XALUPRINE®

(mercaptopurine) 20 mg/ml oral suspension

A fluid approach to acute lymphoblastic leukaemia

Fannin

Accurate and convenient dosing

Mercaptopurine is an established treatment in the maintenance phase of ALL.[8] Xaluprine® (mercaptopurine) 20 mg/ml oral suspension provides accurate, flexible dosing for ALL patients.[6,7] Previously, the use of tablets has made administration difficult for parents and carers of children with ALL.[7,9]

Xaluprine® oral suspension	Mercaptopurine tablets
Dose is easy to calculate and administer[5]	Individualising doses for young children is extremely difficult as the dose needs to be adjusted according to body surface area[7,9]
Can be given accurately, down to a dose of 2mg (0.1ml), using the supplied 1ml (purple) or 5ml (white) oral syringe[5]	Tablet splitting is associated with potential exposure of parents/carers to cytotoxic contamination[7,9]

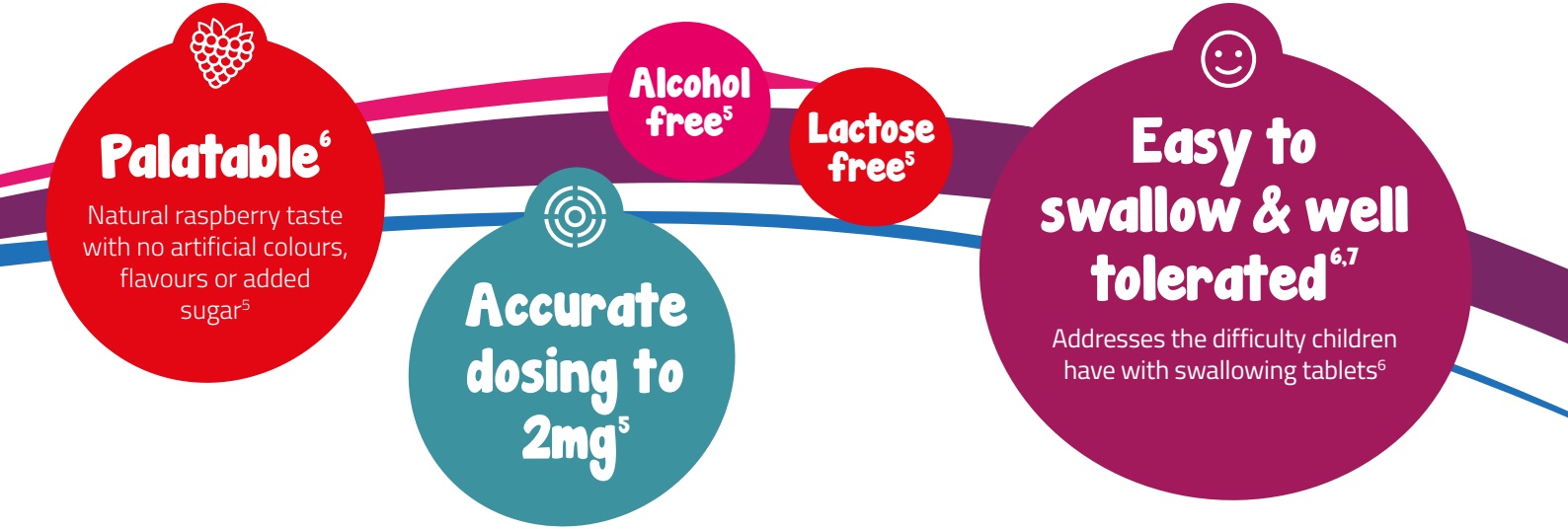
Dosing calculation chart

Age	BSA (m^2)†	Dose‡ (mg)	Volume (ml)
3 months	0.27 - 0.33	20 - 25	1.0 - 1.2
1 year	0.47 - 0.53	35 - 40	1.8 - 2.0
3 years	0.61 - 0.67	46 - 50	2.3 - 2.5
5 years	0.74 - 0.79	56 - 59	2.8 - 3.0
10 years	1.07 - 1.13	80 - 85	4.0 - 4.2
12 years	1.27 - 1.33	95 - 100	4.8 - 5.0
18 years	1.77 - 1.83	133 - 137	6.7 - 6.9

†Based on WHO growth charts for children (may not correspond to the BSA of individual patients)[10]
‡Based on a typical starting dose of 75mg/m^2 [1,5]

Mercaptopurine is part of the gold-standard maintenance regimen for ALL patients.[1]

Xaluprine® (mercaptopurine) 20 mg/ml oral suspension is the **SMC and the AWMSG recommended treatment option for ALL patients.**[2,3] It offers a flexible, accurate dosing alternative to mercaptopurine tablets.[4,5]



Xaluprine® is indicated for the treatment of ALL in adults, adolescents and children.[5] Mercaptopurine is the cornerstone of maintenance therapy for acute lymphoblastic leukaemia and proven to increase disease-free survival.[1,7]

A fluid approach to acute lymphoblastic leukaemia

Systemic exposure to mercaptopurine is critical for remissions in children with acute lymphoblastic leuk

Xaluprine® (mercaptopurine) 20 mg/ml oral suspension offers a palatable medication which is acceptable to children and will help support adherence to therapy[6]

Maximising mercaptopurine adherence and maintaining steady thiopurine exposure minimises relapses in children with ALL.[11]

Non-adherence, or drug interruptions can result in relapse and emergence of resistance.[11]

Adherence to a medicine is related to many factors, but palatability and acceptability of formulations are considered key factors for children.[12]

59% of relapses can be attributed to non-adherence[11]

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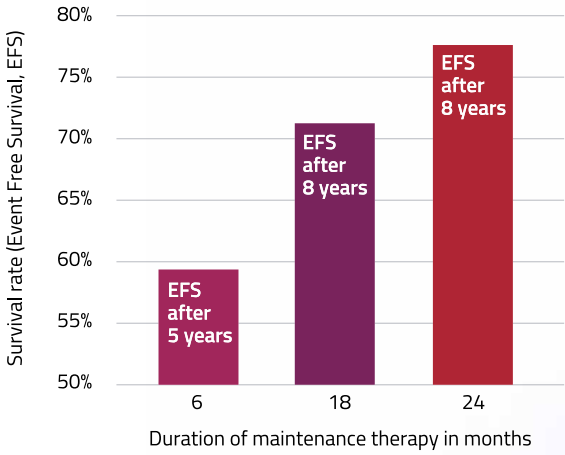
Maintenance therapy with mercaptopurine is essential for patient survival[13,14]

Survival rates (event-free survival) increase with the duration of mercaptopurine administration in maintenance therapy.[13,14]



Schrappe, et al. 2000, Toyoda, et al. 2000

Abbreviated Prescribing Information for Xaluprine® (mercaptopurine) 20 mg/ml oral suspension:

Please refer to the full Summary of Product Characteristics and the treatment protocol when prescribing Xaluprine®.

Presentation: Oral suspension, each 1 ml contains 20 mg mercaptopurine (as monohydrate), 3 mg aspartame, 1 mg methyl hydroxybenzoate (as the sodium salt), 0.5 mg ethyl hydroxybenzoate (as the sodium salt), and sucrose (trace). **Indications:** For the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children. **Dose and administration:** The dose is governed by cautiously monitored haematotoxicity and should be carefully adjusted to suit the individual patient. Starting or target doses vary between 25 - 75mg/m² body surface area per day, but should be lower in patients with reduced or absent Thiopurine Methyl Transferase (TPMT) enzyme activity. *Elderly:* Monitor renal and hepatic function and if there is any impairment, consider reducing the dose. *Renal impairment:* Consider reduced starting doses. Monitor patients for dose related adverse reactions. *Hepatic impairment:* Consider reduced starting doses. Monitor patients for dose related adverse reactions. *Switching between tablet and oral suspension and vice versa:* The oral suspension and tablet are not bioequivalent. Intensified haematological monitoring is advised on switching formulations. *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. *Patients with NUDT15 variant:* Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity. These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes. Genotypic testing of NUDT15 variants may be considered before initiating 6-mercaptopurine therapy. In any case, close monitoring of blood counts is necessary. *Administration:* Redisperse by shaking vigorously at least for 30 seconds. Xaluprine should be taken in the evening and may be taken with food or on an empty stomach. Standardise the method of administration. Xaluprine should not be taken with milk or dairy products but it should be taken at least 1 hour before or 2 hours after milk or dairy products. Administration in the evening compared to morning administration may lower the risk of relapse so the daily dose should be taken in the evening. Water should be taken after each dose. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Concomitant use with yellow fever vaccine. **Special Warnings and Precautions for Use:** *Cytotoxicity and haematological monitoring:* Monitor haematological parameters. Interrupt treatment immediately at the first sign of abnormally large fall in leucocyte and platelet counts. Bone marrow suppression is reversible if 6–mercaptopurine is withdrawn early. Patients with an inherited deficiency of the TPMT enzyme activity require close monitoring of blood counts and substantial dose reductions for homozygous-TPMT deficiency patients. Myelosuppresive effect of 6-mercaptopurine could be exacerbated by coadministration with substances that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. 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. *Immunosuppression:* Immunisations with live organism vaccines are not recommended. *Hepatotoxicity:* Monitor liver function weekly. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. Discontinue Xaluprine if jaundice becomes apparent. *Renal toxicity:* Monitor uric acid levels in blood and urine during remission induction. Hydration and urine alkalinisation may minimize potential renal complications. *Pancreatitis* is a common (frequency of ≥ 1/100 to < 1/10) adverse reaction in patients treated for the unlicensed indication inflammatory bowel disease. *Mutagenicity and carcinogenicity:* 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. A combination of multiple immunosuppressants (including thiopurines), 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. 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 (unlicensed indication) with or without concomitant treatment with anti-TNF alpha antibody. *Macrophage Activation Syndrome (MAS):* A life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (unlicensed indication). If MAS occurs or is suspected, evaluation and treatment should be started and treatment with mercaptopurine should be discontinued. *Infections:* Increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection, and viral reactivation. Prior exposure to or infection with varicella zoster virus should be taken into consideration prior to starting treatment. 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. Dose reduction and close monitoring of blood counts is necessary. *Paediatric population:* Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving 6-mercaptopurine. *Interactions:* When oral anticoagulants are coadministered with 6-mercaptopurine, reinforced monitoring of INR (International Normalised Ratio) is recommended. *Excipients:* Aspartame may be harmful for people with phenylketonuria. Sodium methyl parahydroxybenzoate and sodium ethyl parahydroxybenzoate may cause delayed allergic reaction. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this. Long term use increases the risk of dental caries and it is essential that adequate dental hygiene is maintained. *Safe handling of the suspension:* Avoid Xaluprine contact with skin or mucous membrane. For contact with skin or mucosa, wash immediately and thoroughly with soap and water. **Interactions:** The dose should not be taken with milk or dairy products. Concomitant administration of yellow fever vaccine and other live vaccines is contraindicated in immunocompromised individuals. Serum antiepileptic levels should be closely monitored. When allopurinol and 6–mercaptopurine are administered concomitantly only a quarter of the usual dose of 6– mercaptopurine must be given. Other xanthine oxidase inhibitors should be avoided. Reinforced monitoring of INR is recommended in patients co-administered anti-coagulants. Aminosalicylate derivatives inhibit TPMT enzyme and should be administered with caution. **Pregnancy and Lactation:** Do not use during pregnancy without careful assessment of risk versus benefit. Do not use whilst breast-feeding. Newborns of women exposed to mercaptopurine during pregnancy should be monitored for haematological and immune system disturbances. **Contraception:** Sexually active men and women should use effective methods of contraception during treatment and for at least three months after receiving the last dose. **Fertility:** The effect of 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. **Effects on ability to drive and use machines:** No studies on the effect on the ability to drive and use machines have been performed. **Undesirable effects: Refer to the SPC for full list.** Bone marrow suppression leading to leucopenia and thrombocytopenia is the most common adverse reaction. Anaemia, anorexia, stomatitis, diarrhoea, vomiting, nausea, biliary stasis and hepatotoxicity are common adverse reactions. The following adverse reactions have also been reported from uncommonly to very rarely: infections, arthralgia, skin rash, drug fever, pancreatitis, oral ulceration, hepatic necrosis, neoplasms, facial oedema, alopecia, transient oligospermia, secondary leukaemia, myelodysplasia, and intestinal ulceration. Hepatosplenic T-cell lymphoma, hypoglycaemia, portal hypertension, nodular regenerative hyperplasia, sinusoidal obstruction syndrome and photosensitivity reactions are adverse reactions of unknown frequency. **Overdose:** There is no antidote to Xaluprine. Monitor the blood picture and if necessary provide general supportive measures together with appropriate blood transfusion. Activated charcoal or gastric lavage can be undertaken within 60 minutes of ingestion. **Pack size:** 1 glass bottle containing 100 ml Xaluprine (mercaptopurine) 20mg/ml oral suspension. **Shelf-life/Storage:** 18 months; 56 days after first opening. Do not store above 25°C. **Keep bottle tightly closed**. **Legal category:** POM. **Marketing authorisation number:** EU/1/11/727/001. **Marketing authorisation holder:** Nova Laboratories Ireland Limited, 3rd Floor, Ulysses House, Foley Street, Dublin 1, D01 W2T2, Ireland **Date of latest revision of brief prescribing information:** March 2022.

For a copy of the SmPC or for additional information, please contact medical@dccvital.com

PCRS Code: 43350

Reporting of suspected adverse reactions
Adverse events should be reported. Reporting forms and information can be found on the HPRA website (www.hpra.ie) or by emailing medsafety@hpra.ie. Adverse events should also be reported to Fannin Ltd, Tel 01 1290 7000. Alternatively, send via email to medical@dccvital.com

References: 1. UKALL 2019 Interim Guidelines v1.0 20-Feb-2019 2. Scottish Medicines Consortium mercaptopurine 20mg/mL oral suspension (Xaluprine®) 3. All Wales Medicines Strategy Group, mercaptopurine (Xaluprine®) Ref No. 1252 4. EMA 2011, Committee for Medicinal Products for Human Use assessment report: Mercaptopurine Nova Laboratories. 5. SMPC Nova Laboratories Ltd. Xaluprine 20 mg/ml oral suspension Summary of Product Characteristics 6. Mulla H et al. Journ Onco Pharm Prac. 2015 Jun;22(3):387-95. 7. Mulla H et al. Journ Clin Pharm. 2012 Oct;52(10):1610-3. 8. Haute Authorité de Santé Xaluprine 20 mg/ml, oral suspension Transparency Committee Opinion. 9. Breitkreutz J & Boos J. Paed & Geritic Drug Delivery. 2007 Jan 1;4(1):37-45. 10. WHO, Child Growth Standards 11. Bhatia S et al. JAMA oncol. 2015 Jun 1;1(3):287-95. 12. Venables R. et al. Internal Journ Pharma, 480(1-2), 55–62. doi:10.1016/j.ijpharm.2015.01.023 13. Schrappe et al. Leukemia, 2000, 14, 2205-2222 14. Toyoda et al. Journ Clin Oncol 2000 Apr; 18(7):1508-1516

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