CLINICAL PHARMACOLOGY REVIEW

Division of Clinical Pharmacology I

NDA 21283 SE5-024 **Submission Dates**: May 29 and September 20, 2007
Type: Pediatric Efficacy Supplement, Priority
Brand Name: Diovan®
Generic Name: Valsartan
Dosage Strength: 40 (scored), 80, 160, 320 mg IR tablets
Sponsor: Novartis
Indication: Treatment of arterial hypertension in children in the age range of 1-16 years
Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110
Reviewer: Peter H. Hinderling, MD
Team Leader: Patrick J. Marroum, Ph.D.

1. EXECUTIVER SUMMARY

The submission contained 11 reports and 1 publication. The 11 reports reported the findings of 2 clinical efficacy studies, 4 clinical pharmacology studies and 5 assay methods. An overview of the clinical studies contained in the pediatric efficacy supplement is given in the below table:

Table 1-1 Clinical studies in the valsartan pediatric clinical development program

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan
Efficacy/safety studies in this submission			**351**	
CVAL489A2302 Pivotal study	Children 6 to 16 years of age with hypertension	Efficacy, dose response, safety, tolerability	261	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Pediatric tablet
CVAL489A2307 Supportive study	Children 1 to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	90	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Oral suspension
Clinical pharmacology studies			**106**	
CVAL489A2301-BA	Healthy volunteers 18 to 45 years of age	Bioavailability of 80 mg valsartan tablets compared to 20 mL of oral valsartan suspension (4 mg/mL)	32	Randomized, single- dose, 80 mg valsartan tablet and 20 mL oral valsartan suspension (4 mg/mL) 2-way crossover design.
CVAL489A2304	Healthy volunteers 18 to 45 years of age	Bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablet	24	Single-dose, two-period, crossover design: 40 mg valsartan tablet and 4 x 10 mg valsartan tablets
CVAL489J2308	Healthy volunteers 18 to 50 years of age	Bioavailability of 80 mg valsartan pediatric tablet (CSF) compared to 80 mg valsartan FMI	24	Single- dose, 80 mg valsartan tablet (80 mg CSF, 80 mg FMI) 2-period crossover design
CVAL489A2305	Children 1 to 16 years of age with hypertension	PK of valsartan given as an oral suspension	26	Single-dose, oral suspension 2.0 mg/kg –> 80 mg (max) valsartan dose age-dependent

a: Details of doses received in Study A2302 and Study A2307 are in Figure 1-1.

The pivotal efficacy study was performed in hypertensive children in the age between 6 and 16 years and used 10 mg and 80 mg unapproved pediatric tablets. A supporting study in hypertensive children in the age between 1 and < 6 years used an oral extemporaneous suspension. The four Clinical Pharmacology reports reported on the PK of valsartan in children in the age between 1 and 16 years who received a single oral dose of an oral suspension and the bioavailability of 3 unapproved clinical service formulations including an oral extemporaneous suspension (4 mg/mL), and pediatric 10 mg and 80 mg tablets relative to the marketed 40 mg and 80 mg tablets. The relative bioavailability studies were conducted in healthy adults. The publication reported in vitro and in vivo animal findings on valsartan as substrate for OATP1B1 and OATP1B3 and MRP2 transporters.

Salient Clinical Pharmacology Facts and Findings

Formulations

The proposed commercial formulations for the pediatric population include the adult 80 mg tablets used for making the extemporaneous suspension (4 mg/mL) and the 40, 80, 160 mg adult tablets. All strengths of the commercial adult tablets are compositionally similar. In a previous bioavailability study and multimedia in vitro dissolution tests it was shown that the 40, 80,160 and 320 mg tablets are bioequivalent**.** The 40 mg and 80 mg commercial adult tablets were the reference formulations in the relative bioavailability studies.

The unapproved extemporaneous suspension and the pediatric 10 mg and 80 mg tablets were the test formulations in the relative bioavailability studies. The pediatric 10 mg and 80 mg tablets were used in the efficacy trial in the 6- 16 year old pediatric patients. The unapproved extemporaneous suspension (4 mg/mL) was used in the efficacy trial in the 1 - < 6 year old pediatric patients and in the PK study in the 1-16 year old children.

Salient Results

Single dose PK of Valsartan in 1-16 year old children

The 1-< 6 year old children received a dose of 2 mg/kg valsartan. The dose administered to the school-age children was 1.6 mg/kg valsartan and the adolescents received a dose of 0.9 mg/kg valsartan. The valsartan formulation used was the extemporaneous suspension. The PK parameters of valsartan obtained are shown in the below tables**:**

Geometric Means of the PK Parameters of Valsartan in the Pediatric Population

PK Parameters	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
Dose, mg/kg	2.0	2.0	1.6	0.9
Cmax, ng/mL	3832	4500	4112	2835
tmax[a], h	2.00	2.00	2.00	2.00
AUC0-∞, ng●h/mL	23517	26071	18994	14988
CL/F, (L/h)	1.23	1.60	3.45	5.34
V/F, L	6.69	9.08	26.32	37.93
t1/2, h	3.77	3.92	5.30	4.92

[a] Median

Oral clearance and volume of distribution of valsartan increase with body weight and/or age. In comparing Cmax and AUC0-∞ it should be noted that the dose in mg/kg in the adolescents and school-age children was smaller (1.6 mg/kg and 0.9 mg/kg), respectively, than in the two younger age groups (2.0 mg/kg).

Dose Adjusted[a] Geometric Mean Exposure Measures in the Four Pediatric Age Groups

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
Cmax, ng/mL	3796	4536	4882	6237
AUC0-∞, ng●h/mL	23294	26333	22544	32997

[a]Adjusted to a dose of 2 mg/kg

The mean dose normalized peak exposure to valsartan tends to increase with body weight/age in the four pediatric groups. The mean dose normalized average exposure appears to be slightly greater in the adolescents than in the younger age groups, but the small number of subjects in the different age groups must be considered. These results may suggest that scaling the dose based on body weight may not result in an identical peak exposure to valsartan in the four studied age groups.

Body Weight Adjusted[a] Geometric Mean Oral Clearance and Volume of Distribution in the Four Pediatric Age Groups

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
CL/F, L/(h ● kg)	0.086	0.076	0.089	0.061
V/F, L/kg	0.465	0.432	0.678	0.429

[a] Adjusted to a unit body weight

The body weight adjusted oral clearance and volume of distribution appear to be comparable among the four age groups.

Comparison of the PK Parameters of Valsartan in Pediatric and Adult Populations

The below table shows the exposure parameters in the pediatric groups receiving the extemporaneous suspension (VAL489A 2305) and adults receiving either the marketed formulation (study VAL489A2304) or the extemporaneous suspension (VAL489A2301–BA):

Dose Adjusted[a] Geometric Mean Exposure Measures in the Pediatric Groups and Adults

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y	Adults	
Cmax, ng/mL	3796	4536	4882	6237	2572[b]	5804[c]
AUC0-∞, ng●h/mL	23294	26333	22544	32997	16791[b]	31256[c]
T1/2, h	3.8	4.0	5.3	5.0	4.6[b]	8.6[c]

[a]Adjusted to a dose of 2 mg/kg [b] 40 mg commercial tablet (study 2304) [c] Suspension (study 2301)

The results indicate that peak and average exposure in adults and adolescents receiving the extemporaneous suspension are similar and slightly greater than in the younger pediatric age groups. In contrast, the exposure in the pediatric population receiving the extemporaneous suspension exceeds clearly that of the adults administered the 80 mg adult tablet. There appears to be a difference in t1/2 for valsartan in adults. However, this is most probably the result of the 24 h blood sampling interval used in study 2304 versus the 36 h blood sampling interval used in study 2301. Blood samples in the PK study were collected only for 24 h after administration. It is more appropriate to compare the mean t1/2 value in the pediatric population with that of the adults in study 2304. It can be concluded that the exposure measures when normalized for body weight are similar in children and adults and the t1/2 estimates are also comparable.

Relative Bioavailability Studies

The bioavailability of the unapproved formulations was tested relative to the adult 40 and 80 mg commercial tablets in healthy adults. The results are shown in the below table:

Relative Bioavailability Studies: Geometric Mean Ratios and 90% Confidence Intervals

Study	Formulation	Cmax	AUC
CVAL489A2301	Extemp. Suspension	1.93 (1.60-2.33)	1.56 (1.36-1.78)
	vs. Adult 80 mg Tablet		
VAL489J2308	Pediatric 80 mg Tablet	1.06 (0.86-1.31)	1.08 (0.93-1.36)
	vs. Adult 80 mg Tablet		
VAL489A2304	Pediatric 10 mg Tablet	1.08 (0.90-1.29)	1.12 (0.97-1.31)
	vs. Adult 40 mg Tablet		

The results show that the unapproved pediatric formulations and the adult tablets are not bioequivalent. Mean Cmax and AUC with the extemporaneous suspension are 1.93 and 1.56 times greater, respectively, than with the adult 80 mg tablet. Mean Cmax and AUC with the pediatric 80 mg tablet are 1.06 and 1.08 times greater, respectively, than with the adult 80 mg tablet and mean Cmax and AUC with the pediatric 10 mg tablet are 1.08 and 1.12 times greater, respectively, than with the 40 mg adult tablet.

Comparing the Respective Exposures to Valsartan in the Clinical Trials in 1- < 6 Year Old and 6-16 Year Old Children

The results from the bioavailability studies can be used to estimate the bioavailability of formulations whose relative bioavailability was not tested directly. The computations, as shown in the below table, indicate that valsartan is significantly more bioavailable from the suspension than from the pediatric 10 mg and 80 tablets and the adult 40 mg and 80 mg tablets:

Bioavailability (90% Confidence Interval) of the Unapproved Pediatric Formulations Relative to the Marketed Adult 40 mg or 80 mg Tablet

	Suspension	**Ped. 10 mg Tablet**	**Ped. 80 mg Tablet**	**80 mg Adult Tablet**
Cmax	1.93 (1.60-2.33)	1.08 (0.90-1.29)	1.06 (0.92-1.26)	1.0
AUC	1.56 (1.36-1.78)	1.12 (0.97-1.31)	1.08 (0.86-1.31)	1.0

Bioavailability of the Pediatric 10 mg and 80 mg Tablets Relative to the Suspension

	Ped. 10 mg Tablet	**Ped. 80 mg Tablet**	**Suspension**
Cmax	0.56	0.55	1.0
AUC	0.72	0.69	1.0

The results indicate that in the clinical trials for a given dose level the exposure of the 1- < 6 year old children receiving the extemporaneous suspension is 1.82 (Cmax) and 1.44 (AUC) fold greater than in the 6-16 year old children receiving the pediatric 80 mg tablet. Similarly, the exposure of the 1 - < 6 year old children receiving the extemporaneous suspension is 1.79 (Cmax) and 1.39 (AUC) fold greater than in the 6-16 year old children receiving the pediatric 10 mg tablet.

The results of bioavailability studies also show that the exposure of the 1- < 6 year old children receiving the extemporaneous suspension in the clinical trial was 1.93 (Cmax) and 1.56 (AUC) times greater than in adults receiving the adult tablets. In contrast, the exposure of the 6-16 year

old children receiving the pediatric 10 mg and 80 mg tablets was comparable to adults receiving the adult tablets.

Therefore, when comparing the exposure of the 1 - < 6 year old children with that of the 6-16 year old children or adults the difference in bioavailability of the clinical service formulations used in the clinical trials must be considered. It should be noted that the valsartan dose in children was scaled down from the adult dose without considering the difference in bioavailability among the different formulations used in the clinical trials.

Bioavailability of the Pediatric Formulations used in the Clinical Trials Relative to the Proposed Commercial Formulations

The extemporaneous suspension used in the clinical trial in 1- < 6 year old children is proposed as commercial formulation in this age group.

The difference in bioequivalence between the pediatric 10 mg and 80 mg clinical service formulations used in the clinical trial in 6-16 year old children and the commercial adult formulations is too small to be relevant. The dose of the commercial adult tablets to be used in the 6-16 year old children does not need to be adjusted.

Labeling

Sponsored Proposed Commercial Formulations for the Pediatric Population

Children in the age between 1 and < 6 years: 4 mg/mL suspension made from adult 80 mg tablets

Children in the age between 6 and 16 years of age: 40, 80 and 160 mg adult tablets

Sponsor Proposed Dose Regimen in Children between 1 and 16 years of Age

Starting dose: 1.3 mg/kg qd (up to 40 mg total)
Dose range: 1.3-2.7 mg/kg qd (up to 40-160 mg total)

The sponsor proposed dose regimens are identical for the 1- < 6 year old and the 6-16 year old children. As pointed out earlier the sponsor did not consider the difference in relative bioavailability and resulting exposure between the extemporaneous suspension and the adult 40, 80 and 160 mg tablets. With the sponsor proposed dose regimens and formulations the exposure to valsartan in the 1- < 6 year old children would be consistently 1.82 (Cmax) and 1.44 (AUC) fold greater than in the 6-16 year old children.

The bioinequivalence of the extemporaneous suspension and the adult tablets must also be considered when the suspension is changed for a tablet when a child becomes old enough to

swallow a tablet. The dose of the tablet must be adjusted for the difference in bioavailability between the extemporaneous suspension and the adult 40, 80 or 160 mg tablets.

Impact of Difference in Bioavailability of the Formulations used in the Clinical trials and in the PK trial and the Formulations Proposed for Marketing

In order to compare the range of the doses studies in the clinical trials and the PK trial the difference in bioavailability of the respective formulations used must be considered. Therefore the respective doses were normalized for the bioavailability of the formulations used. The so corrected doses should result in comparable exposures to valsartan and are tabulated below:

Dose Range used in the Clinical Studies and Proposed for Marketing

Study	Population	Dose Range, mg/kg		
	Age range, years	Tested Formulation		Adult Tablets[a]
2302 Clin Trial	6-16	Pediatric tablets	0.4-2.7	0.4-3.0
2307 Clin Trial	1- < 6	Suspension	0.4-3.7	0.6-5.8
2305 PK Trial	12-16	Suspension	0.9	1.4
	6- < 12	Suspension	1.6	2.5
	1-< 6	Suspension	2.0	3.1
	Adults[b]	Adult tablets	1.6.-3.2	1.6-3.2
Label	6-16	Pediatric tablets	1.3-2.7	1.4-3.0
	1- < 6	Suspension	1.3-2.7	2.0-4.2

[a] Dose range of adult tablets that provides same exposure as that of the pediatric tablets or the suspension
[b] Assuming respective doses of 80 mg and 320 mg are administered to 50 kg and 100 kg individuals, respectively

The review of the Clinical Pharmacology part of the submission indicated the following deficiencies:

1. Failure to consider impact of difference in relative bioavailability among the pediatric clinical service formulations used in the clinical trials

The sponsor states that "the protocol specified doses used in clinical studies 2302 (6-16 year old children) and 2307 (1- < 6 year old children) were selected on the basis of expected blood pressure response rather than plasma concentration levels of valsartan. Adult doses were scaled down to corresponding doses for the respective pediatric population based on the body surface area of adults vs. children." In reality doses were scaled down in the basis of body weight in all

four age groups, but the exposure to valsartan in the two younger age groups was 1.8 times (Cmax) and 1.4 times (AUC) greater than in the two older age groups. The bioavailability of valsartan with the extemporaneous suspension administered to the two younger age groups is significantly greater than with the pediatric 10 and 80 mg tablets given to the two older age groups. The significantly higher exposure of the 1- < 6 years old children in the clinical trial should be considered in comparing the dose-response relationship in trials 2302 and 2307.

2. Label does not consider impact of difference in relative bioavailability between the extemporaneous suspension and the commercial adult 40, 80, 160 and 320 mg tablets

The bioavailability of valsartan with the extemporaneous suspension is about 1.9 times (Cmax) and 1.6 times (AUC) greater than with the commercial adult 80 mg tablet. Similarly, the bioavailability of valsartan with the extemporaneous suspension is about 1.8 times (Cmax) and 1.4 times (AUC) greater than with the commercial adult 40 mg tablet. Despite the significant difference in relative bioavailability between the extemporaneous suspension and the adult tablets the label recommends the same doses corrected for body weight for 1-6 year old children and 6-16 year old children.

Also, the label does not state that the dose of the adult tablets should be increased by a factor of 1.6-1.9 when in a pre-school age child the extemporaneous suspension is changed to an adult tablet.

1.1 RECOMMENDATION

From a Clinical Pharmacology viewpoint the submission is acceptable. The sponsor is advised to resolve the above identified issues.

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