SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hanixol 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 50 mg of 6-mercaptopurine monohydrate.

Excipients with known effect:

-Lactose: 59 mg per tablet

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.
Round 7.4 mm yellowish tablet, scored

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hanixol 50 mg tablets is indicated for the treatment of APL (acute promyelocytic leukaemia) and AML M3 (acute myeloid leukaemia M3) in adults, adolescents and children.

Indicated for maintenance of remission in moderate to severe inflammatory bowel disease (IBD) (Ulcerative Colitis or Crohn's disease) in adults.

4.2 Posology and method of administration

Posology
6-mercaptopurine monohydrate treatment should be initiated and supervised by a doctor or other healthcare professional experienced in the management of patients with acute leukemia or IBD.

Method of Administration

6-mercaptopurine monohydrate may be taken with food or on an empty stomach, but patients should standardise the method of administration. 6-mercaptopurine monohydrate should not be taken with milk or dairy products (see section 4.5). 6-mercaptopurine monohydrate should be taken at least 1 hour before or 2 hours after ingestion of milk or dairy products.

6-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.

Haxinol 50mg tablets can be split in half to give 25mg dose increments. A pill cutter, only to be used with Haxinol, should be utilised for this task. Patients should be recommended to perform this task themselves if possible and to wash their hands once this is completed.

Populations

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).

APL and AML M3

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 6-mercaptopurine monohydrate.

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

While no specific data are available on the rounding methodology for dosing, the proposed monitoring, in section 4.4, and the 25mg increments for dosing available with tablet splitting would mean that a normal rounding up and down methodology would be suitable. Dosing could then be adjusted depending on the monitoring results, adverse events and other factors.

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

Studies carried out in children with acute lymphoblastic leukaemia suggested that administration of 6-mercaptopurine monohydrate in the evening lowered the risk of relapse compared with morning administration.

IBD

The usual dose of 6-mercaptopurine is 1-1.25 mg/kg daily for patients with normal thiopurine S-methyltransferase (TPMT) activity. Following TPMT testing a dose of 1 mg/kg should be administered in patients with normal TPMT activity, while in case of low TPMT activity the dose is 0.5 mg/kg. For most adult patients this would correspond to 50 mg daily, or 25mg if TPMT is low. This can be increased to 75 mg daily after about 4 weeks, depending on weight, response and haematological tolerance, to a typical maintenance dose of 1-1.5 mg/kg/day.

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 6-mercaptopurine monohydrate dosage.

Special Populations

Renal impairment

Since 6-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. Patients should be closely monitored for dose related adverse reactions.

Hepatic impairment

Since 6-mercaptopurine pharmacokinetics has not been formally studied in hepatic impairment, no specific dose recommendations can be given. Since there is a potential 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

An oral suspension of 6-mercaptopurine is also available. The 6-mecaptopurine 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 xanthine oxidase inhibitors, such as allopurinol, oxipurinol or thiopurinol and 6-mercaptopurine monohydrate are administered concomitantly, it is essential that only 25 % of the usual dose of 6-mercaptopurine monohydrate is given since allopurinol decreases the rate of catabolism of 6-mercaptopurine monohydrate. Concomitant administration of other xanthine oxidase inhibitors, such as febuxostat, should be avoided (see section 4.5).

Patients on concomitant xanthine oxidase inhibitors should not be given Hanixol for IBD.

TPMT deficient patients

6-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 6-mercaptopurine monohydrate toxicity from conventional doses of 6-mercaptopurine monohydrate and generally require substantial dose reduction.

The optimal starting dose for homozygous deficient patients has not been established (see section 4.4 and section 5.2).

TPMT testing cannot substitute for haematological monitoring in patients receiving mercaptopurine. Genotypic and phenotypic tests of TPMT are available (see section 4.4 and section 5.).

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 4.4). Genotypic testing of NUTD15 variants may be considered before initiating 6-mercaptiopurine therapy. In any case, close monitoring of blood counts is necessary.

4.3 Contraindications

Hypersensitivity to 6-mercaptopurine monohydrate 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 monohydrate is an active cytotoxic agent for use only under the direction of physician experienced in the administration of such agents.
Cholestasis of pregnancy has occasionally been reported in association with Hanixol therapy (see section 4.6). If cholestasis of pregnancy occurs, case by case assessment is necessary considering the risk-benefit profile of the product (potential withdrawal/dose reduction).

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended. In all cases, patients in remission should not receive live organism vaccines until the patient is deemed to be able to respond to the vaccine. The interval between discontinuation of chemotherapy and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medications used, the underlying disease, and other factors.

Co-administration of ribavirin and 6-mercaptopurine monohydrate is not advised. Ribavirin may reduce efficacy and increase toxicity of 6-mercaptopurine monohydrate (see section 4.5).

Safe handling of hanixol Tablets

See section 6.6.

Monitoring

Since 6- mercaptopurine monohydrate is strongly myelosuppressive full blood counts must be taken daily during remission induction in acute myelogenous leukaemia. Patients must be carefully monitored during therapy.

It is recommended that on commencement of treatment with Haxinol for IBD, that FBS, U&E and LFTs are monitored at weeks 2, 4, 8 and 12 and then at least 3-

monthly following. In patients where non-adherence to therapy or adverse events outside of those expected at the given dose, it is recommended that the thiopurine metabolites TGN and/or MeMP are checked where possible to allow for adjustment in treatment.

Cytotoxicity and haematological monitoring
Treatment with 6-mercaptopurine monohydrate causes bone marrow suppression leading to leukopenia and thrombocytopenia and, less frequently, anaemia. 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 6-mercaptopurine monohydrate 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 monohydrate may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression (see section 4.5).

Increased haematological monitoring of the patient is advised when switching between different pharmaceutical formulations of 6- mercaptopurine monohydrate.

Hepatotoxicity
6-mercaptopurine monohydrate is hepatotoxic and liver function tests should be monitored weekly during treatment. The level of gamma glutamyl transferase (GGT) in plasma will be especially important to determine if discontinuation is necessary 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 monohydrate 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.

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 6-mercaptopurine monohydrate and prone to developing rapid bone marrow depression following the initiation of treatment with 6-mercaptopurine monohydrate. This problem could be exacerbated by co-administration with drugs 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 monohydrate 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 6-mercaptopurine monohydrate and 6-tioguanine.

Hypersensitivity
Patients suspected of having suffered a hypersensitivity reaction to 6-mercaptopurine monohydrate should not be recommended to use its pro-drug azathioprine, unless the patient has been confirmed to be hypersensitive to 6-mercaptopurine monohydrate by allergological tests, and tested negative for azathioprine. As azathioprine is a pro-drug of 6-mercaptopurine monohydrate, patients with a previous history of hypersensitivity to azathioprine must be assessed for hypersensitivity to 6-mercapopurine monohydrate prior to initiating treatment.

Renal and/or hepatic impairment:
Caution is advised during the administration of 6-mercaptopurine monohydrate 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 Pharmacokinetic).

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 6-mercaptopurine monohydrate 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 leukaemic patients, in a hypernephroma patient who received an unstated dose of 6-mercaptopurine monohydrate 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) 6 mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

Two cases have been documented of the occurrence of acute non-lymphatic leukaemia in patients who received 6-mercaptopurine monohydrate, 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 monohydrate 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 monohydrate played a causative role.
A patient with Hodgkin's disease treated with 6-mercaptopurine monohydrate and multiple additional cytotoxic agents developed acute myelogenous leukaemia.
Twelve and a half years after 6-mercaptopurine monohydrate treatment for myasthenia gravis, a female patient developed chronic myeloid leukaemia.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease (IBD) population have been received when azathioprine (the prodrug to 6-mercaptopurine monohydrate is used in combination either with or without anti-TNF agents (see section 4.8). This rare type of T cell lymphoma has an aggressive disease course and is usually fatal.

Infections
Patients treated with 6-mercaptopurine monohydrate 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 the varicella zoster 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 appropriate antimicrobial therapy and supportive care.

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

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), and there could potentially be an increased susceptibility for developing the condition with the use of 6-mercaptopurine monohydrate. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with 6-mercaptopurine monohydrate 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
Purine analogues (azathioprine and mercaptopurine) may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Cases of pellagra

have been reported with the use of purine analogues, particularly in patients with chronic inflammatory bowel disease. The diagnosis of pellagra should be considered in patients with a localised pigmented rash (dermatitis), gastroenteritis, or neurological deficits including cognitive deterioration. Appropriate medical care with niacin/nicotinamide supplementation must be initiated.

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

Progressive Multifocal Leukoencephalopathy (PML)
PML, an opportunistic infection caused by the JC virus, has been reported in patients receiving azathioprine, a precursor to 6-mercaptopurine, with other immunosuppressive agents. Immunosuppressive therapy should be withheld at the first sign or symptoms suggestive of PML and appropriate evaluation undertaken to establish a diagnosis.

Neuromuscular agents
Special care is necessary when 6-mercaptopurine is given concomitantly with neuromuscular acting agents like tubocurarine or succinylcholine. It can also potentiate the neuromuscular block that is produced by depolarising agents such as succinylcholine (*see section 4.5*). Patients should be advised.

UV exposure
Patients treated with 6-mercaptopurine monohydrate 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, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Xanthine oxidase inhibitors
When xanthine oxidase inhibitors, such as allopurinol, and 6-mercaptopurine monohydrate are administered concomitantly it is essential that only 25 % of the usual dose of 6-mercaptopurine monohydrate is given, since allopurinol decreases the rate of catabolism of 6-mercaptopurine monohydrate (see section 4.2 and 4.5)

Anticoagulants
Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with 6-mercaptopurine monohydrate ; 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 monohydrate.

When oral anticoagulants are co-administered with 6-mercaptopurine, a reinforced monitoring of INR (International Normalised Ratio) is recommended (see section 4.5)

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.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccination with a live vaccine is not recommended in patients with impaired immune response (see section 4.4)

Concomitant administration of yellow fever vaccine is contraindicated, due to the risk of fatal disease in immunocompromised patients (see section 4.3)

Taking 6-mercaptopurine monohydrate with food may decrease systemic exposure slightly. 6-mercaptopurine monohydrate can be taken with food or on an empty stomach, but patients should use a standard method 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 6-mercaptopurine monohydrate and therefore may lead to reduced plasma concentrations of 6-mercaptopurine monohydrate.

Effect of concomitant medicinal products on 6-mercaptopurine monohydrate:

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 monohydrate and ribavirin; therefore concomitant administration of ribavirin and 6-mercaptopurine monohydrate is not advised (see section 4.4 and 5.2).

Myelosuppressive agents
When 6-mercaptopurine monohydrate 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 monohydrate are administered concomitantly it is essential that only 25 % of the usual dose of 6-mercaptopurine monohydrate is given (see section 4.2).

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

Methotrexate
Methotrexate (20 mg/m2 orally) increased mercaptopurine exposure (area under curve, AUC) by approximately 31% and methotrexate (2 or 5 g/m2 intravenously) increased mercaptopurine AUC by 69% and 93%, respectively. When administered concomitantly with high dose methotrexate, the mercaptopurine dose may need adjustment.

Infliximab
Interactions have been observed between azathioprine, a pro-drug of 6-mercaptopurine, and infliximab. Patients receiving 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.

Neuromuscular blocking agents
There is clinical evidence that azathioprine antagonises the effect of nondepolarizing muscle relaxants. Experimental data confirm that azathioprine reverses the neuromuscular blockade produced by non-depolarising agents (such as tubocurarine), and show that azathioprine potentiates the neuromuscular blockade produced by depolarising agents, such as succinylcholine (see section 4.4). There is considerable variation in the potency of this interaction.

Effect of 6-mercaptopurine monohydrate on other medicinal products

Anticoagulants
Inhibition of the anticoagulant effect of warfarin, when given with 6-mercaptopurine has been reported. Monitoring of the INR (International Normalised Ratio) value is recommended during concomitant administration with oral anticoagulants.

Antiepileptics
Cytotoxic agents may decrease the intestinal absorption of phenytoin. Careful monitoring of the phenytoin serum levels is recommended. It is possible that the levels of other anti-epileptic medicinal products may also be altered. Serum antiepileptic levels should be closely monitored during treatment with 6-mercaptopurine, making dose adjustments as necessary.

4.6 Fertility, pregnancy and lactation

Fertility

The effect of 6-mercaptopurine monohydrate therapy on human fertility is largely unknown but there are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence.

Transient profound oligospermia has been reported following exposure to 6-mercaptopurine monohydrate.

Pregnancy
Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy. Early diagnosis and discontinuation of Hanixol may minimise impact on the foetus. However, a careful assessment of benefit to the

mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed (see section 4.4).

Substantial transplacental and transamniotic transmission of 6-mercaptopurine monohydrate 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 6-mercaptopurine. There have also been reports of congenital abnormalities and spontaneous abortion following either maternal or paternal exposure.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving 6-mercaptopurine monohydrate Tablets, during treatment and for at least three months after receiving the last dose.

Studies of 6-mercaptopurine monohydrate in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data).
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.

Maternal exposure: Normal offspring have been born after 6-mercaptopurine monohydrate 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-mercatopurine monohydrate treatment in combination with other chemotherapy agents.

Paternal exposure: Congenital abnormalities and spontaneous abortion have been reported after paternal exposure to 6-mercaptopurine monohydrate.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine (a prodrug of 6-mercaptopurine) therapy. A careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed.

<u>Breastfeeding</u>

6-mercaptopurine monohydrate has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with a pro-drug of 6-mercaptopurine monohydrate. It is recommended that mothers receiving 6-mercaptopurine monohydrate should not breast feed.

4.7 Effects on ability to drive and use machines

There is no data about the effects of 6-mercaptopurine monohydrate on the ability to drive vehicles and use machines. A detrimental effect on these activities cannot be predicted from the pharmacology of 6-mercaptopurine monohydrate.

4.8 Undesirable effects

Summary of the safety profile
For 6-mercaptopurine monohydrate 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 monohydrate is bone marrow suppression leading to leucopenia and thrombocytopenia.

Tabulated list of adverse reactions

The following convention has been utilised for the classification of frequency:
Very common ≥1/10
Common ≥1/100 and < 1/10
Uncommon ≥1/1000 and <1/100
Rare ≥1/10,000 and <1/1000
Very rare <1/10,000
Not known (frequency cannot be estimated from the available data)

Organ system	**Frequency**	**Adverse effect**
Neoplasms benign, malignant and unspecified	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
	Not known	Hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease (IBD) when used in combination with anti TNF agents (see Section 4.4.).
Blood and lymphatic system disorders	Very common	Myelosuppression: leukopenia and thrombocytopenia
	Common	Anaemia
Immune system disorders	Uncommon	Hypersensitivity reactions with the following manifestations have been

		reported: Arthralgia; skin rash; drug fever.
	Rare	Hypersensitivity reactions with the following manifestations have been reported: Facial oedema
Metabolism and nutrition disorders	Common	Anorexia
	Not known	Hypoglycaemia* Pellagra (see section 4.4)
Gastrointestinal disorders	Common	Nausea; vomiting; pancreatitis in the IBD population, Stomatitis.
	Rare	Oral ulceration, pancreatitis during treatment for APL or AML M3
	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	Temporary oligospermia.
Infections and Infestations	Uncommon	Bacterial and viral infections, infections associated with neutropenia
General Disorders and administration	Not Known	Mucosal inflammation
Investigations	Not Known	Coagulation factors decreased
Hepatobiliary disorders	Uncommon	Cholestasis of pregnancy

*In paediatric population

Description of selected adverse reactions:

Hepatobiliary disorders
6-mercaptopurine monohydrate 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 monohydrate 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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. Haematological toxicity is likely to be more profound with chronic overdosage than with a single ingestion of 6-mercaptopurine monohydrate. Liver dysfunction and gastroenteritis may also occur.
The risk of overdosage is also increased when allopurinol is being given concomitantly with 6-mercaptopurine monohydrate (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 6-mercaptopurine monohydrate 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
6-mercaptopurine monohydrate is sulphydryl analogue of the purine bases, adenine and hypoxanthine, and acts as a cytotoxic antimetabolite.

6-mercaptopurine monohydrate is an inactive pro-drug that acts as purine antagonist after cellular uptake and intracellular conversion into thioguanine-nucleotides (TGN) for cytotoxicity.

6-mercaptopurine monohydrate 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 drug.

Pharmacodynamic effects

The cytotoxic effect of 6-mercaptopurine monohydrate may be related to the levels of thioguanine nucleotides in red blood cells, but not to the plasma concentration of 6-mercaptopurine monohydrate.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of oral 6-mercaptopurine monohydrate 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 monohydrate during first-pass hepatic metabolism.

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

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

Distribution
Concentrations of 6-mercaptopurine monohydrate 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 monohydrate 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 monohydrate 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 monohydrate

may predict adverse drug reactions to 6-mercaptopurine monohydrate 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 monohydrate 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 medicinal product after IV administration. In a study with 7 children patients the mean 6-mercaptopurine monohydrate clearance and half-life after IV infusion was 719 (+/-610) ml/min/m2 and 0.9 (+/-0.3) hours respectively.

Special patient populations

Older population

No specific studies have been carried out in the elderly (see Section 4.2 Posology and method of administration).

Renal impairment

Studies with a pro-drug of 6-mercaptopurine monohydrate have shown no difference in 6-mercaptourine monohydrate pharmacokinetics in uremic patients compared to renal transplant patients. Little is known about the active metabolites of 6-mercaptopurine monohydrate in renal impairment (see Section 4.2 Posology and method of administration).
6-mercaptopurine monohydrate 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 monohydrate 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 monohydrate exposure was 1.6 times higher in patients with hepatic impairment (but no cirrhosis) and 6 times higher in patients with hepatic impairment and cirrhosis, compared to patients without liver disease (see Section 4.2 Posology and method of administration).

5.3 Preclinical safety data

Carcinogenesis, mutagenesis

6-mercaptopurine monohydrate is mutagenic in man and chromosome damage has been reported in mice, rats and man.

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

Teratogenicity
6-mercaptopurine monohydrate causes growth arrest, severe embryo-lethality and teratogenic effects in mice, rats, hamsters and rabbits (such as cleft palate, eye and skeletal malformations) at doses that are nontoxic to pregnant females. 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
After first opening the bottle: 7 months

6.4 Special precautions for storage

Store in the original package in order to protect from light

6.5 Nature and contents of container

Type III 20 ml amber glass bottle containing 25 tablets with a polypropylene child-proof cap and silica gel desiccant.

6.6 Special precautions for disposal

Safe handling:
It is recommended that 6-mercaptopurine monohydrate Tablets should be handled following the prevailing local recommendations and/or regulations for the handling and disposal of cytotoxic agents.

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

7 MARKETING AUTHORISATION HOLDER

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