should be used; dose reductions may be needed based on hematological monitoring (see section 4.4).

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 mercaptopurine 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.

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

Breastfeeding
Mercaptopurine 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 therapy on human fertility is unknown but there are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence. Transient evident 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 mercatopurine treatment in combination with other chemotherapy agents.

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

4.7 Effects on ability to drive and use machines

There is no data about the effects of mercaptopurine on the ability to drive vehicles and use machines and such effects could not be attributed to the pharmacological properties of Purimmun 50 mg tablets.

4.8 Undesirable effects

For mercaptopurine there is a lack of modern clinical documentation which can serve as support for accurately determining the frequency of undesirable effects. The frequency categories assigned to the adverse drug reactions below are estimates for most reactions, suitable data for calculating incidence are not available. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

The main side effect of treatment with mercaptopurine is bone marrow suppression leading to leucopenia and thrombocytopenia.

The following definitions of frequencies are used:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1 000 and < 1/100
Rare	≥ 1/10 000 and < 1/1 000
Very rare	< 1/10 000
Not known	cannot be estimated from the available data

Organ system	**Frequency**	**Adverse effect**
Infections and infestations	Uncommon	Bacterial and viral infections, infections associated with neutropenia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and nonmelanomas), 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)
	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	Anemia
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	Mucosal inflammation
Investigations	Not known	Coagulation factors decreased

*In paediatric population

The most frequently reported side effect of mercaptopurine is dose-dependent myelosuppression, and as a result leukopenia and thrombocytopenia.

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. Hepatotoxicity 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. Healthcare professionals are asked to report any suspected adverse reaction via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
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. Hematological 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 xanthine oxidase inhibitors are being given concomitantly with mercaptopurine (see section 4.5).

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 Center.

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 is an inactive pro-drug that acts as purine antagonist after cellular uptake and intracellular conversion into thioguanine-nucleotides for cytotoxicity.
Mercaptopurine metabolites suppress the *de novo* synthesis of purine and purine-nucleotide formation. The thioguanine nucleotides are also incorporated into nucleic acids and this leads to the cytotoxic effect of the active substance.
Cross-resistance usually exists between mercaptopurine and 6-thioguanine.

Pharmacodynamic effect
The cytotoxic effect of mercaptopurine may be related to the levels of thioguanine nucleotides in red blood cells, but not to the plasma concentration of mercaptopurine.

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 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 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).

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, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression. The predominant enzymes responsible for the metabolism of 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 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 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

Elderly
No specific studies have been carried out in the elderly (see section 4.2).

Renal impairment
Studies with a pro-drug of mercaptopurine have shown no difference in mercaptopurine pharmacokinetics in uremic patients compared to renal transplant patients. Since little is known about the active metabolites of mercaptopurine in renal impairment, consideration should be given to reducing the dosage in patients with impaired renal function (see section 4.2). Mercaptopurine and/or its metabolites are eliminated by hemodialysis, 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).

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 nontoxic 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
Maize starch

Maltodextrin
Stearic acid
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original glass container in order to protect from light.

6.5 Nature and contents of container

Purimmun 50 mg tablets are packed in amber glass container and a child-proof propylene cap with silicagel.

25 tablets in amber glass container.
25 tablets/pack
50 (2x25) tablets/pack

6.6 Special precautions for disposal and other handling

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

Anyone handling Purimmun 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 Purimmun.

Purimmun contact with skin or mucous membrane must be avoided. If Purimmun 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 Purimmun (see section 4.6).

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

Disposal
Purimmun is cytotoxic. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[to be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

2025-04-04