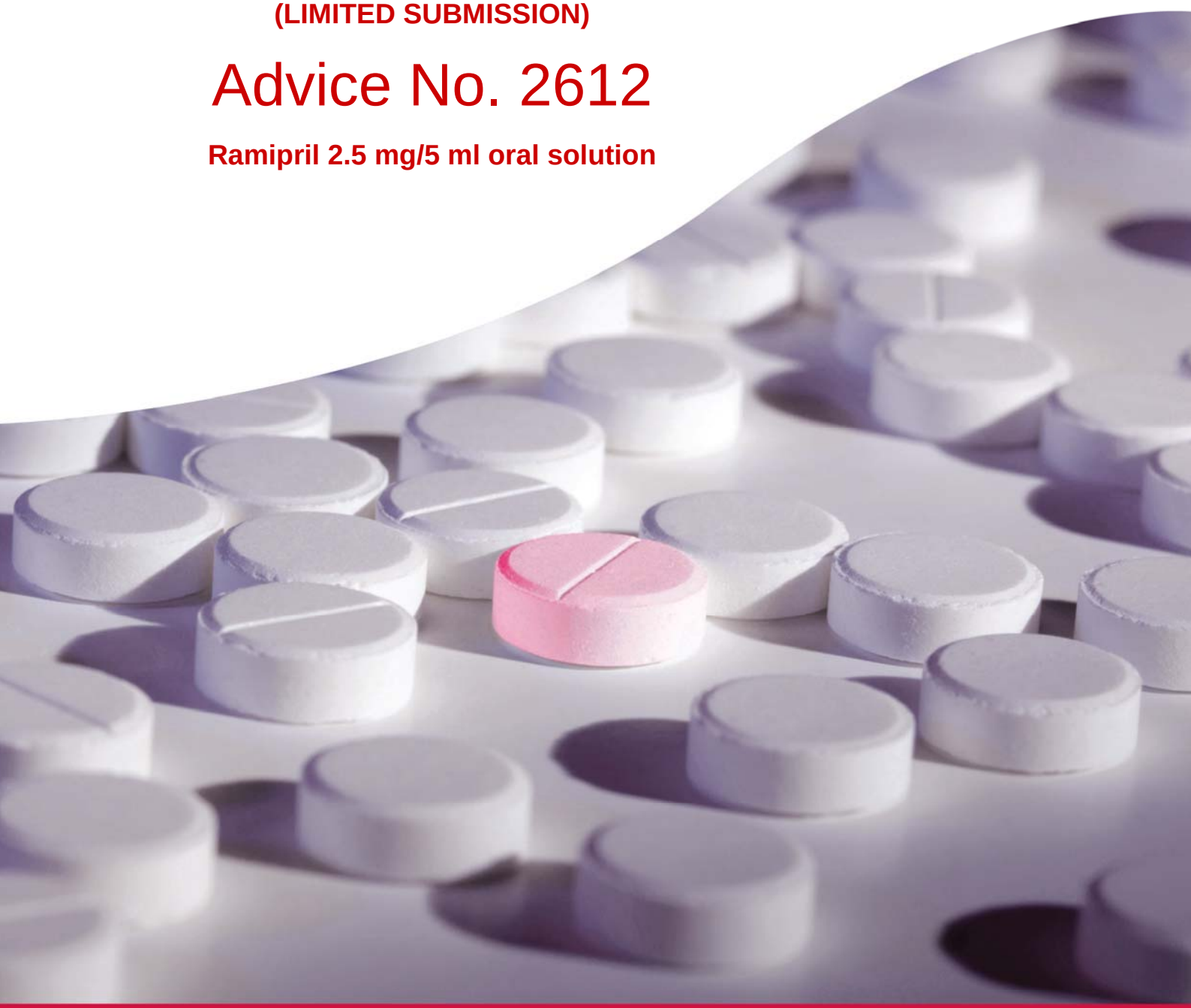
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 2612

Ramipril 2.5 mg/5 ml oral solution



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

AWMSG Secretariat Assessment Report – Advice No. 2612
Ramipril 2.5 mg/5 ml oral solution

This assessment report is based on evidence from a limited submission by Rosemont Pharmaceuticals Ltd on 16 March 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Ramipril 2.5 mg/5 ml oral solution is indicated for:
	• Treatment of hypertension.
	• Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
	  • manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease);
	  • diabetes with at least one cardiovascular risk factor.
	• Treatment of renal disease:
	  • incipient glomerular diabetic nephropathy as defined by the presence of macroalbuminuria;
	  • manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor;
	  • manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day.
	• Treatment of symptomatic heart failure.
	• Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction[2].

Marketing authorisation date	9 November 2011[2].
Comparators	Ramipril 2.5 mg/5 ml oral solution (unlicensed “special”) and ramipril 2.5 mg capsules/tablets.
Limited submission details	Ramipril 2.5 mg/5 ml oral solution for the above indications met the following criteria for eligibility for a limited submission: • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of bioequivalence evidence

The company submission refers to an open-label, single dose, randomised, two-treatment crossover pharmacokinetics study, which compared the bioavailability of ramipril 2.5 mg/5 ml oral solution and ramipril 2.5 mg tablets (as Tritace®[3]) in 36 healthy adult volunteers under fasting conditions[1,4,5]. The 90% confidence intervals for C_{max} and area under the curve (AUC) for ramipril 2.5 mg/5 ml oral solution fell within 80–125% of the reference product, thereby demonstrating bioequivalence of the two products, in line with European Medicines Agency guidelines[5,6]. During the study, one subject (3%) that received ramipril 2.5 mg/5 ml oral solution and one subject (3%) that received a ramipril 2.5 mg tablet experienced adverse events possibly related to ramipril, consisting of headache, nausea, irritated tongue and irritated throat[4]. No deaths or serious adverse events were reported during the study[5].

2.2 Points to note

- The company suggests that ramipril 2.5 mg/5 ml oral solution would be considered for use in patients that cannot swallow or tolerate the capsule or tablet[1]. There is currently no other licensed ramipril oral solution available.
- The Summary of Product Characteristics for ramipril 2.5 mg tablets and capsules state that they must not be chewed or crushed[3,7]. The opening of capsules or crushing of tablets to mix with water would be using the medicine in an unlicensed manner.
- The Medicines and Healthcare products Regulatory Agency stated that no new clinical efficacy or safety data were required to provide marketing authorisation for ramipril 2.5 mg/5 ml oral solution, as it is an alternative formulation of a product that has been licensed for over ten years[5].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company estimates that 5–10 patients would be eligible for treatment with ramipril 2.5 mg/5 ml oral solution in Wales[1]. This is calculated on a pro rata basis, according to company-reported UK sales figures for both its licensed and unlicensed ramipril 2.5 mg/5 ml oral solutions, an assumed displacement of other companies' unlicensed oral solutions/suspensions, and an assumed average daily dose of 5 mg. The company estimates that approximately 24 bottles (150 ml) will be used per patient per year, at a cost of £80 per bottle for the licensed product. This is estimated to result in a cost saving of £23,640 compared to the unlicensed product, which is assumed to cost £178.50 per 150 ml bottle.

3.2 AWTTC critique of the budget impact analysis

The company's analysis is based on a comparison with unlicensed ramipril 2.5 mg/5 ml oral suspension only, despite the availability of other unlicensed liquid formulations listed in the drug tariff at the time of submission[8]. Although some unlicensed ramipril oral liquid formulations had greater acquisition costs than the licensed 2.5 mg/5 ml oral solution, unlicensed ramipril 5 mg/5 ml oral solution was listed at a tariff price of £60.77 per 150 ml[8], which, even when taking into account the additional £20 standard fee for sourcing specials, could have delivered the assumed average 5 mg daily dose at around half the annual cost of the licensed 2.5 mg/5 ml oral solution. As doses up to 10 mg daily may be required for some patients, the cost

differential between the licensed and unlicensed liquid formulations would vary proportionally. Rather than delivering cost savings, it is therefore plausible that the licensed 2.5 mg/5 ml oral solution could have a greater acquisition cost compared with unlicensed liquid formulations available at the time of submission, depending on the extent to which these alternative unlicensed liquid formulations were being used and are now displaced. In addition, as the sales data upon which the eligible patient numbers are based appear to relate only to the licensed and unlicensed 2.5 mg/5 ml oral solutions, this could underestimate the number of patients eligible for treatment. Collectively, the company's projected cost savings are subject to considerable uncertainty and may not reflect the actual budget impact for Wales arising from the use of the licensed ramipril oral solution.

3.3 Comparative unit costs

Table 1 includes comparative costs of licensed and unlicensed ramipril formulations as listed in eDrug Tariff at the time of submission (May 2012)[8]. It should be noted that unlicensed manufactured oral liquid formulations of ramipril (specials) are no longer included in the drug tariff following the introduction of the licensed oral solution. The company suggests that tablet and capsule formulations are not relevant comparators for the licensed ramipril oral solution, as liquid formulations would be appropriate only in those in whom solid dosage forms are not appropriate. However, as the licensed indication does not restrict the use of the licensed ramipril oral solution to these patients, the comparative costs of tablet and capsules are included below for completeness.

Table 1. Examples of medicine acquisition costs for licensed and unlicensed ramipril formulations

Medicine formulation	Example daily dose	Example 28-day cost of treatment*
Licensed ramipril 2.5 mg/5 ml oral solution, 150 ml bottle	1.25 to 10 mg/day (2.5 to 20 ml daily)	£80 to £299
Ramipril 5 mg/5 ml oral solution (unlicensed special), 150 ml bottle†	1.25 to 10 mg/day (1.25 to 10 ml daily)	£61 to £114
Ramipril 2.5 mg/5 ml oral suspension (unlicensed special), 100 ml bottle†	1.25 to 10 mg/day (2.5 to 20 ml daily)	£166 to £927
Ramipril 5 mg/5 ml oral suspension (unlicensed special), 100 ml bottle†	1.25 to 10 mg/day (1.25 to 10 ml daily)	£159 to £445
Ramipril (non proprietary) 1.25, 2.5, 5 and 10 mg tablets	1.25 to 10 mg/day	£1.23 to £1.58
Ramipril (non proprietary) 1.25, 2.5, 5 and 10 mg capsules	1.25 to 10 mg/day	£1.07 to £1.34

See the relevant Summaries of Product Characteristics for indications and full dosing details of licensed products.
**Costs are based on eDrug Tariff list prices as of 29 May 2012[8]. †Unlicensed specials liquid formulations are no longer listed in the eDrug Tariff following the introduction of the licensed formulation.*
Oral liquid formulations are assumed to have a one-month (28-day) shelf-life once opened, as per the licensed oral solution[2]. For low doses, the full cost of a bottle with wastage is assumed.
Unlicensed products ordered as specials attract a standard £20 sourcing fee, which is not included in the above cost estimates.

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, ramipril 2.5 mg/5 ml oral solution may be appropriate for prescribing by all prescribers 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: 10 May 2012
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Rosemont Pharmaceuticals Ltd. Form C: Limited appraisal submission. Ramipril 2.5 mg/5 ml oral solution. Mar 2012.

2 Rosemont Pharmaceuticals Ltd. Ramipril 2.5 mg/5 ml oral solution. Summary of Product Characteristics. Nov 2011. Available at: http://www.medicines.org.uk/EMC/medicine/25596/SPC/Ramipril+2.5mg+5ml+Oral+Solution/. Accessed May 2012.

3 Sanofi-Aventis Ltd. Tritace® 2.5 mg tablets. Summary of Product Characteristics. Nov 2011. Available at: http://www.medicines.org.uk/EMC/medicine/25510/SPC/Tritace+2.5mg+tablets/. Accessed May 2012.

4 Bonhomme MC, Marricco NC, Di Spirito M et al. A comparative, randomized, single-dose, 2-way crossover bioavailability study of a ramipril oral solution versus tablet in healthy adult volunteers. Presented at ASCPT 2012: Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. 14 Mar 2012.

5 Medicines and Healthcare products Regulatory Agency. Public assessment report for ramipril 2.5 mg/5 ml oral solution. Decentralised procedure: UH/2504/01/DC. 2012. Available at: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con140710.pdf. Accessed May 2012.

6 European Medicines Agency. Guideline on the investigation of bioequivalence. 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed May 2012.

7 Accord Healthcare Ltd. Ramipril 2.5 mg capsules. Summary of Product Characteristics. Nov 2011. Available at: http://www.medicines.org.uk/EMC/medicine/25935/SPC/Ramipril+2.5+mg+Capsules/. Accessed May 2012.

8 NHS Business Services Authority. Electronic drug tariff. May 2012. Available at: http://www.ppa.org.uk/ppa/edt_intro.htm. Accessed May 2012.