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.

Excipients with known effect:
-Lactose anhydrous: 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.

4.2 Posology and method of administration

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

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

Populations
Adults and children

For adults and children, the usual dose is 2.5 mg/kg bodyweight per day, or 50 to 75 mg/m^2 body surface area per day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with 6-mercaptopurine.

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

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

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.

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 dosage.

Renal impairment
Consideration should be given to reducing the dosage in patients with impaired renal function (see section 5.2).

Hepatic function
Consideration should be given to reducing the dosage 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. 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 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 (see section 4.4 and section 5.2).

Most patients with heterozygous TPMT deficiency can tolerate recommended 6-mercaptopurine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see section 4.4 and section 5.).

4.3 Contraindications

Hypersensitivity to mercaptopurine or to any of the excipients listed in section 6.1.
In view of the seriousness of the indications there are no other absolute contraindications.

4.4 Special warnings and precautions for use

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

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

Safe handling of Hanixol Tablets
See section 6.6.

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

Bone marrow suppression
Treatment with 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 and careful monitoring of haematological parameters should be conducted during maintenance therapy and more frequently if high dosage is used or if severe renal and/or hepatic disorder is present.

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 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 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 mercaptopurine.

Hepatotoxicity
6-mercaptopurine 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 immediately if jaundice becomes apparent.

Tumour lysis syndrome
During remission induction when rapid cell lysis is occurring, uric acid levels in blood and urine should be monitored as hyperuricaemia and/or hyperuricosuria may develop, with the risk of uric acid nephropathy.

TPMT deficiency
There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of 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 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).

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 and 6-tioguanine.

Hypersensitivity
Patients suspected of having suffered a hypersensitivity reaction to 6-mercaptopurine should not be recommended to use its pro-drug azathioprine, unless the patient has been confirmed to be hypersensitive to 6-mercaptopurine by 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-mercapopurine prior to initiating treatment.

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 Pharmacokinetic).

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

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

Increases in chromosomal aberrations were observed in the peripheral lymphocytes of 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 6mercaptopurine, in combination with other drugs, for non-neoplastic
disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with 6mercaptopurine 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 have been received when 6-mercaptopurine is used in combination with anti-TNF agents as unlicensed indication (see section 4.8).

Infections
Patients treated with 6-mercaptopurine monotherapy or in combination with other immunosuppressive drugs, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection and reactivation of the virus. Infectious disease and complications can be more serious in these patients than in patients who did not undergo treatment.

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

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

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.

Lesch-Nyhan syndrome
Limited evidence suggests that neither the 6-mercaptopurine 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 or azathioprine is not recommended in these patients.

UV exposure
Patients treated with 6-mercaptopurine 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 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 and 4.5)

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

4.5 Interaction with other medicinal products and other forms of interactions

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

Taking 6-mercaptopurine with food may decrease systemic exposure slightly. 6-mercaptopurine 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 and therefore may lead to reduced plasma concentrations of mercaptopurine.

Effect of concomitant medicinal products on 6mercaptopurine:

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 and 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 (see section 4.2).

Other xanthine oxidase inhibitors, such as febuxostat, decrease metabolism of 6-mercaptopurine. Co-administration is not recommended, because data are insufficient to determine an adequate dose reduction.

Aminosalicylates
There is in vitro and in vivo evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulfazalazine) 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 had transient increases in the levels of 6-TGN (6-tioguaninnukleotid, an active metabolite of azathioprine) and decreases in the average number of leukocytes in the first weeks after infusion of infliximab, which returned to previous levels after 3 months.

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

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

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

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.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving 6-mercaptopurine Tablets, 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 Preclinical safety data). The potential risk for humans is largely unknown.

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-mercatopurine treatment in combination with other chemotherapy agents.

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

Breastfeeding
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 mothers receiving 6-mercaptopurine should not breast feed.

4.7 Effects on ability to drive and use machines

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

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 ≥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 (see section 4.4) ; 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	Myelosuppression: leukopenia 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*
Gastrointestinal disorders	Common	Nausea; vomiting; pancreatitis in the IBD population (an unlicensed indication)
	Rare	Oral ulceration, pancreatitis during treatment (in the licensed indications)
	Very rare	Intestinal ulceration.
Hepatobiliary disorders	Common	Biliary stasis; hepatotoxicity
	Rare	Hepatic necrosis
Skin and subcutaneous tissue disorders	Rare	Alopecia.
	Not known	Photosensitivity
Reproductive system and breast disorders	Very rare	Temporary oligospermia.

*In paediatric population

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 HPRA Pharmacovigilance Earlsfort Terrace IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

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. Liver dysfunction and gastroenteritis may also occur.
The risk of overdosage is also increased when allopurinol is being given concomitantly with 6-mercaptopurine (see Section 4.5).

Treatment:
As there is no known antidote, blood counts should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of 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 Center.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Antimetabolites, Purine analogues

ATC-Code: L01BB02.

Mechanism of action
6-mercaptopurine is sulphydryl analogue of the purine bases, adenine and hypoxanthine, and acts as a cytotoxic antimetabolite.

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

6-mercaptopurine metabolites suppress the *de novo* synthesis of purine and purine-nucleotide formation. The thioguanine nucleotides are also incorporated into nucleic acids and this leads to the cytotoxic effect of the drug.

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

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 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 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 Posology and method of administration).

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/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 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 have shown no difference in 6-mercaptourine pharmacokinetics in uremic patients compared to renal transplant patients. Little is known about the active metabolites of 6-mercaptopurine in renal impairment (see Section 4.2 Posology and method of 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 Posology and method of administration).

5.3 Preclinical safety data

Carcinogenesis, mutagenesis
6-Mercaptopurine 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 is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment.

Teratogenicity
6-Mercaptopurine 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 anhydrous
Maize starch
Starch, pregelatinized
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 and other handling

Safe handling:
It is recommended that 6-mercaptopurine 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

Fontus Health Limited
70 Northumberland Road
Ballsbridge
D04 VH66
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22756/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th August 2019

10 DATE OF REVISION OF THE TEXT

March 2020