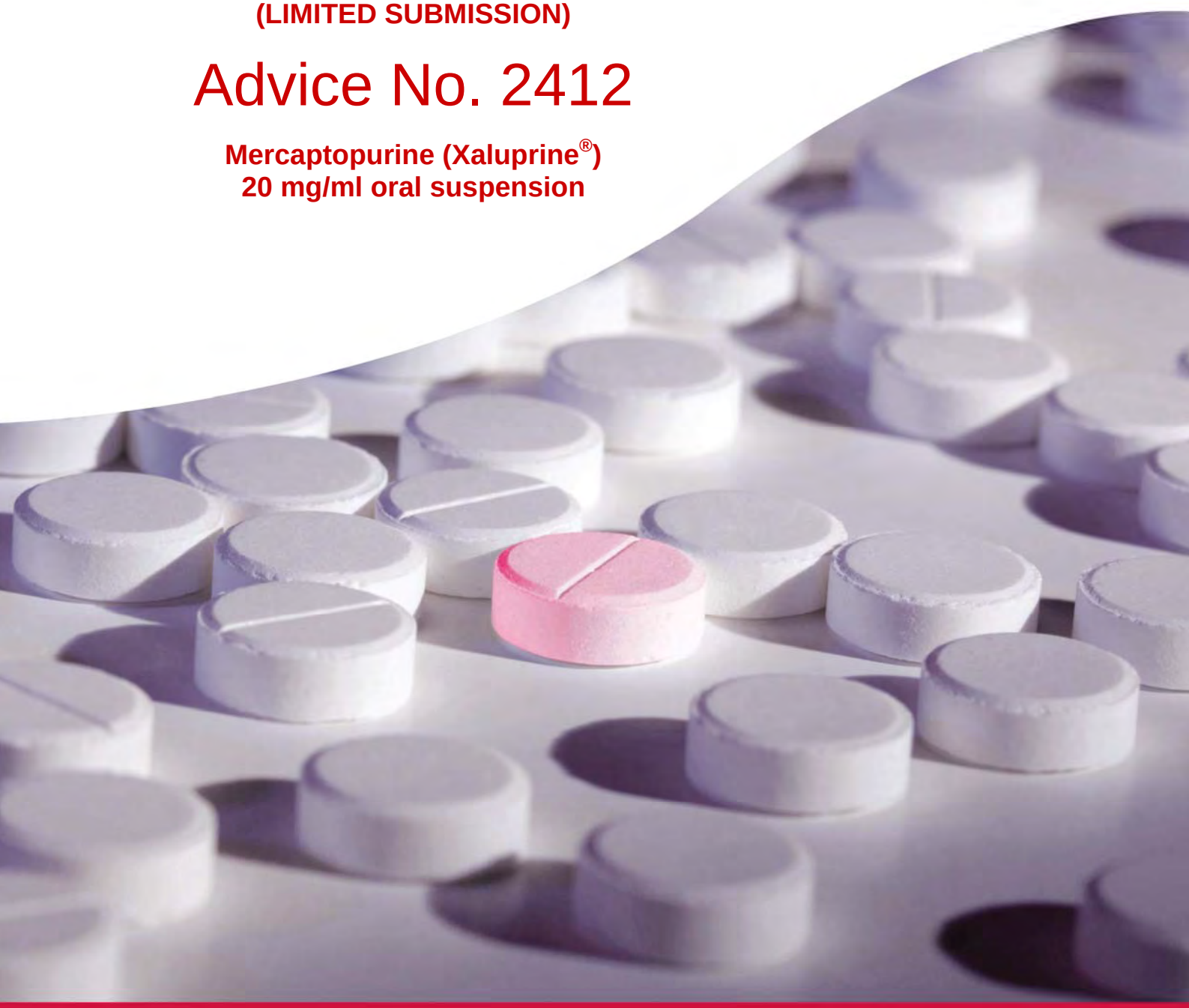
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 2412

Mercaptopurine (Xaluprine®) 20 mg/ml oral suspension



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 2412
Mercaptopurine (Xaluprine®) 20 mg/ml oral suspension

This assessment report is based on evidence from a limited submission by Nova Laboratories Ltd on 13 March 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Mercaptopurine (Xaluprine®) oral suspension is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children[2].
Marketing authorisation date	9 March 2012[3].
UK launch date	Anticipated launch date: May 2012[1].
Comparators	Mercaptopurine (PURI-NETHOL®) tablets. Mercaptopurine liquid (unlicensed special).
Limited submission details	For the indication under consideration, Xaluprine® met the following criteria for a limited submission: • Anticipated minimal budgetary impact in NHS Wales. • Estimated small difference in cost compared to comparators.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence provided in submission

The company submission aims to demonstrate bioequivalence of Xaluprine® with the existing mercaptopurine tablet formulation[1], the pharmacokinetics of which are well characterised[4]. Evidence was supplied from one randomised, crossover bioavailability study of 60 subjects. Although this was conducted in healthy volunteers, this is considered acceptable by the European Medicines Agency (EMA) for studies of this type[5]. Each volunteer received a 50 mg dose of mercaptopurine tablet and a 50 mg dose of mercaptopurine oral suspension (as Xaluprine®), separated by a washout period (≥ 72 hours)[1,6].

Whilst not all predefined bioequivalence criteria were met in this study (bioavailability being higher for the oral suspension than the tablet, and outside the predefined margin for bioequivalence for some parameters), the results showed that there was less between-subject variation in bioavailability with Xaluprine® than with mercaptopurine tablets[4,6].

In the bioequivalence study, both Xaluprine® and mercaptopurine tablets were well tolerated in study subjects[1,6]. Additional data, submitted to the EMA as part of the application for marketing authorisation, did not identify any differences in the safety profile of Xaluprine® versus mercaptopurine tablets[4].

2.2 Points to note

- Mercaptopurine has an established role in the treatment of acute lymphoblastic leukaemia (ALL), a common childhood malignancy[4,7]. Dosing of mercaptopurine is complex: the basic daily dose is determined according to

either patient weight or body surface area, and this is adjusted dependent on the nature and dosage of other agents given in combination with mercaptopurine, as well as factors such as absolute neutrophil count and platelet count[2,4]. Up to 90% of paediatric patients may require a daily dose that cannot be obtained with a whole 50 mg tablet[8].

- Xaluprine® is the first licensed liquid formulation of mercaptopurine. Prior to the marketing authorisation of Xaluprine® being granted, the only licensed presentation of mercaptopurine available has been the 50 mg tablet; in many patients to obtain the correct dose necessitated the breaking or crushing of tablets, or the use of mercaptopurine as an unlicensed liquid special[2,4]. The use of a liquid formulation has the potential to provide more accurate doses compared to splitting or crushing tablets.
- The company have submitted clinical evidence comparing Xaluprine® with one of the requested comparators, mercaptopurine tablets. No evidence has been included comparing the clinical effectiveness of Xaluprine® with other mercaptopurine liquids (i.e. unlicensed specials).
- Comparison of Xaluprine® with mercaptopurine tablets comes from one published paper comparing only the pharmacokinetics of the two formulations; no evidence for efficacy or safety has been included. Predefined bioequivalence criteria were not met for some measured parameters, and the absorption of Xaluprine® was higher than that of mercaptopurine tablets. Although the bioavailability of mercaptopurine is known to vary considerably between individuals[4], the oral suspension was shown to have more consistent bioavailability across the population tested. In light of these findings, the Committee for Medicinal Products for Human Use considered the pharmacokinetic data sufficient for a new licensed formulation[4].
- As mercaptopurine is cytotoxic[2] and will be administered to children for the indication considered, a liquid formulation is advantageous as the potential for exposure of parents or carers to mercaptopurine is lower when handling the liquid as compared to the tablets. The risks of exposure are particularly important if mercaptopurine tablets need to be split or crushed by parents or carers to achieve the correct dose.
- Given the differences in pharmacokinetics between the tablet and liquid formulations, intensified haematological monitoring is recommended if a patient is switched from one formulation to the other[2].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence[1]

Using an average prevalence of ALL in the EU population, the applicant company estimated that 48 patients, primarily children, will be eligible for treatment with Xaluprine® in Wales. The company submission presents simple examples of the daily and annual acquisition costs per patient for Xaluprine® and the unlicensed mercaptopurine oral solution for the treatment of ALL. Mercaptopurine is dosed on the basis of body surface area (BSA) and the example costs provided by the company appear to relate to children, who have lower BSA than adults. Assuming that patients will receive one 100 ml bottle of Xaluprine® per month (at a company-reported cost of £175 per 100 ml), the maximum annual cost per patient is estimated to be £2,100, compared with £1,560 for the unlicensed formulation (at a company-reported cost of £130 per 100 ml).

3.2 Critique of the budget impact analysis

No estimates of the number of patients with ALL in Wales currently treated with oral liquid formulations of mercaptopurine are provided to guide likely uptake of the licensed product. There is uncertainty about the unit cost of unlicensed mercaptopurine assumed in the company's analysis, as this is not included in Part VIIIB of the NHS Drug Tariff[9]. It is also unclear whether the assumed costs of the unlicensed product include all relevant costs associated with procurement of specials. The company assumes that most patients would be children, who would require one 100 ml bottle of Xaluprine® per month or two 60 ml bottles of unlicensed mercaptopurine per month. Both products have an in-use shelf life of one month, and the amount of wastage of the licensed and unlicensed formulations would depend on individual dosing requirements. Overall, the licensed product is priced higher than the unlicensed formulation, but there is uncertainty in the actual budget impact of the use of the licensed formulation in NHS Wales.

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if given a positive recommendation, Xaluprine® oral suspension is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 13 April 2012.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Nova Laboratories Ltd. Form C: limited appraisal submission. Mercaptopurine (Xaluprine®). Mar 2012.

2 Nova Laboratories Ltd. Mercaptopurine Nova Laboratories 20 mg/ml oral suspension [Xaluprine]. Summary of Product Characteristics. Mar 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002022/WC500124645.pdf. Accessed Apr 2012.

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