

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mercaptopurine Silver Pharma 50 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:

Each tablet contains 46.13 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pale yellow 6 mm round tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mercaptopurine is indicated for the treatment of acute leukaemia in adults, adolescents and children.. It may be utilised in:

- Acute promyelocytic leukaemia (APL)/Acute myeloid leukaemia M3 (AML M3).

4.2 Posology and method of administration

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

Posology

Adults and paediatric population

For adults and children the usual recommended dose is 2.5 mg/kg bodyweight per day, or 50 to 75mg/m² body surface area per day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with 6-mercaptopurine.

Daily dose intake in the evening is recommended (see Method of administration in this section).

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

In overweight children, dose may be close to the maximum daily dose. Therefore, close monitoring of the response to treatment is recommended (see section 5.2).

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

Elderly

It is advisable to monitor renal and hepatic function in these patients, and if impaired function is observed, reduction of the 6-mercaptopurine dosage should be considered.

Renal impairment

Consideration should be given to reduce the dose in patients with impaired renal function (see section 5.2).

Hepatic impairment

Consideration should be given to reduce the dose in patients with impaired hepatic function (see section 5.2).

Medicinal product interactions

When xanthine oxidase inhibitors, such as allopurinol, and 6-mercaptopurine are administered concomitantly it is essential that only 25 % of the usual dose of 6-mercaptopurine is given since allopurinol decreases the rate of catabolism of 6-mercaptopurine (see section 4.5).

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe 6-mercaptopurine toxicity from conventional doses of 6-mercaptopurine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established. Most patients with heterozygous TPMT deficiency can tolerate recommended 6-mercaptopurine doses, but some may require dose reduction (see section 4.4 Special warnings and precautions for use: Monitoring and section 5.2 Pharmacokinetic properties).

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity (see 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 6-mercaptopurine therapy. In any case, close monitoring of blood counts is necessary.

Method of administration

For oral use.

6-mercaptopurine may be taken with food or on an empty stomach, but patients should standardise the method of administration.

6-mercaptopurine tablets should not be taken with milk or dairy products (see section 4.5). 6-mercaptopurine should be taken at least 1 hour before or 2 hours after milk or dairy products.

6-mercaptopurine shows diurnal variation in its pharmacokinetics and efficacy. Studies carried out in children with acute lymphoblastic leukaemia suggested that administration of 6-mercaptopurine in the evening lowered the risk of relapse compared with morning administration. Therefore, the daily dose is recommended to be taken at night.

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

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

Safe handling of 6-mercaptopurine tablets

See section 6.6 for a safe handling of the tablets.

Cytotoxicity and haematological monitoring

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

Treatment with 6-mercaptopurine causes bone marrow suppression leading to leukopenia and thrombocytopenia and less frequently, 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 there is severe renal and/or hepatic impairment.

6-mercaptopurine is also available as an oral suspension. The tablet and oral suspension forms of 6-mercaptopurine are not bioequivalent from the plasma peak point of view. It is therefore advisable to intensify the hematological monitoring of the patient during the change of formulation.

The leukocyte and platelet counts continue to decline after treatment is stopped, so at the first sign of an abnormally large fall in the counts, treatment should be interrupted immediately.

Bone marrow suppression is reversible if 6-mercaptopurine is withdrawn early enough.

During remission induction in acute myelogenous leukaemia, the patient may frequently have to survive a period of relative bone marrow aplasia and it is important that adequate supportive facilities are available.

The dosage of 6-mercaptopurine may need to be reduced when this agent is combined with other medicinal products whose primary or secondary toxicity is myelosuppression (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 6-mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with 6-mercaptopurine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6 mercaptopurine in combination with other cytotoxics (see section 4.8 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.

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-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 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.

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 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 6-mercaptopurine is not advised. Ribavirin may reduce efficacy and increase toxicity of 6-mercaptopurine (see section 4.5 Interaction with other medicinal products and other forms of interactions).

Hepatotoxicity

6-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 6-mercaptopurine immediately if jaundice becomes apparent.

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.

Cross Resistance

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

Hypersensitivity

Patients suspected to have previously presented with a hypersensitivity reaction to 6-mercaptopurine should not be recommended to use its pro-drug azathioprine, unless the patient has been confirmed as hypersensitive to 6-mercaptopurine with allergological tests, and tested negative for azathioprine. As azathioprine is a pro-drug of 6-mercaptopurine, patients with

a previous history of hypersensitivity to azathioprine must be assessed for hypersensitivity to 6-mercaptopurine prior to initiating treatment.

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

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

Renal and/or hepatic impairment

Caution is advised during the administration of 6-mercaptopurine in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored (see section 4.2 and section 5.2).

Mutagenicity and carcinogenicity

Increases in chromosomal aberrations were observed in the peripheral lymphocytes of leukaemic patients, in a hypernephroma patient who received an unstated dose of 6-mercaptopurine and in patients with chronic renal disease treated at doses of 0.4 to 1.0 mg/kg/day.

Two cases have been documented of the occurrence of acute non-lymphatic leukaemia in patients who received 6-mercaptopurine, in combination with other drugs for non-neoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with 6-mercaptopurine and later developed acute non-lymphatic leukaemia, but it is not clear whether this was part of the natural history of the disease or if the 6-mercaptopurine played a causative role.

A patient with Hodgkin's disease treated with 6-mercaptopurine and multiple additional cytotoxic agents developed acute myelogenous leukaemia.

Twelve and a half years after 6-mercaptopurine treatment for myasthenia gravis, a female patient developed chronic myeloid leukaemia.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease (IBD) population (unlicensed indication) have been received when 6-mercaptopurine is used in combination with anti-TNF agents (see section 4.8).

Patients receiving immunosuppressive therapy, including mercaptopurine are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

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 6-mercaptopurine alone or in combination with other immunosuppressive agents, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection, and viral reactivation. The infectious disease and complications may be more severe in these patients than in non-treated patients.

Prior exposure to or infection with varicella zoster virus should be taken into consideration prior to starting treatment. Local guidelines may be considered, including prophylactic therapy if necessary. Serologic testing prior to starting treatment should be considered with respect to hepatitis B. Local guidelines may be considered, including prophylactic therapy for cases which

have been confirmed positive by serologic testing. Cases of neutropenic sepsis have been reported in patients receiving 6-mercaptopurine for ALL.

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

Lesch-Nyhan syndrome

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

UV exposure

Patients treated with 6-mercaptopurine are more sensitive to the sun. Exposure to sunlight and UV light should be limited, and patients should be recommended to wear protective clothing and to use a sunscreen with a high protection factor.

Xanthine oxidase inhibitors

Patients treated with the xanthine oxidase inhibitors allopurinol, oxipurinol or thiopurinol, and 6-mercaptopurine should only receive 25 % of the usual dose of 6-mercaptopurine since allopurinol decreases the rate of catabolism of 6-mercaptopurine (see Section 4.2 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 6-mercaptopurine; therefore higher doses of the anticoagulant may be needed (see section 4.5).

Paediatric population

Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving 6-mercaptopurine (see section 4.8). The majority of reported cases were in children under the age of six or with a low body mass index.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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). The administration of 6-mercaptopurine with food may decrease systemic exposure slightly. 6-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 6-mercaptopurine and might therefore lead to reduced plasma concentrations of mercaptopurine.

Effect of concomitant medicinal products on 6-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 6-mercaptopurine and ribavirin; therefore concomitant administration of ribavirin and 6-mercaptopurine is not advised (see section 4.4 Special warnings and precautions for use and section 5.2).

Myelosuppressive agents

When 6-mercaptopurine is combined with other myelosuppressive agents caution should be used; dose reductions may be needed based on haematological monitoring (see section 4.4).

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol, which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxipurinol and/or thiopurinol and 6-mercaptopurine are administered concomitantly it is essential that only 25 % of the usual dose of 6-mercaptopurine is given since allopurinol decreases the rate of catabolism of 6-mercaptopurine (see section 4.2).

Other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of 6-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, meslazine or sulfasalazine) inhibit the TPMT enzyme. Therefore, lower doses of 6-mercaptopurine may need to be considered when administered concomitantly with aminosalicylate derivatives (see section 4.4).

Methotrexate

Methotrexate (20 mg/m² orally) increased 6-mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m² intravenously) increased 6-mercaptopurine AUC by 69 and 93%, respectively. Therefore, when 6-mercaptopurine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

Infliximab

Interactions have been observed between azathioprine and infliximab. Patients treated with azathioprine was hit by transient increases in the levels of 6-TGN (6-thioguanine nucleotide, 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.

Effect of 6-mercaptopurine on other medicinal products

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with 6-mercaptopurine; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with 6-mercaptopurine.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving 6-mercaptopurine tablets. Sexually active men and women should use effective contraception during treatment and for at least three months after receiving the last dose.

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

Pregnancy

Substantial transplacental and transamniotic transmission of 6-mercaptopurine and its metabolites from the mother to the foetus have been shown to occur.

The use of 6-mercaptopurine should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

Breast-feeding

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

Fertility

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

There are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence. Transient oligospermia has been reported following exposure to 6-mercaptopurine.

Maternal exposure:

Normal offspring have been born after 6-mercaptopurine therapy administered as a single chemotherapy agent during human pregnancy, particularly when given prior to conception or after the first trimester.

Abortions and prematurity have been reported after maternal exposure. Multiple congenital abnormalities have been reported following maternal 6-mercaptopurine treatment in combination with other chemotherapy agents.

Paternal exposure:

Congenital abnormalities and spontaneous abortions have been reported after paternal exposure to 6-mercaptopurine.

4.7 Effects on ability to drive and use machines

There are no data on the effect of 6-mercaptopurine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the medicinal product.

4.8 Undesirable effects

Summary of the safety profile

For 6-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 6-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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known

Infections and infestations	
Uncommon	Bacterial and viral infections, infections associated with neutropenia
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Very Rare	Secondary Leukaemia and myelodysplasia (see section 4.4)
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).
Not known	Hepatosplenic T-cell lymphoma in patients with 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	
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 (In the paediatric population)
Gastrointestinal Disorders	
Common	Nausea; vomiting; stomatitis; diarrhoea; 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: erythema nodosum
Reproductive system and breast disorders	
Very Rare	Transient oligospermia

Description of selected adverse reactions:Hepatobiliary disorders

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

The incidence of hepatotoxicity varies considerably and can occur with any dose but more frequently when the recommended dose of 2.5 mg/kg bodyweight daily or 75 mg/m² body surface area per day is exceeded.

Monitoring of liver function tests may allow early detection of hepatotoxicity. Gamma glutamyl transferase (GGT) levels in plasma may be particularly predictive of withdrawal due to hepatotoxicity. This is usually reversible if 6-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 reactions via the national reporting system:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 OverdoseSymptoms and signs

Gastro-intestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of overdose having occurred. The principal toxic effect is on the bone marrow, resulting in myelosuppression. Haematological toxicity is likely to be more profound with chronic overdose than with a single ingestion of 6-mercaptopurine. Liver dysfunction and gastroenteritis may also occur.

The risk of overdose is also increased when allopurinol is being given concomitantly with 6-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 activated charcoal) may not be effective in the event of 6-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

6-Mercaptopurine is sulphhydryl analogue of the purine base hypoxanthine and acts as a cytotoxic anti-metabolite

6-Mercaptopurine is an inactive pro-drug, which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for cytotoxicity. The TGNs and other metabolites (e.g. 6-methyl-mecaptopurine

ribonucleotides) inhibit de novo purine synthesis and purine nucleotide interconversions. The thioguanine nucleotides are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the drug.

Pharmacodynamic effects

The cytotoxic effect of 6-mercaptopurine can be related to the levels of red blood cell 6-mercaptopurine derived thioguanine nucleotides, but not to the plasma 6-mercaptopurine concentration.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of oral 6-mercaptopurine shows considerable inter-individual variability. When administered at a dosage of 75 mg/m² to 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 6-mercaptopurine during first-pass hepatic metabolism.

After oral administration of 6-mercaptopurine 75 mg/m² to 14 children with acute lymphoblastic leukaemia, the mean C_{max} was 0.89 µM, with a range of 0.29-1.82 µM and T_{max} was 2.2 hours with a range of 0.5-4 hours.

The mean relative bioavailability of 6-mercaptopurine was approximately 26 % lower following administration with food and milk compared to an overnight fast. 6-mercaptopurine is not stable in milk due to the presence of xanthine oxidase (30 % degradation within 30 minutes). (see Section 4.2).

Distribution

The mean apparent distribution volume of mercaptopurine is 0.9 (± 0.8) L / Kg, although this data may be underestimated because mercaptopurine has a clearance through the body (not only through the liver).

Concentrations of 6-mercaptopurine in cerebrospinal fluid (CSF) are low or negligible after IV or oral administration (CSF: plasma ratios of 0.05 to 0.27). Concentrations in the CSF are higher after intrathecal administration.

Biotransformation

6-mercaptopurine is extensively metabolized by many multi-step pathways to active and inactive metabolites, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression. The predominant enzymes responsible for the metabolism of 6-mercaptopurine or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT), xanthine oxidase, inosine monophosphate dehydrogenase (IMPDH), and hypoxanthine guanine phosphoribosyltransferase (HPRT). Additional enzymes involved in the formation of active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which form TGNs) and inosine triphosphate pyrophosphatase (ITPase). There are also multiple inactive metabolites formed via other pathways.

There is evidence that polymorphisms in the genes encoding the different enzyme systems involved with metabolism of 6-mercaptopurine may predict adverse drug reactions to 6-mercaptopurine therapy. For example, individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations (see Section 4.4).

Thiopurine S-Methyltransferase (TPMT)

The activity of the TPMT enzyme is inversely related to the concentration in the red blood cells of the nucleotides derived from thioguanine; a higher concentration of thioguanine nucleotides results in a greater decrease in the white blood cell count and neutrophils. People with TPMT enzyme deficiency develop a higher concentration of cytotoxic thioguanine nucleotides.

Genotype tests can determine a patient's allele pattern. Currently, 3 alleles - TPMT * 2, TPMT * 3A and TPMT * 3C - account for about 95% of people with reduced levels of TPMT enzyme activity. Approximately 0.3% (1: 300) of patients have two non-functional alleles (homozygous deficiency) of the TPMT enzyme gene and have little or no detectable enzyme activity. Approximately 10% of patients have a non-functional TPMT enzyme allele (heterozygous) resulting in low or intermediate activity of the TPMT enzyme and 90% of people have a normal TPMT enzyme activity with both alleles functional. There may also be a group of approximately 2% who have a high activity of the TPMT enzyme. Phenotype tests determine the nucleotide level of thiopurine or TPMT activity in red blood cells and may also be informative (see section 4.4).

Elimination

In a study with 22 patients the mean 6-mercaptopurine clearance and half-life after IV infusion was 864 mL/min/m² and 0.9 hours respectively. The mean renal clearance reported in 16 of these patients was 191 mL/min/m². Only about 20 % of the dose was excreted in the urine as intact drug after IV administration. In a study with 7 children patients the mean 6-mercaptopurine clearance and half-life after IV infusion was 719 (+/-610) ml/min/m² and 0.9 (+/-0.3) hours respectively.

Special populations

Elderly

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

Renal impairment

Studies with a pro-drug of 6-mercaptopurine have shown no difference in 6-mercaptopurine pharmacokinetics in uremic patients compared to renal transplant patients. Since little is known about the active metabolites of 6-mercaptopurine in renal impairment, consideration should be given to reducing the dosage in patients with impaired renal function (*see Dosage and Administration*).

6-mercaptopurine and/or its metabolites are eliminated by haemodialysis, with approximately 45 % of radioactive metabolites eliminated during dialysis of 8 hours.

Hepatic impairment

A study with a pro-drug of 6-mercaptopurine was performed in three groups of renal transplant patients: those without liver disease, those with hepatic impairment (but no cirrhosis) and those with hepatic impairment and cirrhosis. The study demonstrated that 6-mercaptopurine exposure was 1.6 times higher in patients with hepatic impairment (but no cirrhosis) and 6 times higher in patients with hepatic impairment and cirrhosis, compared to patients without liver disease (see Section 4.2).

Overweight children

In a clinical study conducted in the United States, 18 children (between 3 and 14 years old) were uniformly divided into two groups; whether they are weight / height ratio above or below the 75th percentile. Each child was in maintenance treatment with mercaptopurine at a dose calculated based on their body surface area. The median mercaptopurine AUC (0-∞) in the group of children with a percentile above the 75th percentile was 2.4 times lower than in the group below the 75th percentile.

5.3 Preclinical safety data

Genotoxicity

6-Mercaptopurine, in common with other antimetabolites, is potentially mutagenic in man and chromosome damage has been reported in mice and rats, and man.

Carcinogenesis

In view of its action on cellular deoxyribonucleic acid (DNA) 6-mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

Teratogenicity

6-Mercaptopurine causes embryoletality and severe teratogenic effects in mice, rats, hamsters and rabbits at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and type of malformations is dependent on the dose and the stage of gestation at the time of administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packed in two Alu-PVC blisters of 12 tablets each one, packed inside a carton pack.

Pack size:: 24 tablets

6.6 Special precautions for disposal

Safe handling

It is recommended to handle mercaptopurine tablets following the local recommendations in force and/or recommendations for handling and elimination of cytotoxic drugs.

Elimination

Cytotoxic The disposal of the unused medication and of all the materials that have been in contact with it, will be carried out in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER

Silver Pharma S.L.
Avenida Del Camino De Lo Cortao 16
Industrial Zona Sur
San Sebastian De Los Reyes
Madrid
28703
Spain

8 MARKETING AUTHORISATION NUMBER

PA23137/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd July 2021

Date of last renewal: 30th April 2023

10 DATE OF REVISION OF THE TEXT

October 2022