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 (as monohydrate).

Excipients with known effect
One ml of suspension contains 3 mg aspartame, 1 mg methyl hydroxybenzoate (as the sodium salt), 0.5 mg ethyl hydroxybenzoate (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) 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

6-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).

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 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 section 4.4).

Switching between tablet and oral suspension and vice versa
A tablet form of 6-mercaptopurine is also available. The 6-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 6-mercaptopurine. When allopurinol and 6-mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of 6-mercaptopurine is given. Other xanthine oxidase inhibitors should be avoided (see section 4.5).

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 NUDT15 variants may be considered before initiating 6-mercaptopurine therapy. In any case, close monitoring of blood counts is necessary.

Method of administration
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.

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 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 6-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 6-mercaptopurine is withdrawn early enough.

There are individuals with an inherited deficiency of the TPMT enzyme activity who are very 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 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 6-mercaptopurine in combination with other cytotoxics (see section 4.8).

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.

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

Prior exposure to or infection with varicella zoster virus should be taken into consideration prior to starting treatment. Local guidelines may be considered, including prophylactic therapy if necessary. Serologic testing prior to starting treatment should be considered with respect to hepatitis B. Local guidelines may be considered, including prophylactic therapy for cases which have been confirmed positive by serologic testing. Cases of neutropenic sepsis have been reported in patients receiving 6-mercaptopurine for ALL.

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.

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

Interactions
When oral anticoagulants are coadministered with 6-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

The administration of 6-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 6–mercaptopurine and might therefore lead to reduced plasma concentrations of mercaptopurine.

Effects of mercaptopurine on other medicinal products
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).

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.

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
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 6-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.

As there is *in vitro* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfazalazine) inhibit the TPMT enzyme, which metabolises 6-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 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.

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.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Evidence of the teratogenicity of 6-mercaptopurine in humans is equivocal. Both sexually active men and women should use effective methods of contraception during treatment and for at least three months 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 6-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 6-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 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.

Breast-feeding
6-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 6-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 6-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 6-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
	Uncommon	Pancreatitis, oral ulceration
	Very rare	Intestinal ulceration
	Not known	Stomatitis, cheilitis
Hepatobiliary disorders	Common	Biliary stasis, hepatotoxicity
	Uncommon	Hepatic necrosis

System organ class	Frequency	Adverse reaction
	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

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 is exceeded.

Monitoring of liver function tests may allow early detection of 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 Website: www.hpra.ie.

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 6-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 6-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
6-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 6-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 6-mercaptopurine and 6-thioguanine.

5.2 Pharmacokinetic properties

Absorption
The bioavailability of oral 6-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 6-mercaptopurine is catalysed by several enzymes to eventually form 6-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). 6-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 6-mercaptopurine into the inactive metabolite, 6-thiouric acid. This is excreted in the urine. Approximately 7% of an oral dose is excreted as unchanged 6-mercaptopurine within 12 hours after administration.

Elimination
The elimination half-life of 6-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 6-mercaptopurine into the cerebrospinal fluid.

The main route of elimination for 6-mercaptopurine is by metabolism.

5.3 Preclinical safety data

Genotoxicity
6-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, 6-mercaptopurine is potentially carcinogenic.

Teratogenicity
6-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
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

Nova Laboratories Ireland Limited
3rd Floor, Ulysses House
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D01 W2T2
Ireland

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

20 June 2024

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