ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xaluprine 20 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of suspension contains 20 mg mercaptopurine monohydrate.

Excipients with known effect
One ml of suspension contains 3 mg aspartame, 1 mg methyl parahydroxybenzoate (as the sodium salt), 0.5 mg ethyl parahydroxybenzoate (as the sodium salt) and sucrose (trace).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

The suspension is pink to brown in colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xaluprine is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.

4.2 Posology and method of administration

Xaluprine treatment should be supervised by a physician or other healthcare professionals experienced in the management of patients with ALL.

Posology
The dose is governed by cautiously monitored haematotoxicity and the dose should be carefully adjusted to suit the individual patient in accordance with the employed treatment protocol. Depending on phase of treatment, starting or target doses generally vary between 25-75 mg/m^2 body surface area (BSA) per day, but should be lower in patients with reduced or absent Thiopurine Methyl Transferase (TPMT) or nudix hydrolase 15 (NUDT15) enzyme activity (see section 4.4).

25 mg/m^2			**50 mg/m^2**			**75 mg/m^2**		
BSA (m^2)	Dose (mg)	Volume (ml)	BSA (m^2)	Dose (mg)	Volume (ml)	BSA (m^2)	Dose (mg)	Volume (ml)
0.20 - 0.29	6	0.3	0.20 - 0.23	10	0.5	0.20 - 0.23	16	0.8
0.30 - 0.36	8	0.4	0.24 - 0.26	12	0.6	0.24 - 0.26	20	1.0
0.37 - 0.43	10	0.5	0.27 - 0.29	14	0.7	0.27 - 0.34	24	1.2
0.44 - 0.51	12	0.6	0.30 - 0.33	16	0.8	0.35 - 0.39	28	1.4
0.52 - 0.60	14	0.7	0.34 - 0.37	18	0.9	0.40 - 0.43	32	1.6
0.61 - 0.68	16	0.8	0.40 - 0.44	20	1.0	0.44 - 0.49	36	1.8
0.69 - 0.75	18	0.9	0.45 - 0.50	24	1.2	0.50 - 0.55	40	2.0
0.76 - 0.84	20	1.0	0.51 - 0.58	28	1.4	0.56 - 0.60	44	2.2
0.85 - 0.99	24	1.2	0.59 - 0.66	32	1.6	0.61 - 0.65	48	2.4
1.0 - 1.16	28	1.4	0.67 - 0.74	36	1.8	0.66 - 0.70	52	2.6
1.17 - 1.33	32	1.6	0.75 - 0.82	40	2.0	0.71 - 0.75	56	2.8
1.34 - 1.49	36	1.8	0.83 - 0.90	44	2.2	0.76 - 0.81	60	3.0
1.50 - 1.64	40	2.0	0.91 - 0.98	48	2.4	0.82 - 0.86	64	3.2
1.65 - 1.73	44	2.2	0.99 - 1.06	52	2.6	0.87 - 0.92	68	3.4
			1.07 - 1.13	56	2.8	0.93 - 0.97	72	3.6
			1.14 - 1.22	60	3.0	0.98 - 1.03	76	3.8
			1.23 - 1.31	64	3.2	1.04 - 1.08	80	4.0
			1.32 - 1.38	68	3.4	1.09 - 1.13	84	4.2
			1.39 - 1.46	72	3.6	1.14 - 1.18	88	4.4
			1.47 - 1.55	76	3.8	1.19 - 1.24	92	4.6
			1.56 - 1.63	80	4.0	1.25 - 1.29	96	4.8
			1.64 - 1.70	84	4.2	1.30 - 1.35	100	5.0
			1.71 - 1.73	88	4.4	1.36 - 1.40	104	5.2
						1.41 - 1.46	108	5.4
						1.47 - 1.51	112	5.6
						1.52 - 1.57	116	5.8
						1.58 - 1.62	120	6.0
						1.63 - 1.67	124	6.2
						1.68 - 1.73	128	6.4

Special populations

Elderly
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 Xaluprine dose.

Renal impairment
Since mercaptopurine pharmacokinetics has not been formally studied in renal impairment, no specific dose recommendations can be given. Since impaired renal function may result in slower elimination of mercaptopurine and its metabolites and therefore a greater cumulative effect, consideration should be given to reduced starting doses in patients with impaired renal function. Patients should be closely monitored for dose related adverse reactions.

Hepatic impairment
Since mercaptopurine pharmacokinetics has not been formally studied in hepatic impairment, no specific dose recommendations can be given. Since there is a 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 section 4.4).

Switching between tablet and oral suspension and vice versa
A tablet form of mercaptopurine is also available. The mercaptopurine oral suspension and tablet are not bioequivalent with respect to peak plasma concentration, and therefore intensified haematological monitoring of the patient is advised on switching formulations (see section 5.2).

Combination with xanthine oxidase inhibitors
Allopurinol and other xanthine oxidase inhibitors decrease the rate of catabolism of mercaptopurine. When allopurinol and mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of mercaptopurine is given. Other xanthine oxidase inhibitors should be avoided (see section 4.5).

Patients with TPMT variant
Mercaptopurine is metabolised by the polymorphic TPMT enzyme. Patients with little or no inherited TPMT activity are at increased risk for severe toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction. TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. TPMT testing cannot substitute for haematological monitoring in patients receiving Xaluprine. The optimal starting dose for homozygous deficient patients has not been established (see section 4.4).

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

<u>Method of administration</u>
Xaluprine is for oral use and requires redispersing (by shaking vigorously at least for 30 seconds) prior to dosing.

Two dosing syringes (a 1 ml and a 5 ml) are provided for accurate measurement of the prescribed dose of the oral suspension. It is recommended that the healthcare professional advises the patient or carer which syringe to use to ensure that the correct volume is administered.

Xaluprine 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). Xaluprine should be taken at least 1 hour before or 2 hours after milk or dairy products.

Mercaptopurine displays diurnal variation in pharmacokinetics and efficacy. Administration in the evening compared to morning administration may lower the risk of relapse. Therefore the daily dose of Xaluprine should be taken in the evening.

To assist accurate and consistent dose delivery to the stomach water should be taken after each dose of Xaluprine.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Cytotoxicity and haematological monitoring
Treatment with mercaptopurine causes bone marrow suppression leading to leucopenia and thrombocytopenia and, less frequently, to anaemia. Careful monitoring of haematological parameters should be conducted during therapy. The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in the counts, treatment should be interrupted immediately. Bone marrow suppression is reversible if mercaptopurine is withdrawn early enough.

Patients with TPMT variant
Patients with inherited variant in the TPMT gene resulting in a deficiency or absence of the TPMT enzyme, are very sensitive to the myelosuppressive effect of mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine. This problem could be exacerbated by coadministration with active substances that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is necessary. Substantial dose reductions are generally required for homozygous-TPMT deficiency patients to avoid the development of life threatening bone marrow suppression.

A possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving mercaptopurine in combination with other cytotoxics (see section 4.8).

Patients with NUDT15 variant
Patients with inherited variant in the NUDT15 gene are at increased risk for severe mercaptopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being NUDT15 variant homozygotes (see section 4.2). The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans. In any case, close monitoring of blood counts is necessary.

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

In all cases, patients in remission should not receive live organism vaccines until the patient is 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.

The dosage of mercaptopurine may need to be reduced when this agent is combined with other medicinal products whose primary or secondary toxicity is myelosuppression (see Section 4.5).

Hepatotoxicity
Xaluprine is hepatotoxic and liver function tests should be monitored weekly during treatment. 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 Xaluprine immediately if jaundice becomes apparent (see section 4.8).

Renal toxicity
During remission induction when rapid cell lysis is occurring, uric acid levels in blood and urine should be monitored as hyperuricaemia and/or hyperuricosuria may develop, with the risk of uric acid nephropathy. Hydration and urine alkalinisation may minimize potential renal complications.

Pancreatitis in off-label treatment of patients with inflammatory bowel disease
Pancreatitis has been reported to occur at a frequency of ≥ 1/100 to < 1/10 ("common") in patients treated for the unlicensed indication inflammatory bowel disease.

Mutagenicity and carcinogenicity
Patients receiving immunosuppressive therapy, including mercaptopurine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and 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 renal cell carcinoma patient who received an unstated dose of mercaptopurine and in patients with chronic renal disease treated at doses of 0.4 – 1.0 mg/kg/day.

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

Hepatosplenic T-cell lymphoma has been reported in patients with inflammatory bowel disease* treated with azathioprine (the prodrug to mercaptopurine) or mercaptopurine, either with or without concomitant treatment with anti-TNF alpha antibody. This rare type of T-cell lymphoma has an aggressive disease course and is usually fatal (see also section 4.8).
*inflammatory bowel disease (IBD) is an unlicensed indication.

Macrophage activation syndrome
Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD) (unlicensed indication), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with mercaptopurine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

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

Prior exposure to or infection with varicella zoster virus should be taken into consideration prior to starting treatment. Local guidelines may be considered, including prophylactic therapy if necessary. Serologic testing prior to starting treatment should be considered with respect to hepatitis B. Local guidelines may be considered, including prophylactic therapy for cases which have been confirmed positive by serologic testing. Cases of neutropenic sepsis have been reported in patients receiving mercaptopurine for ALL.

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

Metabolic and nutritional 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.

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

Interactions
When oral anticoagulants are coadministered with mercaptopurine, a reinforced monitoring of INR (International Normalised Ratio) is recommended (see section 4.5).

Excipients
This medicinal product contains aspartame (E951), a source of phenylalanine. May be harmful for people with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

It also contains sodium methyl parahydroxybenzoate and sodium ethyl parahydroxybenzoate which may cause allergic reaction (possibly delayed).

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Long term use increases the risk of dental caries and it is essential that adequate dental hygiene is maintained.

Safe handling of the suspension
Parents and care givers should avoid Xaluprine contact with skin or mucous membrane. If the suspension comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of food on mercaptopurine
The administration of mercaptopurine with food may decrease systemic exposure slightly but this is unlikely to be of clinical significance. Therefore, Xaluprine 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 since they contain xanthine oxidase, an enzyme which metabolises mercaptopurine and might therefore lead to reduced plasma concentrations of mercaptopurine.

Effects of mercaptopurine on other medicinal products

Vaccines

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

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

Anticoagulants

Inhibition of the anticoagulant effect of warfarin, when given with 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 Xaluprine, making dose adjustments as necessary.

Effects of other medicinal products on mercaptopurine

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol, which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol and Xaluprine are administered concomitantly it is essential that only a quarter of the usual dose of Xaluprine is given since allopurinol decreases the rate of metabolism of mercaptopurine via xanthine oxidase. Also other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of mercaptopurine and concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction.

Aminosalicylates

As there is *in vitro* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfazalazine) inhibit the TPMT enzyme, which metabolises mercaptopurine, they should be administered with caution to patients receiving concurrent Xaluprine therapy (see section 4.4).

Infliximab

Interactions have been observed between azathioprine, a pro-drug of 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.

Methotrexate

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

Ribavirin

Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active thioguanine nucleotides (TGNs). Severe myelosuppression has been reported following concomitant administration of a prodrug of mercaptopurine and ribavirin; therefore concomitant administration of ribavirin and mercaptopurine is not advised (see section 5.2).

Myelosuppressive agents

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Evidence of the teratogenicity of mercaptopurine in humans is equivocal. Both sexually active men and women should use effective methods of contraception during treatment and for at least three or six months respectively after receiving the last dose. Animal studies indicate embryotoxic and embryolethal effects (see section 5.3).

Pregnancy
Xaluprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.

There have been reports of premature birth and low birth weight following maternal exposure to mercaptopurine. There have also been reports of congenital abnormalities and spontaneous abortion following either maternal or paternal exposure. Multiple congenital abnormalities have been reported following maternal mercaptopurine treatment in combination with other chemotherapy agents.

A more recent epidemiological report suggests that there is no increased risk of preterm births, low birth weight at term, or congenital abnormalities in women exposed to mercaptopurine during pregnancy.

It is recommended that newborns of women exposed to mercaptopurine during pregnancy are monitored for haematological and immune system disturbances.

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

Breast-feeding
Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment and thus women receiving Xaluprine should not breast-feed.

Fertility
The effect of mercaptopurine therapy on human fertility is unknown but there are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence. Transient profound oligospermia has been reported following exposure to mercaptopurine in combination with corticosteroids.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. A detrimental effect on these activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

Summary of the safety profile

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

For mercaptopurine there is a lack of modern clinical documentation which can serve as support for accurately determining the frequency of adverse reactions.

Tabulated list of adverse reactions

The following events have been identified as adverse reactions. The adverse reactions are displayed by system organ class and frequency: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1000 to < 1/100), rare (≥1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Bacterial and viral infections, infections associated with neutropenia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ (see section 4.4)
	Very rare	Secondary leukaemia and myelodysplasia
	Not known	Hepatosplenic T-cell lymphoma* (see section 4.4)
Blood and lymphatic system disorders	Very common	Bone marrow suppression; leucopenia and thrombocytopenia
	Common	Anaemia
Immune system disorders	Uncommon	Arthralgia, skin rash, drug fever
	Rare	Facial oedema
Metabolism and nutrition disorders	Common	Anorexia
	Not known	Hypoglycaemia†, pellagra (see section 4.4)
Gastrointestinal disorders	Common	Diarrhoea, vomiting, nausea, pancreatitis*
	Uncommon	Oral ulceration
	Rare	Pancreatitis
	Very rare	Intestinal ulceration
	Not known	Stomatitis, cheilitis
Hepatobiliary disorders	Common	Biliary stasis, hepatotoxicity
	Uncommon	Hepatic necrosis
	Not known	Portal hypertension*, nodular regenerative hyperplasia*, sinusoidal obstruction syndrome*
Skin and subcutaneous tissue disorders	Rare	Alopecia
	Not known	Photosensitivity reaction, erythema nodosum
Reproductive system and breast disorders	Rare	Transient oligospermia
General disorders and administration site conditions	Not known	Mucosal inflammation
Investigations	Not known	Coagulation factors decreased

* In patients with inflammatory bowel disease (IBD), an unlicensed indication.
† In the paediatric population.

Description of selected adverse reactions

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 is exceeded.

Monitoring of liver function tests may allow early detection of hepatotoxicity. This is usually reversible if mercaptopurine therapy is stopped soon enough but fatal liver damage has occurred.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs
Gastrointestinal effects, including nausea, vomiting and diarrhoea and anorexia may be early symptoms of overdose having occurred. The principal toxic effect is on the bone marrow, resulting in myelosuppression. Haematological toxicity is likely to be more profound with chronic overdose than with a single ingestion of Xaluprine. Liver dysfunction and gastroenteritis may also occur.
The risk of overdose is also increased when xanthine oxidase inhibitors is being given concomitantly with mercaptopurine (see section 4.5).

Management
As there is no known antidote the blood picture 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 or gastric lavage) may not be effective in the event of mercaptopurine overdose unless the procedure can be undertaken within 60 minutes of ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, purine analogues, ATC code: L01BB02

Mechanism of action
Mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides for cytotoxicity. The mercaptopurine metabolites inhibit *de novo* purine synthesis and purine nucleotide interconversions. The thioguanine nucleotides are also incorporated into nucleic acids and this contributes to the cytotoxic effects of the active substance.

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

5.2 Pharmacokinetic properties

Absorption
The bioavailability of oral mercaptopurine shows considerable inter-individual variability, which probably results from its first-pass metabolism. When administered orally at a dosage of 75 mg/m^2 to 7 paediatric patients, the bioavailability averaged 16% of the administered dose, with a range of 5 to 37%.

In a comparative bioavailability study in healthy adult volunteers (n=60), 50mg of Xaluprine oral suspension was demonstrated to be bioequivalent to the reference 50mg tablet for AUC, but not $C_{max.}$ The mean (90% CI) C_{max} with the oral suspension was 39% (22% - 58%) higher than the tablet although there was less between-subject variability (%C.V) with the oral suspension (46%) than the tablet (69%).

Biotransformation
The intracellular anabolism of mercaptopurine is catalysed by several enzymes to eventually form thioguanine nucleotides (TGNs), but a variety of intermediary TGNs are formed en route to the TGNs. The first step is catalysed by hypoxanthine-guanine phosphoribosyl transferase yielding thioinosine monophosphate (TIMP). Later steps involve the enzymes inosine monophosphate dehydrogenase (IMPDH) and guanine monophosphate synthetase. Mercaptopurine is also subject to S-methylation by the enzyme thiopurine S-methyltransferase (TPMT), yielding methylmercaptopurine, which is inactive. However, TPMT also catalyses the S-methylation of the principle nucleotide metabolite, TIMP, to form methylthioinosine monophosphate (mTIMP). Both TIMP and mTIMP are inhibitors of phosphoribosyl pyrophosphate amidotransferase, an enzyme which is important in de novo purine synthesis. Xanthine oxidase is the main catabolic enzyme and it converts the mercaptopurine into the inactive metabolite, 6-thiouric acid. This is excreted in the urine. Approximately 7% of an oral dose is excreted as unchanged mercaptopurine within 12 hours after administration.

Elimination
The elimination half-life of mercaptopurine is 90 ± 30 minutes, but the active metabolites have a longer half-life (approximately 5 hours) than the parent compound. The apparent body clearance is 4832 ± 2562 ml/min/m^2. There is low entry of mercaptopurine into the cerebrospinal fluid.

The main route of elimination for mercaptopurine is by metabolism.

5.3 Preclinical safety data

Genotoxicity
Mercaptopurine, in common with other antimetabolites, is mutagenic and causes chromosomal aberrations *in vitro* and *in vivo* in mice and rats.

Carcinogenicity
Given its genotoxic potential, mercaptopurine is potentially carcinogenic.

Teratogenicity
Mercaptopurine causes embryolethality and severe teratogenic effects in the mouse, rat, hamster and rabbit at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and the type of malformations are dependent on the dose and stage of the gestation at the time of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Xanthan gum
Aspartame (E951)
Concentrated raspberry juice
Sucrose
Sodium methyl parahydroxybenzoate (E219)
Sodium ethyl parahydroxybenzoate (E215)
Potassium sorbate (E202)
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

After first opening: 56 days.

6.4 Special precautions for storage

Do not store above 25ºC.
Keep the bottle tightly closed (see section 6.6).

6.5 Nature and contents of container

Amber type III glass bottle with tamper evident child-resistant closure (HDPE with expanded polyethylene liner) containing 100 ml of oral suspension.

Each pack contains one bottle, an LDPE bottle adaptor and 2 dosing syringes (a syringe graduated to 1 ml and a syringe graduated to 5 ml).

6.6 Special precautions for disposal and other handling

Safe handling
Anyone handling Xaluprine should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling Xaluprine.

Xaluprine contact with skin or mucous membrane must be avoided. If Xaluprine comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water. Spillages must be wiped immediately.

Women who are pregnant, planning to be or breast-feeding should not handle Xaluprine.

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

Keep the bottle tightly closed to protect the integrity of the product and minimise the risk of accidental spillage.

The bottle should be shaken vigorously for at least 30 seconds to ensure the oral suspension is well mixed.

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

7. MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/727/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 March 2012
Date of latest renewal: 18 November 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pronav Clinical Ltd.
Unit 5
Dublin Road Business Park
Carraroe, Sligo
F91 D439
Ireland

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xaluprine 20 mg/ml oral suspension
mercaptopurine monohydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of suspension contains 20 mg mercaptopurine monohydrate.

3. LIST OF EXCIPIENTS

Also contains: sodium methyl parahydroxybenzoate (E219), sodium ethyl parahydroxybenzoate (E215), potassium sorbate (E202), sodium hydroxide, aspartame (E951) and sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension.

100 ml glass bottle
Bottle adaptor
1 ml and 5 ml dosing syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take as directed by your doctor using the dosing syringes provided.

Shake vigorously before use for at least 30 seconds.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP:
Discard 56 days after first opening.
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/727/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xaluprine 20 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Xaluprine 20 mg/ml oral suspension
mercaptopurine monohydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of suspension contains 20 mg mercaptopurine monohydrate.

3. LIST OF EXCIPIENTS

Also contains: sodium methyl parahydroxybenzoate (E219), sodium ethyl parahydroxybenzoate (E215), potassium sorbate (E202), sodium hydroxide, aspartame (E951) and sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension.

100 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take as directed by your doctor using the dosing syringes provided.

Shake vigorously before use for at least 30 seconds.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP:
Discard 56 days after first opening.
Open date: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/727/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xaluprine 20 mg/ml oral suspension
mercaptopurine monohydrate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xaluprine is and what it is used for

Xaluprine contains mercaptopurine monohydrate. This belongs to a group of medicines called cytotoxics (also called chemotherapy).

Xaluprine is used for acute lymphoblastic leukaemia (also called acute lymphocytic leukaemia or ALL). This is a fast-growing disease which increases the number of new white blood cells. These new white blood cells are immature (not fully formed) and unable to grow and work properly. They therefore cannot fight infections and may cause bleeding.

Ask your doctor if you would like more explanation about this disease.

2. What you need to know before you take Xaluprine

- **Do not take Xaluprine** if you are allergic to mercaptopurine or any of the other ingredients of this medicine (listed in section 6).
- **Do not get vaccinated** with yellow fever vaccine whilst you are taking Xaluprine because it may be fatal.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Xaluprine
- if you have recently received, or are due to receive, a vaccination (vaccine).
- if you have been vaccinated with yellow fever vaccine.
- if you have kidney or liver problems, as your doctor will need to check that they are working properly.
- if you have a condition where your body produces too little of the enzyme called TPMT (thiopurine methyltransferase) or NUDT15 (nudix hydrolase 15), as your doctor may need to adjust the dose.
- if you are planning to have a baby. This applies to both men and women. Xaluprine may harm your sperm or eggs (see ‘Pregnancy, breast-feeding and fertility’ below).

If you are receiving immunosuppressive therapy, taking Xaluprine could put you at greater risk of:
- tumours, including skin cancer. Therefore, when taking Xaluprine, avoid excessive exposure to sunlight, wear protective clothing and use protective sunscreen with a high protection factor
- lymphoproliferative disorders
    - o treatment with Xaluprine increases your risk of getting a type of cancer called lymphoproliferative disorder. With treatment regimen containing multiple immunosuppressants (including thiopurines), this may lead to death.
    - o A combination of multiple immunosuppressants, given concomitantly increases the risk of disorders of the lymph system due to a viral infection (Epstein-Barr virus (EBV)-associated lymphoproliferative disorders).

Taking Xaluprine could put you at greater risk of:
- developing a serious condition called Macrophage Activation Syndrome (excessive activation of white blood cells associated with inflammation), which usually occurs in people who have certain types of arthritis.

Some patients with inflammatory bowel disease who have received mercaptopurine have developed a rare and aggressive type of cancer called Hepatosplenic T-cell Lymphoma (see section 4, Possible side effects).

Infections
When you are treated with Xaluprine the risk of viral, fungal and bacterial infections is increased and the infections may be more serious. See also section 4.

Tell your doctor before starting treatment whether or not you have had chickenpox, shingles or hepatitis B (a liver disease caused by a virus).

Blood tests
Treatment with mercaptopurine may affect your bone marrow. This means you may have a reduced number of white blood cells, platelets and (less commonly) red blood cells in your blood. Your doctor will carry out frequent and regular blood tests during treatment. This is in order to monitor the levels of these cells in your blood. If the treatment is stopped early enough, your blood cells will return to normal.

Liver function
Mercaptopurine is toxic to your liver. Therefore, your doctor will carry out frequent and regular liver function tests when you are taking mercaptopurine. If you already have liver disease, or if you are taking other medications which may affect your liver, your doctor will carry out more frequent tests. If you notice the whites of your eyes or your skin turn yellow (jaundice) tell your doctor immediately as you may need to stop your treatment immediately.

TPMT and NUDT15 gene variants
If you have inherited variants of the TPMT and/or the NUDT15 genes (genes which are involved in the break-down of Xaluprine in the body), you have a higher risk of infections and hair loss and your doctor may in this case give you a lower dose.

Vitamin B3 deficiency (pellagra)
Tell your doctor immediately if you have diarrhoea, localised pigmented rash (dermatitis) or deterioration of your memory, reasoning and thinking skills (dementia), as these symptoms may indicate a vitamin B3 deficiency. Your doctor will prescribe vitamin supplements (niacin/nicotinamide) to improve your condition.

Avoid contact of Xaluprine with your skin, eyes or nose. If you accidentally get some in your eyes or nose, flush the area with water.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Xaluprine.

Children and adolescents
Low blood sugar has sometimes been seen in children, mainly in children under the age of six or with a low body mass index. Talk to your child´s doctor if this happens.

Other medicines and Xaluprine
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor, nurse or pharmacist if you are taking any of the following:

- ribavirin (used to treat viruses)
- other cytotoxic medicines (chemotherapy) - when used with Xaluprine there is a greater chance of side effects, such as anaemia
- allopurinol, thiopurinol, oxipurinol or febuxostat (used to treat gout)
- oral anticoagulants (used to thin the blood)
- olsalazine or mesalazine (used for a bowel disorder called ulcerative colitis)
- sulfasalazine (used for rheumatoid arthritis or ulcerative colitis)
- methotrexate (used to treat cancer, rheumatoid arthritis or skin disease (severe psoriasis))
- anti-epileptic medicines such as phenytoin, carbamazepine. Blood levels of anti-epileptic medicines may need to be monitored and doses adjusted if necessary
- infliximab (used to treat certain bowel diseases (Crohn’s disease and ulcerative colitis), rheumatoid arthritis, ankylosing spondylitis or skin disease (severe psoriasis))

Having vaccines while you are taking Xaluprine
If you are going to have a vaccination it is important to speak to your doctor or nurse before you have it. Vaccination with live vaccines (like polio, measles, mumps and rubella) is not recommended, as these vaccines may give you an infection if you have them whilst you are taking Xaluprine.

Xaluprine with food and drink
Xaluprine may be taken with food or on an empty stomach. However, the choice of method should be consistent from day to day.

Do not take Xaluprine at the same time as milk or dairy products, as they can make the medicine less effective. Xaluprine should be taken at least 1 hour before or 2 hours after milk or dairy products.

Pregnancy, breast-feeding and fertility
Do not take Xaluprine if you are planning to have a baby without first speaking to your doctor for advice. This applies to both men and women. Xaluprine may harm your sperm or eggs. Reliable contraception must be used to avoid pregnancy whilst you or your partner are taking Xaluprine. Men should continue to use effective contraception for at least 3 months, and women should continue for at least 6 months after stopping treatment. If you are already pregnant, you must talk to your doctor before taking Xaluprine.

Taking Xaluprine during pregnancy may cause severe, excessive itching without a rash. You may also experience nausea and loss of appetite at the same time, which may indicate a condition called cholestasis of pregnancy (a disease of the liver during pregnancy). Talk with your doctor immediately, as this condition can cause harm to your unborn child.

Xaluprine should not be handled by women who are or planning to be pregnant or breast-feeding.

Do not breast-feed while taking Xaluprine. Ask your doctor, pharmacist or midwife for advice.

Driving and using machines
It is not expected that Xaluprine will affect your ability to drive or use machines but no studies have been done to confirm this.

Xaluprine contains aspartame, sodium methyl parahydroxybenzoate (E219), sodium ethyl parahydroxybenzoate (E215) and sucrose
This medicine contains 3 mg aspartame (E951) in each 1 ml. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Xaluprine also contains sodium methyl parahydroxybenzoate (E219) and sodium ethyl parahydroxybenzoate (E215) which may cause allergic reactions (possibly delayed).

Xaluprine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. May be harmful to the teeth.

3. How to take Xaluprine

Xaluprine should only be given to you by a specialist doctor who is experienced in treating blood problems.

- When you take Xaluprine your doctor will take regular blood tests. This is to check the number and type of cells in your blood and to ensure your liver is working correctly.
- Your doctor may also ask for other blood and urine tests to monitor your uric acid levels. Uric acid is a natural body chemical, levels of which can rise while taking Xaluprine.
- Your doctor may sometimes change your dose of Xaluprine as a result of these tests.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The usual starting dose for adults, adolescents and children is between 25-75 mg/m^2 body surface area each day. Your doctor will prescribe the correct dose for you. Carefully check the dose and strength of the oral suspension to ensure you take the correct dosage as shown in the tables below. Sometimes the doctor may change your dose of Xaluprine for example as a result of different tests. If you are not sure how much medicine to take, always ask your doctor or nurse.

It is important to take Xaluprine in the evening to make the medicine more effective.

You can take your medicine with food or on an empty stomach but the choice of method should be consistent from day to day. You should take your medicine at least 1 hour before or 2 hours after having milk or dairy products.

Your pack of Xaluprine contains a bottle of medicine, a cap, a bottle adaptor and two dosing syringes (a 1 ml syringe and a 5 ml syringe). Always use the syringes provided to take your medicine.

It is important that you use the correct dosing syringe for your medicine. Your doctor or pharmacist will advise which syringe to use depending on the dose that has been prescribed.

The **smaller** 1 ml syringe, marked from 0.1 ml to 1 ml, is for measuring doses of less than or equal to 1 ml. You should use this one if the total amount you have to take is less than or equal to 1 ml (each graduation of 0.1 ml contains 2 mg of mercaptopurine). The table below shows the dose (mg) to volume (ml) conversion for the 1 ml syringe.

Dose (mg)	Volume (ml)
6	0.3
8	0.4
10	0.5
12	0.6
14	0.7
16	0.8
18	0.9
20	1.0

The **larger** 5 ml syringe, marked 1 ml to 5 ml, is for measuring doses of more than 1 ml. You should use this one if the total amount you have to take is more than 1 ml (each graduation of 0.2 ml contains 4 mg of mercaptopurine). The table below shows the dose (mg) to volume (ml) conversion for the 5 ml syringe.

Dose (mg)	Volume (ml)
24	1.2
28	1.4
32	1.6
36	1.8
40	2.0
44	2.2
48	2.4
52	2.6
56	2.8
60	3.0
64	3.2
68	3.4
72	3.6
76	3.8

Dose (mg)	Volume (ml)
80	4.0
84	4.2
88	4.4
92	4.6
96	4.8
100	5.0
104	5.2
108	5.4
112	5.6
116	5.8
120	6.0
124	6.2
128	6.4

If you are a parent or care giver administering the medicine, wash your hands before and after administering a dose. Wipe up spillages immediately. To decrease the risk of exposure disposable gloves should be used when handling Xaluprine.

If Xaluprine comes into contact with skin, eyes or nose, it should be washed immediately and thoroughly with soap and water.

When you use the medicine follow the instructions below:


Figure 1

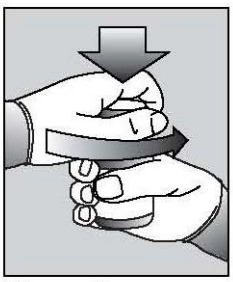
Figure 2

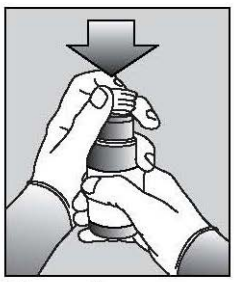
Figure 3

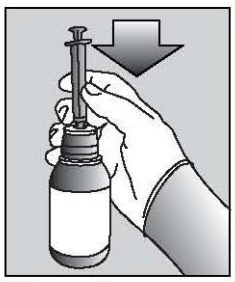
Figure 4

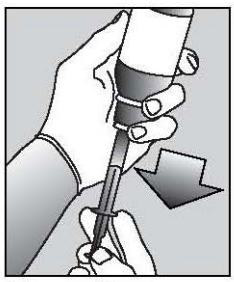
Figure 5

1. Put on disposable hand gloves before handling Xaluprine.
2. **Shake the bottle vigorously for at least 30 seconds** to ensure the medicine is well mixed **(figure 1)**.
3. Remove the bottle cap **(figure 2)** and push the adaptor firmly into the top of the bottle and leave in place for future doses **(figure 3)**.

4. Push the tip of the dosing syringe into the hole in the adaptor **(figure 4)**. **Your doctor or pharmacist will advise you of the correct syringe to use, either the 1 ml or the 5 ml in order to give the correct dose**.
5. Turn the bottle upside down **(figure 5)**.
6. Pull the plunger of the syringe back so that the medicine is drawn from the bottle into the syringe. Pull the plunger back to the point on the scale that corresponds to the dose prescribed **(figure 5)**. If you are not sure about how much medicine to draw into the syringe, always ask your doctor or nurse for advice.
7. Turn the bottle back the right way up and carefully remove the syringe from the adaptor, holding it by the barrel rather than the plunger.
8. Gently put the tip of the syringe into your mouth and to the inside of your cheek.
9. Slowly and gently push the plunger down to gently squirt the medicine into the inside of your cheek and swallow it. DO NOT forcefully push down the plunger, or squirt the medicine to the back of your mouth or throat, as you may choke.
10. Remove the syringe from your mouth.
11. Swallow the dose of oral suspension then drink some water, making sure no medicine is left in your mouth.
12. Put the cap back on the bottle with the adaptor left in place. Ensure that the cap is tightly closed.
13. Wash the syringe with warm water and rinse well. Hold the syringe under water and move the plunger up and down several times to make sure the inside of the syringe is clean. Let the syringe air dry completely before you use that syringe again for dosing. Do not wipe dry. Store the syringe in a hygienic place with the medicine.

Repeat the above for each dose as instructed by your doctor or pharmacist.

If you take more Xaluprine than you should
If you take more Xaluprine than you should, tell your doctor or go to a hospital immediately. You may feel sick, vomit or have diarrhoea. Take the medicine pack and this leaflet with you.

If you forget to take Xaluprine
Tell your doctor. **Do not take a double dose to make up for a forgotten dose.**

If you stop taking Xaluprine
Do not stop taking your medicine unless your doctor tells you to or you may get a relapse of your condition.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following side effects, talk to your specialist doctor or go to hospital immediately:

- Allergic reaction, the signs may include:
  - skin rashes
  - high temperature
  - joint pain
  - swollen face
  - skin nodules (erythema nodosum) (the frequency is unknown)

- Any signs of fever or infection (sore throat, sore mouth or urinary problems)

- Any **unexpected** bruising or bleeding, as this could mean that too few blood cells of a particular type are being produced

- If you **suddenly** feel unwell (even with a normal temperature) and have abdominal pain and sickness, as this could be a sign of an inflamed pancreas

- Any yellowing of the whites of the eyes or skin (jaundice)

- If you have diarrhoea

Talk to your doctor if you have any of the following side effects which may also happen with this medicine:

Very common (affects more than 1 in 10 people)
- a drop in the number of white blood cells and platelets (may show up in blood tests)

Common (affects less than 1 in 10 people)
- feeling or being sick (nausea or vomiting)
- liver damage - this may show up in blood tests
- a drop in red blood cells which may make you tired, weak or breathless (called anaemia)
- loss of appetite
- diarrhoea
- inflammation of the pancreas (pancreatitis) in inflammatory bowel disease patients

Uncommon (affects less than 1 in 100 people)
- mouth ulcers
- joint pain
- skin rash
- fever
- permanent damage to the liver (hepatic necrosis)

Rare (affects less than 1 in 1,000 people)
- hair loss
- in men: temporary low sperm count
- allergic reaction leading to swollen face
- various types of cancers including blood, lymph and skin cancers
- inflammation of the pancreas (pancreatitis) in patients with leukaemia (cancer of the blood)

Very rare (affects less than 1 in 10,000 people)
- a different type of leukaemia to that being treated
- ulcers in the intestines

Other side effects (the frequency is unknown)
- a rare type of cancer (hepatosplenic T-cell lymphoma, in patients with a condition called Inflammatory Bowel Disease) (see section 2, Warnings and Precautions).
- burning or tingling sensation in the mouth or lips (inflammation of the mucosa, stomatitis).
- cracked or swollen lips (cheilitis).
- vitamin B3 deficiency (pellagra) associated with a localised pigmented skin rash, diarrhoea or decrease in memory, reasoning or other thinking skills.
- sensitivity to sunlight causing skin reactions.
- a decrease in clotting factors.

Additional side effects in children and adolescents
Low blood sugar (hypoglycaemia) - the frequency is unknown.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xaluprine

- Keep this medicine out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle after 'EXP'. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Keep the bottle tightly closed to prevent spoilage of the medicine and reduce the risk of accidental spillage.
- After first opening of the bottle, discard any unused contents after 56 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xaluprine contains
The active substance is mercaptopurine monohydrate. One ml of suspension contains 20 mg of mercaptopurine monohydrate.

The other ingredients are xanthan gum, aspartame (E951), concentrated raspberry juice, sucrose, sodium methyl parahydroxybenzoate (E219), sodium ethyl parahydroxybenzoate (E215), potassium sorbate (E202), sodium hydroxide and purified water (see section 2 Xaluprine contains aspartame, sodium methyl parahydroxybenzoate (E219), sodium ethyl parahydroxybenzoate (E215) and sucrose).

What Xaluprine looks like and contents of the pack
Xaluprine is a pink to brown oral suspension. It comes in glass bottles of 100 ml capped with a child-resistant closure. Each pack contains one bottle, a bottle adaptor and two dosing syringes (a syringe graduated to 1 ml and a syringe graduated to 5 ml). Your doctor or pharmacist will advise which syringe to use depending on the dose that has been prescribed.

Marketing Authorisation Holder and Manufacturer
Lipomed GmbH
Hegenheimer Strasse 2
79576 Weil am Rhein
Germany

Manufacturer
Pronav Clinical Ltd.
Unit 5
Dublin Road Business Park
Carraroe, Sligo
F91 D439
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu