AWMSG Secretariat Assessment Report – Advice no. 0211
Valsartan (Diovan®▼) tablets for the treatment of hypertension in children and adolescents 6 to 18 years of age

This assessment report is based on evidence from a limited submission by Novartis Pharmaceuticals UK Limited on 7 September 2010

1.0 PRODUCT DETAILS

Licensed indication	Valsartan (Diovan®▼) tablets for the treatment of hypertension in children and adolescents 6 to 18 years of age[1–4].
Dosing	The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum recommended doses, refer to the summary of product characteristics (SPC)[1–4].
Marketing authorisation date	28 May 2010[5].
UK Launch date	Available for the original indication since 1996[6]. Further tablet strengths launched in October 2010[5].

2.0 DECISION CONTEXT

2.1 Background

In children, hypertension is defined as a persistent systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥ 95th percentile for age, gender and height[6]. In older children and adolescents, common causes of hypertension are obesity, insulin resistance, inactivity, family history of the disease and ethnic predisposition to essential hypertension. In younger children (aged < 10 years) hypertension is more commonly due to secondary causes such as renal or reno-vascular disease[6]. For children with renal disease, the most widely used agents are those inhibiting the renin-angiotensin system, mainly angiotensin converting enzyme inhibitors (ACEIs), or angiotensin II receptor antagonists (ARAs) if intolerance to ACEIs exists[7].

Based on an estimated 1–2% prevalence of hypertension in school-age children[6] and StatsWales population data for this age group[8], the company estimates that between 3,871 and 7,742 6–17 year-olds in Wales have hypertension[9]. Figures obtained directly from StatsWales by the Welsh Medicines Partnership (WMP) give the most recent (2009) population for 6–17 year olds in Wales as 425,916[8]; assuming a 1–2% prevalence, this gives an estimated 4,259 to 8,518 6–17 year olds in Wales with hypertension.

Valsartan is an ARA[10] licensed for treatment of adults with hypertension, first marketed in Europe in 1996 at doses of 80–160 mg and in a higher dose of 320 mg since 2006[6]. In May 2010 the licence for the tablet formulation (40 mg[1], 80 mg[3], 160 mg[4] or 320 mg[2]) was extended to include patients aged 6–18 years[5]; use in this patient group is the focus of this assessment. An oral solution of valsartan is also licensed for use in children[11], but the company estimate this will not be launched in the UK until 2012[5].

2.2 Comparators

The comparator requested by WMP is losartan (Cozaar®).

Expert opinion sought by WMP suggests that candesartan (Amias®) or telmisartan (Micardis®▼) would also be alternatives to valsartan in children and adolescents.

2.3 Guidance and related advice

- European Society of Hypertension. Management of high blood pressure in children and adolescents; June 2009[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission provided brief details of five completed clinical trials of valsartan in children[5,12]. These included two trials of valsartan in tablet formulation carried out in children aged 6–18 years (see below). The remaining studies were carried out in children aged less than 6 years, treated with valsartan as an extemporaneous suspension prepared from tablets. Since the latter use is outside the licensed age and formulation of the product, these studies will not be discussed further. The company submission did not compare the clinical efficacy of valsartan and losartan.

3.1 Study A2302

Study A2302 was a phase III double-blind, randomised, multicentre study conducted in children aged 6–16 years with hypertension[6]. The study consisted of a four-week double-blind period followed by a 52-week, open label extension period. The double-blind period was divided into two equal-length phases. In the first two weeks all patients were randomised to a low, medium or high dose of valsartan (10, 40, or 80 mg for patients weighing < 35 kg; 20, 80 or 160 mg for patients ≥ 35 kg); in the subsequent two weeks patients were re-randomised in a 1:1 ratio to either continue the same valsartan dose or switch to placebo. All treatments were administered once daily. A total of 261 patients entered the randomisation period and 245 completed the study.

The primary outcome measure of study A2302 was change from baseline in sitting SBP after two weeks of valsartan treatment[13]. Relevant secondary outcomes were change from baseline in SBP and DBP after both 4 and 52 weeks and change from baseline in DBP after two weeks. The company state that valsartan was efficacious in dose-dependent SBP reduction compared with placebo, but do not provide any detailed results in their submission. The European Medicines Agency (EMA) Assessment Report for the valsartan licence extension[6] states that during the placebo phase, a significant ($p < 0.0001$) increase in SBP was observed in the placebo group, but there was no significant change in SBP in patients continuing on valsartan. A dose-dependent decrease in SBP was observed after two weeks of valsartan treatment, which was the primary outcome measure.

No detailed results are available from the open-label extension period: the EMA Assessment Report states that mean SBP achieved during the double-blind period was maintained, but no further details are provided.

3.2 Study K2302

Study K2302 was a phase III, multicentre, randomised, active-controlled trial in children with hypertension aged 6–17 years. A total of 300 patients entered the randomisation period and 281 completed the study. Equal numbers of patients were randomised to 12 weeks of treatment with either valsartan or enalapril once daily. Dosing was weight-dependent. The primary outcome measure was reduction in mean sitting SBP from

baseline to week 12[14]. Relevant secondary outcomes were decrease in mean sitting DBP, and the safety and tolerability of valsartan compared with enalapril (see section 4.0). Valsartan was demonstrated to be non-inferior to enalapril in terms of change in mean SBP[6]. The company note that similar results were obtained for mean DBP[5,12].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

The company's limited submission contains no information on the clinical safety of valsartan[5,12]. Evidence has therefore been drawn from the SPC[1–4] and the EMA assessment report for this extension to the valsartan licence[6].

The safety profile is based on the two studies described in section 3.0. In general, the observed profile of adverse events (AEs) was as expected in the paediatric population and in line with the drug class; the incidence of valsartan-related AEs was low and did not appear dose-dependent[6]. There were no major clinically relevant differences between the safety profiles of valsartan and enalapril, although discontinuation rates were higher in the valsartan arm[6]. Gastrointestinal AEs were observed more frequently in the valsartan arm than in the placebo or enalapril arms, and were a reason for discontinuation[6].

Existing safety data suggest that AEs may be more common in patients with chronic kidney disease[6]. Use in paediatric patients with a creatinine clearance < 30 ml/min and in paediatric patients undergoing dialysis has not been studied; therefore valsartan is not recommended in these patients. Furthermore, as in adults, valsartan is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and cholestasis[1–4].

As with clinical efficacy, no information is available comparing the clinical safety of valsartan with losartan.

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- No data comparing valsartan with losartan for treatment of hypertension in children has been provided by the company, and an independent literature search by WMP did not identify any relevant evidence in the published literature. The clinical effectiveness of valsartan versus losartan for treatment of hypertension in children therefore remains uncertain.
- The only active comparator trial for which data is available compares valsartan with the ACEI enalapril[5,12]. Although this study demonstrates that valsartan is non-inferior to enalapril, no rationale has been provided by the company as to why a comparison with enalapril has been chosen over losartan or indeed any other antihypertensive treatments available.
- Although the studies described in sections 3.0 and 4.0 appear to show that valsartan is efficacious and safe in the treatment of children with hypertension, the data provided by the company is limited. Furthermore, no results of the pivotal studies have been published from which independent conclusions could be drawn.
- In the pooled safety analysis from studies A2302 and K2302, gastrointestinal AEs were observed more frequently in the valsartan arm than in the placebo or enalapril arms and were a reason for discontinuation[6]. Gastrointestinal AEs also occurred more frequently in children treated with valsartan than in the adult valsartan-treated population.

- The demographics of patients participating in study A2302 were notably different from those of patients in Wales: 48.7% (127 of 261) of patients were black[5,12].

- The primary outcome of the pivotal study A2302 was change in SBP after two weeks[13], but four weeks of treatment is considered necessary to observe near-maximum efficacy of valsartan[6]. However, the EMA Assessment Report states that there was minimal change in SBP between weeks two and four of treatment, suggesting that valsartan was efficacious in SBP reduction for at least four weeks.

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

6.1.1 Context

The company submission does not include any evidence on the cost effectiveness of the use of valsartan in paediatric patients aged 6–18 years[5,12].

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of valsartan in the paediatric patient population.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and methods

The company submission does not include any evidence on the budget impact of the use of valsartan in paediatric patients aged 6–18 years[5,12].

7.2 Comparative unit costs

The company considers that treatment options in the paediatric hypertension patient population are limited. European Society of Hypertension guidelines (see section 2.3)[7], contain recommended initial doses of antihypertensive agents drawn from all drug classes (i.e. diuretics, beta-blockers, calcium channel blockers, ACEIs and ARAs), although some of these may not be licensed for use in this patient population.

Table 1 provides example 28-day treatment costs with valsartan, and selected ACEIs and other ARAs that are licensed for use in this population. Costs are based on the initial and recommended maximum doses specified in relevant SPCs, and non-proprietary drug costs, where available, from the British National Formulary (BNF)[10]. These examples assume paediatric patients are able to take oral tablet formulations; unlicensed oral solutions ordered via “special” manufacturers would likely attract significantly greater costs.

Table 1. Example 28-day costs of ACEIs and ARAs for treating paediatric hypertension.

Drug	Example initial and maximum daily regimen	28-day cost[10]
Valsartan (Diovan®▼) tablets[1]	Body weight < 35 kg: 40 mg to 80 mg once daily	£13.96 to £13.97
	Body weight ≥ 35 kg to < 80 kg: 80 mg to 160 mg once daily	£13.97 to £18.41
	Body weight ≥ 80 kg: 80 mg to 320 mg once daily	£20.23 if dose = 320 mg per day using 320 mg tablets
Losartan (Non-proprietary)[15]	Body weight < 50 kg: 25 mg to 50 mg once daily	£1.99
	Body weight > 50 kg: 50 mg to 100 mg once daily	£1.99
Captopril (Non-proprietary)[16]	0.3 mg/kg three times per day: E.g. Body weight 42 kg*	£2.28
Enalapril (Non-proprietary)[17]	Body weight < 50 kg: 2.5 mg to 20 mg once daily	£1.29 to £1.39
	Body weight ≥ 50 kg: 5 mg to 40 mg once daily	£1.16 to £2.78
Lisinopril (Non-proprietary)[18]	Body weight < 50 kg: 2.5 mg to 20 mg once daily	£1.00 to £1.39
	Body weight ≥ 50 kg: 5 mg to 40 mg once daily	£1.05 to £2.78
This table does not imply therapeutic equivalence of the drugs or doses. Doses relate to recommended initial and maximum daily treatment doses and need to be titrated to individual response. Assumes paediatric patients can take solid oral dose forms. See the individual SPCs and BNF for recommendations. All costs calculated from least costly BNF list prices[10]. **Chosen to reflect nearest dose achievable with whole tablet dosing.*		

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that valsartan (Diovan®▼) tablets may be suitable for shared care within NHS Wales, initiated in secondary care with subsequent prescribing in primary care.

8.2 Ongoing studies

The company submission provided brief details of an ongoing 14 week extension study to K2302, in which patients receive valsartan or enalapril as monotherapy or combination therapy. This study is designed primarily to evaluate safety. The expected date of completion is not known.

REFERENCES

1 Novartis Pharmaceuticals UK Ltd. Diovan®▼ 40 mg film-coated tablets. Summary of product characteristics. May 2010. Available at: http://www.medicines.org.uk/EMC/medicine/23162. Accessed Oct 2010.

2 Novartis Pharmaceuticals UK Ltd. Diovan®▼ 320 mg film-coated tablets. Summary of product characteristics. Jun 2010. Available at: http://www.medicines.org.uk/EMC/medicine/23163. Accessed Nov 2011.

3 Novartis Pharmaceuticals UK Ltd. Diovan®▼ 80 mg film-coated tablets. Summary of product characteristics. May 2010. Accessed Oct 2010.

4 Novartis Pharmaceuticals UK Ltd. Diovan®▼ 160 mg film-coated tablets. Summary of product characteristics. May 2010. Accessed Oct 2010.

5 Novartis Pharmaceuticals UK Ltd. Form C. AWMSG limited submission. Sep 2010.

6 European Medicines Agency. Assessment report for Diovan and associated names. Procedure No. EMEA/H/A-29 PAD/1219. May 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diovan_1219_29_Paediatrics/WC500093237.pdf. Accessed Nov 2010.

7 Lurbe E, Cifkova R, Cruickshank JK et al. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. *J Hypertens* 2009; 27 (9): 1719-42.

8 StatsWales. Mid-year population estimates by age. Feb 2010. Available at: http://statswales.wales.gov.uk/index.htm. Accessed Nov 2010.

9 Novartis Pharmaceuticals UK Ltd. Form A. Initial appraisal information. Jul 2010.

10 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary No. 59.* Mar 2010.

11 European Medicines Agency. Assessment report for Diovan and associated names. Procedure No. EMEA/H/A-29 PAD/1220. May 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diovan_1220_29_Paediatrics/WC500093266.pdf. Accessed Nov 2010.

12 Novartis Pharmaceuticals UK Ltd. Form C. AWMSG limited submission. Appendix: paediatric clinical studies. Sep 2010.

13 ClinicalTrials.gov. A study of valsartan used to treat hypertension for up to 13 months in hypertensive children ages 6 to 16 years of age. Apr 2007. Available at: http://clinicaltrials.gov/ct2/show/NCT00171041. Accessed Nov 2010.

14 ClinicalTrials.gov. Effect of valsartan compared to enalapril on sitting systolic blood pressure in children with high blood pressure. Oct 2009. Available at: http://clinicaltrials.gov/ct2/show/NCT00433836. Accessed Nov 2010.

15 Pfizer Ltd. Losartan potassium 25 mg, 50 mg and 100 mg tablets. Summary of product characteristics. Mar 2010. Available at: http://www.medicines.org.uk/EMC/medicine/23272. Accessed Oct 2010.

16 E.R.Squibb & Sons Ltd. Capoten® 12.5 mg, 25 mg, and 50 mg tablets. Summary of product characteristics. Sep 2008. Available at: http://www.medicines.org.uk/EMC/medicine/550. Accessed Oct 2010.

17 Winthrop Pharmaceuticals UK Ltd. Enalapril maleate 10 mg tablets. Summary of product characteristics. May 2010. Available at: http://www.medicines.org.uk/EMC/medicine/22427. Accessed Oct 2010.

18 Winthrop Pharmaceuticals UK Ltd. Lisinopril 2.5 mg tablets. Summary of product characteristics. Aug 2010. Available at: http://www.medicines.org.uk/EMC/medicine/22413. Accessed Oct 2010.