1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that valsartan be “approvable” for use in pediatric patients. Outstanding issues include: understanding how to dose in order to write appropriate instructions for use; and the sponsor providing convincing evidence of safety with regard to transaminase elevations seen in several cases in study A2307.

In addition, two deaths were seen in the open-label phase of the valsartan study in two 1 year-old patients (severe vomiting and diarrhea in one case with no other available data; in the other case, fatal pneumonitis with respiratory failure occurring 11 days after a hospitalization for pneumonitis and hepatitis with valsartan discontinued due to hepatitis).

The question of dosing arises from study A2307 (1-5 year olds), which showed a flat dose-response in the dose-ranging phase; and the results of weight-adjusted dosing in A2302 (6-16 year olds), which showed a high degree of variability, small effects, and do not appear to fit linear, log-linear, or Emax models.

If dosing and titration can be clarified, then the other outstanding issue involves cases of transaminase elevation in A2307; since similar cases were not seen in the older children, it would then be recommended that valsartan be approved in hypertensive patients aged 6-16 years old.
If approved, it is recommended that proposed labeling be amended to include appropriate efficacy and safety information.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

Appropriate information should be communicated to patients and physicians.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor conducted two clinical studies with nearly identical designs (Written Request Trial C). Study A2302 was the pivotal study conducted in hypertensive children aged 6-16 years. Study A2307 was a supportive study in hypertensive children aged 1-5 years. Per the Trial C design, each study incorporated a two-week double-blind dose-response phase (Phase 1), a two-week double-blind placebo-controlled randomized withdrawal phase (Phase 2), and a voluntary open-label extension.

1.3.2 Efficacy

In both studies, results of the randomized withdrawal phase showed a statistically significant different between pooled valsartan and placebo.
In study A2302, results of the two-week dose-ranging phase showed a negative slope of the mm Hg systolic blood pressure per unit increase in dose ratio that was significantly different from zero, supporting a dose-dependent decrease in systolic blood pressure. From additional analyses, these data, when weight-adjusted (mg/kg), showed slope analyses that were significantly different from zero when fit to a linear, linear model on log transformed weight-adjusted dose, and Emax models; however, the data did not "best fit" any of these models.
In study A2307, results of the two-week dose-ranging phase showed a flat dose-response with decreases from baseline in all dose groups (no placebo arm); the slope analyses was not significantly different from zero.

1.3.3 Safety

In A2307 (1-5 years), markedly elevated transaminases were seen at the end-of-study visit in two patients. A third patient subsequently discontinued the study due to hepatitis.

In the A2302 (6-16 years) open-label population, serum creatinine increased by 10% from baseline; in the A2307 open-label population, BUN increased by 15% from baseline. There were two discontinuations from the clinical studies due renal impairment (A2307) and increased creatinine (A2302), respectively.

Two deaths during (or after premature discontinuation from) open-label were noted in A2307. No deaths occurred in A2302.

1.3.4 Dosing Regimen and Administration

Study A2302 employed unapproved tablets. A2307 used an unapproved extemporaneous suspension. According to the clinical pharmacology reviewer, exposure of the 1-5 year old children receiving the extemporaneous suspension was higher than in adults receiving

the adult 80 mg tablet; the exposure of the 6-16 year old children receiving pediatric 10 and 80 mg tablets was comparable to adults receiving the adult tablet.
The dosing regimen in the two clinical studies is summarized in Figure 1-1, below.

Figure 1-1 Study Design, Study A2302 and Study A2307

Screening	Double-blind treatment			Open-Label
Screening Phase[a]	**Phase 1[b] (dose-response)**		**Phase 2[c] (placebo withdrawal)**	**Open Label[d]**
Day -7 to Day 0	**Day 0 to Day 14 Randomized 2:1:2 (L: M: H) dose**		**Days 14 – 28 Re-randomize**	**Weeks 4 to 52**
	Study A2302 (Ages 6 - 16 years)	**Study A2307 (Ages 1 – 5 years)**	**1:1 Ratio**	Based on trough blood pressure: 40mg, 80mg , 160mg or 160 +HCTZ 12.5 mg for children 6-16 years old. 20mg, 40 mg, 80mg, and 80mg +HCTZ 12.5 mg for children 1-5 years old
	Dose	**Dose**		
	Weight < 35 kg	Weight < 18 kg		
Placebo Wash-out	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d.	Low 5 mg o.d Medium 20 mg o.d. High 40 mg o.d.	Continue Phase 1 dose OR Switch to Placebo	
	Weight ≥ 35 kg	Weight ≥ 18 kg		
	Low 20 mg o.d. Medium 80 mg o.d. High 160 mg o.d.	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d		

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