SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MERCAPTOPURINE EQUITY, 50 mg 6-mercaptopurine, Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg 6-mercaptopurine.

Excipient with known effect:

Contains sugar (59,00 mg lactose anhydrous per tablet).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets.

Round, yellowish scored tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

MERCAPTOPURINE EQUITY is indicated in combination with other medicines for the treatment of acute leukaemia in adults, adolescents and children.

MERCAPTOPURINE EQUITY is indicated for:

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

4.2 Posology and method of administration

Posology

MERCAPTOPURINE EQUITY treatment should be supervised by a medical practitioner experienced in the management of patients with ALL and APL (AML M3) (see section 4.4).

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

MERCAPTOPURINE EQUITY may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products (see section 4.5). MERCAPTOPURINE EQUITY should be taken at least one hour before or two hours after milk or dairy products (see section 5.1).

Special populations

Adults and paediatric population

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 medicines given in conjunction with MERCAPTOPURINE EQUITY.

The dosage should be adjusted according to individual response and tolerance.

MERCAPTOPURINE EQUITY has been used in various combination therapy schedules for acute leukaemia and the literature and current treatment guidelines should be consulted for details.

MERCAPTOPURINE EQUITY should be administered to children with ALL in the evening to lower the risk of relapse.

Elderly population

No specific studies have been carried out in the elderly. However, 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 EQUITY dosage.

Renal impairment

Consideration should be given to reducing the dose in renal impairment.

Hepatic impairment

Consideration should be given to reducing the dose in hepatic impairment.

Medicine interactions

When the xanthine oxidase inhibitors, such as allopurinol and MERCAPTOPURINE EQUITY are administered concomitantly it is essential that only a quarter (25 %) of the usual dose of MERCAPTOPURINE EQUITY is given since these medicines decreases the rate of catabolism of MERCAPTOPURINE EQUITY. Concomitant administration of other xanthine oxidase inhibitors, such as febuxostat, should be avoided (see section 4.5).

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase TPMT activity are at increased risk for severe MERCAPTOPURINE EQUITY toxicity from conventional doses of MERCAPTOPURINE EQUITY 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 MERCAPTOPURINE EQUITY doses, but some may require dose reduction.

The optimal starting dose for homozygous deficient patients has not been established (see section 4.4).

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and generally require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established.

Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations (see section 5.1).

Paediatric population

Currently available data are described in section 4.2 Special populations; Adults and paediatric population.

Method of administration

For oral use.

Instructions for use/handling

It is recommended that the handling of MERCAPTOPURINE EQUITY tablets follows the "Guidelines for the Handling of Cytotoxic Drugs" according to prevailing local recommendations and/or regulations.

Surplus MERCAPTOPURINE EQUITY tablets should be destroyed in a manner appropriate to the prevailing local recommendations for the destruction of dangerous substances (see section 6.6).

4.3 Contraindications

Known hypersensitivity to mercaptopurine or to any of the excipients of MERCAPTOPURINE EQUITY listed in 6.1.

In view of the seriousness of the indications there are no other absolute contraindications.

4.4 Special warnings and precautions for use

MERCAPTOPURINE EQUITY IS AN ACTIVE CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF CLINICAL PRACTITIONER EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

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 EQUITY is not advised. Ribavirin may reduce efficacy and increase toxicity of MERCAPTOPURINE EQUITY (see section 4.5).

Safe handling of MERCAPTOPURINE EQUITY Tablets

See section 6.6 Instructions for disposal; Safe handling

Monitoring:

Since MERCAPTOPURINE EQUITY 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 EQUITY 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, full 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 leukocyte 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 EQUITY 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 EQUITY may need to be reduced when this medicine is combined with other medicines whose primary or secondary toxicity is myelosuppression (see section 4.5).

Hepatotoxicity

MERCAPTOPURINE EQUITY 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 EQUITY immediately if jaundice becomes apparent (see section 4.8).

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. Hydration and urine alkalinisation may minimize potential renal complications.

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 EQUITY and prone to developing rapid bone marrow depression following the initiation of treatment with MERCAPTOPURINE EQUITY. This problem could be exacerbated by co-administration with medicines that inhibit TPMT, such as olsalazine, mesalazine or sulfazalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6–mercaptopurine in combination with other cytotoxics (see section 4.8). 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. 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.

Cross Resistance

Cross resistance usually exists between 6-mercaptopurine (e.g. MERCAPTOPURINE EQUITY) 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 MERCAPTOPURINE EQUITY prior to initiating treatment.

Renal and/or hepatic impairment

Caution is advised during the administration of MERCAPTOPURINE EQUITY 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 5.2).

Mutagenicity and carcinogenicity

Patients receiving immunosuppressive therapy, including MERCAPTOPURINE EQUITY 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 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 medicines, for non-neoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with 6-mercaptopurine as in MERCAPTOPURINE EQUITY 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 (MERCAPTOPURINE EQUITY) played a causative role.

A patient with Hodgkin's disease treated with 6-mercaptopurine as in MERCAPTOPURINE EQUITY and multiple additional cytotoxic medicines developed acute myelogenous leukaemia.

Twelve and a half years after 6-mercaptopurine as in MERCAPTOPURINE EQUITY 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 as in MERCAPTOPURINE EQUITY is used in combination with anti-TNF medicines (see section 4.8).

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 EQUITY. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with MERCAPTOPURINE EQUITY should be discontinued. Medical practitioners 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 (MERCAPTOPURINE EQUITY) alone or in combination with other

immunosuppressive medicines, 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 as in MERCAPTOPURINE EQUITY for ALL.

Lesch-Nyhan syndrome

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

UV exposure

Patients treated with MERCAPTOPURINE EQUITY 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 MERCAPTOPURINE EQUITY should only receive 25 % of the usual dose of MERCAPTOPURINE EQUITY since allopurinol decreases the rate of catabolism of 6-mercaptopurine (see section 4.2 and 4.5).

Anticoagulants

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

4.5).

MERCAPTOPURINE EQUITY contains lactose anhydrous

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

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

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

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

Effect of concomitant medicines on MERCAPTOPURINE EQUITY

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 MERCAPTOPURINE EQUITY is not advised (see section 4.4 and 5.2).

Myelosuppressive medicines

When MERCAPTOPURINE EQUITY is combined with other myelosuppressive medicines 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 MERCAPTOPURINE EQUITY are administered concomitantly it is essential that only 25 % of the usual dose of MERCAPTOPURINE EQUITY is given (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, mesalazine or sulphasalazine) inhibit the TPMT enzyme. Therefore, lower doses of MERCAPTOPURINE EQUITY may need to be considered when administered concomitantly with aminosalicylate derivatives (see section 4.4).

Methotrexate

Methotrexate (20 mg/m^2 orally) increased 6-mercaptopurine AUC by approximately 31 % and methotrexate (2 or 5 g/m^2 intravenously) increased 6-mercaptopurine AUC by 69 and 93 %, respectively. Therefore, when MERCAPTOPURINE EQUITY 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 6-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 EQUITY on other medicines

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with 6-mercaptopurine as in MERCAPTOPURINE EQUITY; 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 EQUITY.

4.6 Fertility, pregnancy and lactation

The safety of MERCAPTOPURINE EQUITY in pregnancy and lactation has not been established.

Pregnancy

The use of MERCAPTOPURINE EQUITY 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.

Abortions and prematurity have been reported after maternal exposure. Multiple. congenital abnormalities have been reported following maternal MERCAPTOPURINE EQUITY treatment in combination with other chemotherapy medicines.

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

Adequate contraceptive precautions should be advised if either partner is receiving MERCAPTOPURINE EQUITY tablets during treatment and for at least three months after receiving the last dose.

In utero exposure to thiopurines has not been associated with negative effects on long-term childhood development or susceptibility for infectious disease. Normal offspring with normal Apgar scores directly after birth in most cases, have been born after 6-mercaptopurine therapy administered during pregnancy.

Paternal exposure:

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

Breastfeeding

MERCAPTOPURINE EQUITY is excreted into breast milk. Mothers receiving MERCAPTOPURINE EQUITY should not breastfeed.

Fertility

The effect of MERCAPTOPURINE EQUITY therapy on human fertility is unknown.

Oligospermia has been reported following exposure to 6-mercaptopurine as found in MERCAPTOPURINE EQUITY (see section 4.8).

4.7 Effects on ability to drive and use machines

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that MERCAPTOPURINE EQUITY does not adversely affect their ability to do so safely.

4.8 Undesirable effects

a. Summary of the safety profile

For MERCAPTOPURINE EQUITY 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 medicines.

The main side effect of treatment with MERCAPTOPURINE EQUITY is bone marrow suppression leading to leukopenia and thrombocytopenia.

b. Tabulated summary of adverse reactions

MedDRA System Organ Class	**Side Effects**	
Infections and infestations	*Less frequent*	Bacterial and viral infections, infections associated with neutropenia

Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Less frequent*	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), secondary leukaemia and myelodysplasia (see section 4.4); hepatosplenic T-cell lymphoma in patients with IBD (an unlicensed indication) when used in combination with anti-TNF medicines (see section 4.4.)
Blood and lymphatic system disorders	*Frequent*	Bone marrow suppression; leukopenia and thrombocytopenia, anaemia
Immune system disorders	*Less frequent*	Hypersensitivity reactions with the following manifestations have been reported: arthralgia; skin rash; drug fever, hypersensitivity reactions with the following manifestations have been reported: facial oedema
Metabolism and nutrition disorders	*Less frequent*	Anorexia
	Frequency unknown	Hypoglycaemia#
Gastrointestinal disorders	*Frequent*	Nausea; vomiting; pancreatitis in the IBD population (an unlicensed indication)
	Less frequent	Oral ulceration; pancreatitis (in the licensed indications), intestinal ulceration, mild diarrhoea and sprue-like symptoms have been reported
Hepatobiliary disorders	*Frequent*	Biliary stasis; hepatotoxicity
	Less frequent	Hepatic necrosis
Skin and subcutaneous tissue disorders	*Less frequent*	Alopecia
	Frequency unknown	Photosensitivity

Reproductive system and breast disorders	*Less frequent*	Transient oligospermia

In the paediatric population

c. Description of selected adverse reactions:

Hepatobiliary disorders

MERCAPTOPURINE EQUITY 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 EQUITY therapy is stopped soon enough but fatal liver damage has occurred.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 6-mercaptopurine. Liver dysfunction and gastroenteritis may also occur.

The risk of overdosage is also increased when allopurinol is being given concomitantly with MERCAPTOPURINE EQUITY (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 EQUITY 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

Category and class: A 26 Cytostatic agents

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.

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-mercaptopurine ribonucleotides) inhibit de novo purine synthesis and purine nucleotide interconversions. TGNs are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the medicine.

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/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 6-mercaptopurine during first-pass hepatic metabolism.

After oral administration of 6-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 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

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. 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 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 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).

Elimination

In a study with 22 adult patients the mean 6-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 medicine 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/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).

Renal impairment

Studies with a pro-drug of 6-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 6-mercaptopurine in renal impairment (see section 4.2).

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous

Magnesium stearate

Maize starch

Maltodextrin

Stearic acid

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store the tablets at or below 25 °C.

Keep the bottle tightly closed.

6.5 Nature and contents of the container

MERCAPTOPURINE EQUITY tablets are presented in 20 ml amber glass type III bottles and child-proof propylene cap with silica gel.

25 tablets in amber glass container.

25 tablets/pack

50 (2 x 25) tablets/pack

Bottles are packed in a carton box.

6.6 Special precautions for disposal and other handling

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive, Irene

Pretoria

8. REGISTRATION NUMBER

55/26/0846

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 May 2023

10. DATE OF REVISION OF THE TEXT

06 November 2024