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
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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 1.93 (Cmax) and 1.56 (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.

3. Failure to include in the label results from a published study showing evidence for valsartan to be a substrate of OATP and MRP2

A publication by Yamashiro et al., Drug Metab Dispos 2006;34:1247-1254, shows in vitro evidence for involvement of OATP1B1 and OATP1B3 in hepatic uptake and MRP2 in hepatic extrusion of valsartan. The authors showed further delayed elimination of valsartan using mrp2 deficient rats. The findings suggest that valsartan may be susceptible to interactions when co-administered with OATP inhibitors such as e.g. rifampicin or cyclosporine or drugs interfering with the activity of MRP2, such as e.g. ritonavir or probenecid. The label of valsartan should include the results from this study.

1.1 RECOMMENDATION

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

2. QUESTION BASED REVIEW

2. 1.1 What are the Stipulations of the Written Request?

The most recent version of the Written Request issued June 18, 2003, stipulated the following key Clinical Pharmacology and related Clinical issues:

Strategy

The requested data will provide guidance for the use of valsartan to reduce blood pressure in pediatric populations. These data will be derived from:

- Pharmacokinetic sampling in patients spanning the same age range as those studied for effectiveness
- A dose ranging trial of effectiveness in hypertensive pediatric patients; and
- Safety data derived from the controlled trial(s) and a 1-year open treatment phase following the effectiveness trial, and a summary of all available information on the safety of the drug in hypertensive pediatric patients. The safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data.

Pediatric Subgroups

Age Groups

- Infants and toddlers (age 1- < 2 y)
- Pre-school children (age 2- < 6 y)
- School age children (age 6- < Tanner stage 3 or age 12), preferred group for effectiveness study
- Adolescents (Tanner stage 3 or age 12 < 17 y)

Regarding effectiveness, studies of anti-hypertensive drugs must include ≥ 50% pre-pubertal patients as the course of disease and the effects of drugs in adolescents are not likely to differ from adults.

School Age Children

- Are usually able to swallow solid dosage forms
- Tolerate doses similar to the smallest doses approved in adults
- Are fairly often diagnosed with hypertension of no specific cause

Pre-School Age Children

For children < 6 years of age formulations issues are more important and hypertension is attributed to renal disease or other specific causes

Racial Groups

Because of antihypertensive response differences in black and non-black adults, 40-60 % black patients should be enrolled

Formulation Issues

Formulations must be well characterized and appropriate to age and clinical setting. Any unapproved formulation will need to be supported by a study of the relative bioavailability of valsartan. These studies can be performed in adults. If a potentially marketable formulation cannot be developed the sponsor must document an attempt to do so and will need to obtain an agreement with Agency regarding the adequacy of the formulation to be used. Full study reports of any relative bioavailability studies must be submitted to the Agency.

Pharmacokinetic Trials

Pharmacokinetic data must be obtained over the range of doses studied for effectiveness. Patients should have a grossly normal metabolic function. Traditional or sparse sampling methods to determine PK parameters can be used.

Data must be collected for valsartan and any metabolites that make substantial contributions to its efficacy and /or toxicity. For parent drug and each metabolite AUC, t1/2, CL/F, V/F, Cmax and tmax in all pediatric groups investigated should be provided.

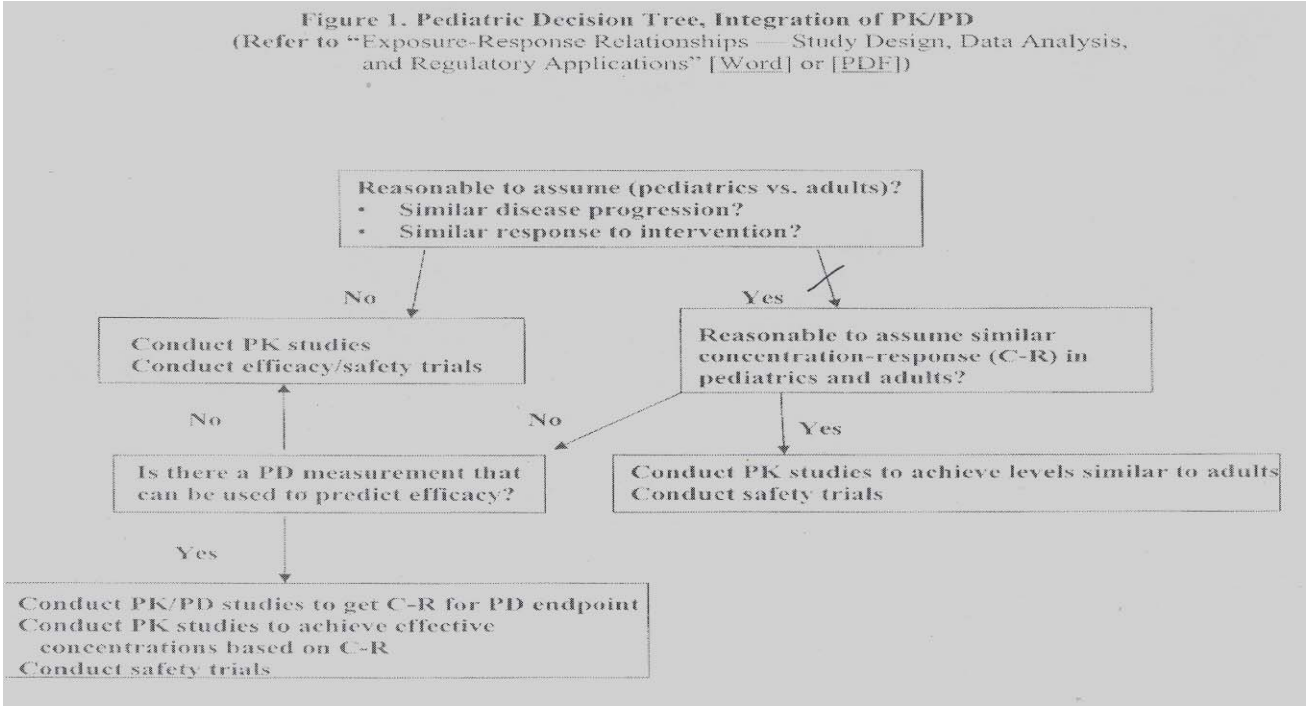
Labeling Changes

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Reporting

Full study reports of the requested trials, including full analysis, assessment, and interpretation, must be submitted in the usual format. The submission must include electronic datasets for all clinical and pharmacokinetic trial data for these studies, submitted according to available guidance.

2.1.2 What is the rationale for the studies requested by the written request?



Hypertension in children may have different causes than in adults. Secondary hypertension is more frequent in < 10 year old children than in adults in whom essential hypertension is the most frequent type of hypertension. A number of past studies with antihypertensive agents have shown that the efficacy of antihypertensive agents in children may be smaller than in adults. Therefore, similar disease progression and response to intervention cannot be assumed. Blood pressure is a PD predictor (surrogate) for cardiovascular events and mortality.
In adults a relation between drug action and plasma concentration does not exist for valsartan. There may also be age/body weight related differences of the pharmacokinetics between pediatric and adult

populations. The clinical trials performed by the sponsor used unapproved clinical service formulations (suspension, 10 and 80 mg tablets) of unknown bioavailability. The requested clinical safety and efficacy studies, the PK study in the pediatric population and the relative bioavailability studies in adults are justified.

2.1.3 Is the submitted clinical pharmacology information in compliance with the Written Request (WR)?

Comparability of age and race of children enrolled in the PK trial and in the effectiveness studies.

The pharmacokinetic samples were collected in children of the same age range as those studied for effectiveness. The PK study in children enrolled infants and toddlers (n=6), pre-school children (n=6), school age children (n=7) and adolescents (n=7). The WR did not define the number of subjects in the different age groups to be enrolled in the PK study, and the number of enrolled subjects is acceptable. More than 50% pre-pubertal patients were enrolled in the PK trial. Thirty one (31) % of the children were black, a slightly smaller percentage than the 40-60% black children recommended by the WR to be enrolled in the clinical trial.

Adequacy of formulations tested

An extemporaneous suspension formulation (4 mg/mL) was used in the clinical trial with pre-school children and pediatric 10 mg and 80 mg tablets were used in the clinical trial with school children and adolescents. The relative bioavailability of all three unapproved formulations was tested relative to the marketed adult 40 mg or 80 mg tablet in healthy adult subjects.

Doses used in the PK trial

A single dose study with the suspension and an extensive sampling schedule was used in hypertensive children in the age between 1 and 16 years. The mean doses of valsartan administered in infants/ toddlers, pre-school children, school age children and adolescents were 30.5 mg, 40.7 mg, 68.4 mg and 80 mg, respectively. When normalized for body weight these values become 2.0 mg/kg, 2.0 mg/kg, 1.6 mg/kg and 0.9 mg/kg, respectively. The individual doses ranged between 30.0 mg to 80.0 mg and when normalized for weight ranged between 0.71 mg/kg to 2.07 mg/kg.

Doses used in the clinical trials and resulting exposure

The three mean dose levels (body weight adjusted) used in clinical trial 2302 in patients 6-16 years of age are 0.4 mg/kg, 1.3 mg/kg and 2.7 mg/kg. The three mean dose levels (body weight adjusted) administered in clinical trial 2307 in patients 1- < 6 years of age are 0.4 mg/kg, 1.6 mg/kg and 3.4 mg/kg indicating a greater range of exposure of the two younger age groups compared to the two older age groups. The true exposure to valsartan in infants/ toddlers and pre-school children was by an additional factor of about 1.81 (Cmax) and 1.42 (AUC) greater in the younger children than in the older ones.

Comparison of doses and resulting exposures in the clinical trials and in the PK trial

The mean doses normalized for body weight in the single dose PK trial in the 1- < 6 year old children is 2.0 mg/kg. The corresponding figure in school children and adolescents is 1.6 mg/kg and 0.9 mg/kg, respectively. The mean doses normalized for body weight tested in the clinical trial in 1- < 6 year old children range between 0.4 mg/kg and 3.4 mg/kg. The mean doses normalized for body weight in 6-16

year old children range between 0.4 mg/kg and 2.7 mg/kg. With the exception of the adolescents the mean dose normalized for body weight used in the PK trial were in the middle of the dose range used in the clinical trial. In the adolescents the mean dose normalized for body weight in the PK trial was in the lower part of the dose range used in the clinical trial. A comparison of the exposures in the clinical and PK trials based on doses normalized for body weight is only appropriate for the children in the age between 1- < 6 years, because they received the same formulation, the suspension, in both the PK and clinical trial. However, it should be noted that the exposure in the PK trial was by factors of 1.81 (Cmax) and 1.42 (AUC) greater than predicted form the mean body weight normalized doses. Thus, the mean exposure to valsartan in the 6-16 year old children in the PK trial was in the upper part of the range of exposures attained in the clinical trial.

Comparison of doses and resulting exposures in children and adults

The minimum and maximum recommended doses of valsartan for the treatment of hypertension in adults are 80 mg and 320 mg qd, respectively. The bodyweight of most hypertensive adults ranges between 50 kg to 100 kg. A 50 kg weighing subject could receive a low dose of 80 mg valsartan and a subject weighing 100 kg could receive a high dose of 320 mg valsartan daily.

The body weight normalized doses for the two adult subjects are 1.6 mg/kg and 3.2 mg/kg, respectively. The dose range tested with the 1-< 6 year children (0.4 mg/kg-3.4 mg/kg) is clearly larger than with the adults as recommended by the WR. Considering the difference in bioavailability between extemporaneous suspension and commercial adult tablets the de facto tested dose range in the 1-< 6 year old children is by a factor of 1.4 greater (0.6- 4.8 mg/kg) than the nominal dose range. The dose range tested with the children 6-16 years of age is (0.4-2.7 mg/kg) starts and ends with a lower value than the adult dose range.

Linearity of PK and PK Parameters

The PK of valsartan have been shown to be dose proportionate and there is no overt evidence challenging this notion in children. In accordance with the WR AUC, t1/2, CL/F, V/F, Cmax and tmax were determined in the children of the 4 age groups. The submission discusses the PK results obtained in the children with those in adults.

Measurement of Active Compounds

Only the parent drug, valsartan, was measured in plasma. The absolute bioavailability of valsartan is about 25 % in adults. About 20% of valsartan is metabolized in adults and the remainder is excreted unchanged in the bile. Valsartan is the major circulating compound in adults. The activity of the metabolites has not been determined. It is reasonable to assume that the extent of metabolism in the 2-16 year old children tested is similar to that in adults.

Reporting

Full study reports were submitted for all PK studies.

The below table summarizes the findings regarding compliance with the Written Request;

Clinical Pharmacology Stipulations of Written Request

Requested	Compliance
PK in patients of same age range as studied for efficacy	√
Infants/toddlers, pre-school, school-age, adolescents	√
40-60% blacks	
>50% pre-pubertal	√
Ped. formulations appropriate for age and characterized	√
PK data over clinical dose range	√
Adult blood levels attained in clinical trials	√
Traditional or sparse sampling	√
Valsartan & active metabolites: AUC, Cmax, tmax, CL/f, V/F	√
Reporting in full study reports	√

2.2 What are the general attributes of the drug in adults

The initial approval for valsartan in the US was in 1996**.** Currently, valsartan in adults is approved for:

- Treatment of hypertension
- Treatment of heart failure (NYHA Class II-IV). Valsartan significantly reduced hospitalization for heart failure
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction

The starting dose in hypertensive adults is 80 mg or 160 mg once daily and the recommended dose range is 80-320 mg once daily.

2.3 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Valsartan is a hydrophilic anionic compound with a log D value of - 0.34.

The marketed drug products in adults are 40 mg (scored), 80 mg,160 mg and 320 mg tablets. The tested pediatric formulations include the pediatric extemporaneous suspension of 4 mg/mL, and pediatric 10 mg and 80 mg tablets.

2.4 What are the proposed mechanism(s)?

Valsartan is an angiotensin II receptor blocker (ARB). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects on vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal re-absorption of sodium.

2.5 General clinical pharmacology

2.5.1 What are the pharmacokinetic characteristics of valsartan in adults?

Peak plasma concentrations of valsartan are reached 2 h to 4 h after administration. After intravenous administration valsartan shows a biexponential decay with an apparent terminal half life of 6 h. Absolute bioavailability of valsartan is about 25%. Food decrease exposure to valsartan by about 40% (AUC) and 50% (Cmax). AUC and Cmax of valsartan increase approximately linearly with increasing dose over the clinical range. The plasma protein binding of valsartan is 95% and the steady-state volume of distribution is 17 L after intravenous administration. Valsartan does not accumulate appreciably in plasma following repeated administration.

Valsartan administered as oral solution is recovered by about 83% and 13% of the dose in feces and in urine, respectively. The recovery is mainly as valsartan, with only about 20% of the dose recovered as metabolites. The primary metabolite accounting for about 9% of the dose is valeryl 4-hydroxy valsartan. The activity of the metabolites is not known. The enzymes responsible for the metabolism of valsartan have not been identified, but do not seem to be CYP 450 isozymes. Total and renal clearances of valsartan are about 33 mL/min and 10 mL/min, respectively.

Special Populations

Elderly

In the elderly exposure to valsartan is increased by 70% and the half-life is 35% longer compared to young subjects.

Sex

The pharmacokinetics of valsartan do not differ significantly between males and females.

Renal Impairment

There is no apparent correlation between creatinine clearance and AUC for valsartan in patients with mild and moderate renal impairment and dose adjustment is not necessary. The impact of severe renal impairment (CLcr <10 mL/min) on the exposure to valsartan has not been investigated and care should be exercised with dosing in these patients. Hemodialysis does not remove valsartan from plasma.

Hepatic Impairment

The exposure (AUC) to valsartan in patients with mild to moderate chronic liver disease, including patients with biliary obstructive disorders, is increased by 100%. Care should be exercised in dosing of patients with liver disease.

Heart Failure

The oral clearance of valsartan in patients with heart failure is 75 mL/min. Valsartan in patients with heart failure accumulates by a factor of 1.7, whereas valsartan in patients without heart failure does not accumulate. Time to peak concentration and half- life in patients with heart failure and healthy subjects appear to be similar.

Drug Interactions

PK

No clinically significant pharmacokinetic drug interactions were observed when Diovan (valsartan) was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. Co-administration of valsartan and warfarin did not change the pharmacokinetics or time course of the anticoagulant properties of warfarin.

The enzymes responsible for valsartan metabolism have not been identified, but CYP 450 enzymes appear not to be involved. The inhibition or induction potential of valsartan is not known either.

PD

The valsartan-atenolol combination is more antihypertensive than either component, but it does not lower heart rate more than atenolol alone.

As with other drugs that block angiotensin or its effects, concomitant use of potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride) potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

2.5.2 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

See table below:

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.

2.5.3 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics PD) and how are they measured in clinical pharmacology and clinical studies?

Blood pressure is an established surrogate endpoint. Hypertension is associated with an increased risk for myocardial infarction, stroke and mortality in adults. It is reasonable to assume that hypertension in children is associated with the same increased risk.

2.5.4 Are the active moieties in the plasma (or other biological fluids) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Valsartan is the principal active circulating moiety in adults. It is reasonable to assume that the same is true for children.

2.5.5 Exposure-response

2.5.6. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy in children? What is time of onset and offset of the desirable pharmacological response or clinical endpoint in children?

The hypotensive effect of valsartan increases with increasing dose in adults and in children. After single dose administration of valsartan the time of onset of the hypotensive effect of valsartan is 2 h after dosing. The peak effect occurs at about 6 h after administration and the hypotensive effect lasts for 24 h. With increasing dose the difference between peak and trough effect becomes smaller. After repeated doses given qd a substantial effect on blood pressure is present within 2 weeks of initiation of treatment and a maximum reduction is achieved after 4 weeks. The offset kinetics of the hypotensive effect after multiple dose administration in adults has not been determined. In adults the hypotensive effect of valsartan does not correlate with the plasma concentrations of the drug. The onset and offset of the hypotensive effect of valsartan in the pediatric population is also unknown.

2.5.7 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety?*

The hypotensive effect of valsartan increases with dose. The risk for orthostatic hypotension is small with valsartan, and could increase with increasing dose in adults and children. There was no clear dose dependency of orthostatic hypotension in the tested children. The risk for hyperkalemia is also expected to increase with dose. There was only one case of hyperkalemia in the tested pediatric population.

2.5.8 Does the drug prolong the QT/QTc interval?

The impact of valsartan on the QT/QTc intervals has not been determined in adults or children

2.5.9 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issue

The dose and dose regimens selected by the sponsor are consistent with the dose-efficacy relationship in children. A direct relationship between plasma concentration and efficacy does not appear to exist in adults. The relationship between plasma concentrations and hypotensive effect of valsaratan has not been investigated in children.

2.5.10 What are the PK Characteristics of the drug and its major metabolites?

2.5.10.1 What are the single and multiple dose PK parameters in children and how do they compare to those in adults?

The single and multiple dose pharmacokinetics of valsartan have been determined in adults. In children only single dose PK have been determined. The salient features of the PK of valsartan in children are**:**

Arithmetic Means (SD) of the Uncorrected PK Parameters of Valsartan in the Pediatric Population

PK Parameters	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**
Cmax, ng/mL	4307 (43)	4818 (39)	4254 (27)	3069 (41)
tmax, h	2.00	2.00	2.00	2.00
AUC0-∞, ng●h/mL	25823 (43)	26800 (26)	20214 (36)	15944 (35)
CL/F, (L/h)	1.50 (67)	1.63 (21)	3.80 (43)	5.75 (45)
t1/2, h	3.79 (10)	3.95 (13)	5.33 (12)	4.97 (15)

The results indicate that the oral clearance of valsartan increases with body weight and/or age. The half life shows also a weak trend to increase with body weight and/or age. In comparing Cmax and AUC0-∞ it should be noted that the dose in mg/kg in the oldest children was considerably smaller (0.9 mg/kg) than in the other 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 results indicate the body weight normalized exposure is largest in the oldest age groups.

Body Weight Adjusted Mean Oral Clearance 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)	0.097	0.078	0.098	0.076

The results indicate that the body weight adjusted oral clearance among the four age groups is comparable.

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] Study 2304 [c] 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 sample collection interval in study 2304 versus the 36 h blood sampling interval used in study 2301. Since in the PK study blood samples were collected only for 24 h after administration it is more appropriate to compare the t1/2 values 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 adult and the t1/2 estimates are also comparable.

2.5.10.2 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In adults the PK of valsartan are approximately dose proportionate.

2.5.10.3 How do the PK parameters change with time?

A possible impact of time on the PK of valsartan has not been examined in adults.

2.5.10.4 How do the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The label of valsartan does not indicate whether the PK of the drug in healthy adults and in hypertensive adults are different, but it is probable that the PK in the two populations when matched for age, and body weight are similar. In the pediatric population the pharmacokinetics of valsartan were only investigated in children with hypertension. The existence of active metabolites is unknown.

2.5.10.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject Variation (CV, %) of the Unapproved and Approved Valsartan Formulations in Adults

Formulation	Adult 80 mg		Adult 40 mg	Ext. Suspension	Ped. 10 mg	Ped. 80 mg
Cmax	54.4	30.1	27.6	37.5	36.4	50.3
AUC	42.9	32.4	32.4	39.4	39.6	48.1

In the bioavailability studies submitted in the present submission the inter-subject variation in Cmax and AUC of the unapproved pediatric formulation tested in healthy adults ranges between 28% -54% and 32% and 48%, respectively. In hypertensive children in the age between 1 and 16 years the inter-subject variation of Cmax and AUC with the unapproved extemporaneous suspension ranges between 27-43% and 26-43%, respectively. In healthy adults the inter-subject variation of Cmax and AUC is 38% and 39%, respectively. It can be concluded that the inter-subject variation of the unapproved pediatric

formulations in healthy adults is comparable as is the inter-subject variation of the extemporaneous formulation in healthy adults and hypertensive children.

The labeling does not indicate the inter- and intra-subject variation of the PK parameters for valsartan in adults.

2.6. Intrinsic factors

2.6.1 What intrinsic factors (age, gender, race, disease, genetic polymorphism, pregnancy, organ dysfunction influence exposure?

At comparable doses elderly patients experience greater plasma levels than younger subjects (AUC is increased by a factor of 1.7 and t1/2 by a factor 1.4). In adults mild and moderate hepatic impairment increase the plasma levels by a factor of 2.0. The exposure to valsartan in adult patients with mild and moderate renal impairment is not relevantly increased. The impact of severe renal impairment (CLcr < 10 mL/min) has not been studied. It appears that subjects with CLcr in the range between 11-29 mL/min have not been studied either. Age, gender and race have no effect on the hypotensive effect of valsartan. In adults the hypotensive effect of valsartan is not different between black and white adults.

2.6.2 What pharmacogenetic information is there in the application and is it important or not?

No pharmacogenetic information is provided in adults or children for valsartan.

2.6.3 What is known about drug-drug interactions

No PK based interactions were found when valsartan was co-administered together with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin in adults.

No interaction studies were performed in children.

2.6.4. Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. The results of a published study suggest that the anionic hydrophilic valsartan is a substrate of the OATP and MRP2. Rifampicin and cyclosporine A, known inhibitors of OATP, if co-administered with valsartan, could result in a PK based drug- interaction.

2.7 Extrinsic Factors

2.7.1 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

The enzymes responsible for the metabolism of valsartan have not been identified, but it seems that CYP 450 enzymes are not involved. It is unknown whether the metabolism of valsartan is influenced by pharmacogenetics/genomics.

2.7.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The status of valsartan as an inhibitor or inducer in vitro or in vivo has not been determined.

2.7.3. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

It is not known whether valsartan is a substrate or inhibitor of P-glycoprotein.

2.7.4 Are there other metabolic/transporter pathways that may be important?

Valsartan is a hydrophilic anionic compound. In vitro data suggest that valsartan may be a substrate of the hepatic uptake transporter OATP and the efflux transporter MRP2.

2.7.5 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

2.7.6 What other co-medications are likely to be administered to the target population?

Other antihypertensives, diuretics, hypocholesterinemic drugs.

2.7.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.7.8 Is there a known mechanistic basis for pharmacodynamic dug-drug interactions, if any?

Co-administration of other antihypertensive agents may result in orthostatic hypotension. Co-administration of potassium sparing diuretics, aldosterone antagonists,ACE-inhibitors or potassium containing salts may result in hyperkalemia.

2.7.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Enzymes involved in metabolism of valsartan and activity of main metabolite have not been determined.

2.7.10 What issues related to dose, dose regimens, or administration are unresolved and represent significant omissions?

None (?)

2.8 General biopharmaceutics

This section should summarize the salient points about the attributes of the drug product

2.8.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The BCS classification of valsartan has not been determined. The extemporaneous suspension made form the commercial adult 80 mg tablet is the only new formulation.

2.8.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Two clinical trials were performed: In the first trial 6-16 year old hypertensive children were enrolled. They received the unapproved pediatric 10 mg and 80 mg tablets. In the second trial 1-< 6 year old children were enrolled and were administered the unapproved 4 mg/mL extemporaneous suspension. The bioavailability of the suspension relative to the unapproved pediatric 10 mg and 80 mg tablets is 1.8 times (Cmax) and 1.4 times (AUC) greater. The bioavailability of the suspension relative to the commercial adult 40 mg and 80 mg tablets is 1.9 times greater (Cmax) and 1.6 (AUC) times greater.

2.8.3 What data support or do not support a waiver of in vivo BE data?

- ***BCS classification system***
- ***Formulation ingredient information***
- ***Dissolution profiles***
- ***Others***

NA

2.8.4 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

The 1- < 6 year old children received the same mg/kg doses as the older children, but as a result of the increased bioavailability of the suspension relative to the unapproved and approved solid dosage formulations the exposure of the 1- < 6 year old children in the clinical trial was significantly greater than that of the 6-16 year old children or adults.

2.8.5 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to be marketed product?

There was no overt evidence for a safety issue of valsartan in the younger and older pediatric age groups. It is critical that the dose be adjusted in accordance with the difference in bioavailability if the suspension is changed to a solid dosage form in a pre-school child old enough to swallow a tablet.

2.8.6 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food decreases Cmax and AUC by about 40% and 50%, respectively, in adults receiving the tablet. It is not known whether food interacts with the drug substance or the drug product. The impact of food was not investigated in children receiving the suspension. An interaction of food with the suspension cannot be excluded.

2.8.5When would a fed BE study be appropriate and was one conducted

NA

2.8.6 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

NA

2.8.7 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to be marketed product?

NA

2.8.8 If the NDA is for a modified release formulation of an approved immediate release product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

NA

2.8.9 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

NA

2.8.10 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None

2.9 Analytical section

This section should address issues related to the analytical and bioanalytical methods used to support the clinical pharmacology and biopharmaceutics studies

2.9.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Valsartan has been shown to be the main active circulating compound in adults. It is reasonable to assume that the same is true for children.

2.9.2 Which metabolites have been selected for analysis and why?

Metabolites of valsartan have not been measured in children. About 20 % of the dose is recovered as metabolites in adults with 9% of the dose as valeryl 4-hydroxy valsartan.

2.9.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (bound + unbound) concentrations of valsartan in plasma were measured in adults and in children. The plasma protein binding of valsartan has been shown to be linear within the therapeutic range in adults. It is reasonable to assume that the same is true for children.

2.9.4 ***What bioanalytical methods are used to assess concentrations?***

2.9.4.1 What is the range of the standard curve?

See below table:

Study	Assay	Calibration Curve		LLOQ	Accuracy Range %	Precision %
		ng/mL	R	ng /mL	interday	interday
CVAL489A2301	HPLC-	50-5000	≥ 0.9992			
VAL489J2308	HPLC-MS/MS	2-10000	≥ 0.9996			
VAL489A2304	HPLCMS/MS	2-5000	≥ 0.9969			
VAL489A2305	HPLC-MS/MS	2-5000	≥ 0.9962			

How does it relate to the requirements for clinical studies?

The range measured represents the range of valsartan concentrations attained under clinical conditions

What curve fitting techniques are used?

Linear functions are fitted to the calibration standard data with the HPLC- detection assay and the HPLC-MS/MS assays. The data are weighted by 1/Y or 1/ Y^2.

2.9.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See above table.

2.9.4.3 What are the accuracy, precision, and selectivity at these limits?

See above table.

2.9.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample handling, sample transport, autosampler)?

Valsartan in plasma is stable when kept for 72 h at room temperature. Valsartan is also stable when stored for 4 weeks at -20 ° C and when exposed to a single freeze-thaw cycle.

2.9.4.5 What is the QC sample plan?

QC samples were measured along with the samples with unknown plasma concentrations of valsartan.

3. LABELING RECOMMENDATIONS

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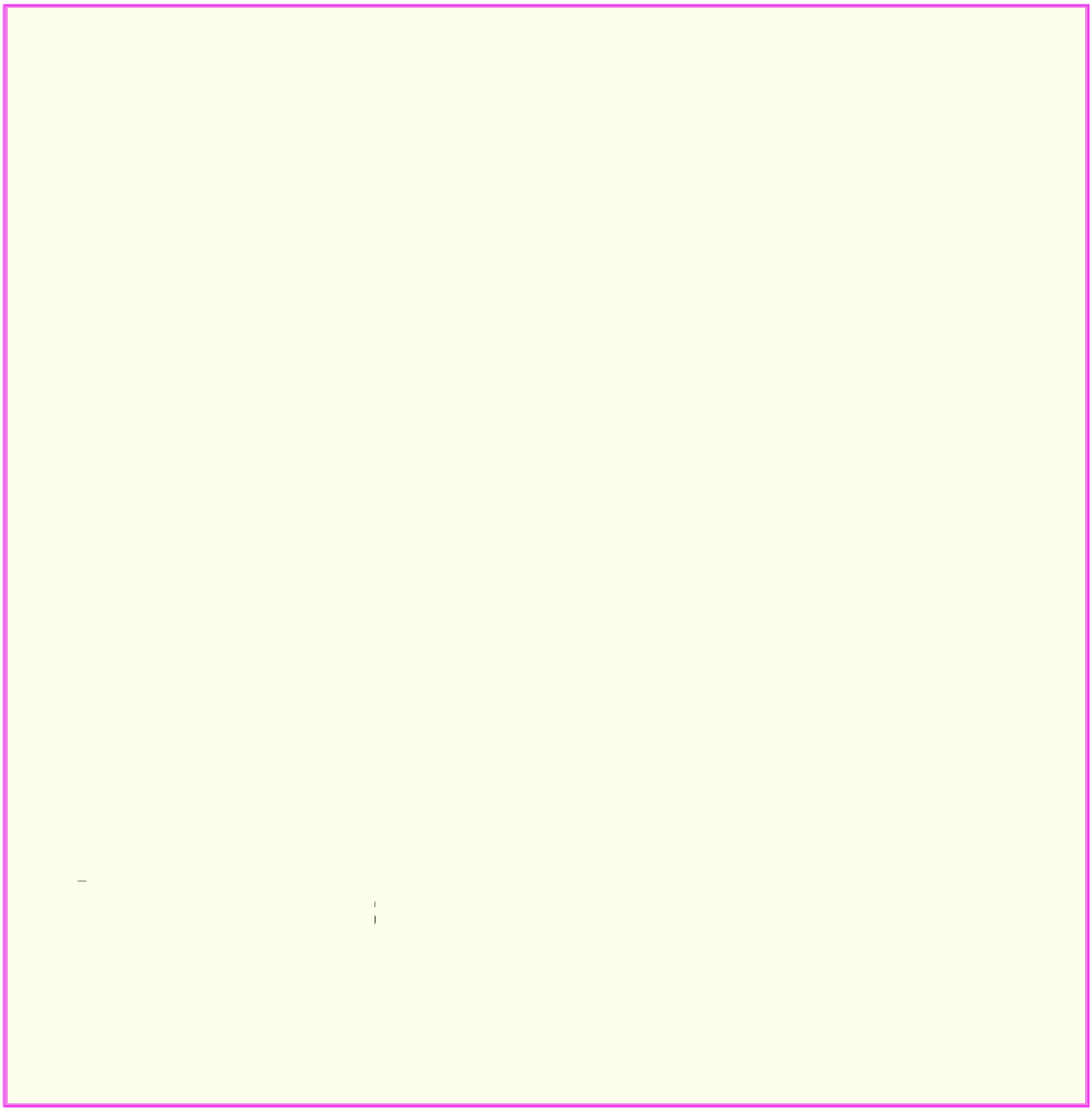


4. INDIVIDUAL STUDY REPORTS

4.1 Study Report: CVAL489A2301-BA " A Randomized, Open-Label, Crossover Study Comparing the Relative Bioavailability of 20 mL of 4 mg/mL Valsartan Oral Suspension and one 80 mg Valsartan Tablet "

Study Site and Investigator

Objectives

The primary objective of this study was to assess the relative bioavailability of 20 mL of 4 mg/mL valsartan extemporaneous oral suspension and one 80 mg valsartan tablet in healthy volunteers

Investigational Drugs/Formulations

Valsartan extemporaneous oral suspension: 20 mL (4 mg/mL) prepared from 80 mg tablets (Lot No.: 01-368US) (Test treatment), Ora Plus suspending vehicle, manufactured by Paddock Laboratories, Inc. Lot No.: 172930, Ora Sweet SF sweetening vehicle, manufactured by Paddock Laboratories, Inc. (Lot No.:132736)

Valsartan 80 mg tablets, manufactured by Novartis Pharmaceutical Corporation, Lot No.: 01-368US (reference treatment)

The pharmacist at the study site prepared the 4 mg/mL valsartan extemporaneous suspension using 80 mg tablets from the bulk supply, according to the instructions given by the sponsor.

Design

The study used a randomized, open-label, two-period, crossover design. A total of 32 male and non-fecund female subjects in the age range 18-45 years and in good health, as determined by past medical history, physical examination, vital signs, ECG, and laboratory test at screening, were to be enrolled in the study. A seven day inter-dose wash-out period was maintained. The subjects were admitted to the study center on the eve of the dosing day and discharged from the unit 36 h after dosing. The subjects fasted 10 h prior to dosing. Study medication was administered together with 180 mL water.

A scheme of the scheduled study activities is shown below:

Table 3.5-1 Evaluation and visit schedule

Study Phase	Screening Day -21 to -1	Period 1 Check-in Day -1	Period 1 Day 0	Washout Days 0-6	Period 2 Check-in Day 6	Period 2 Day 7	End of Study Day 8
Visit number	1	2	3		4	5	6
Evaluation							
Inclusion/Exclusion Criteria	X						
Relevant Medical History Current Medical Conditions	X						
Intervisit Medical History		X					
Demography	X						
Physical Examination	X						X
Hepatitis and HIV Screen	X						
Urine Alcohol & Drug Screen Urine Cotinine	X	X			X		
Pregnancy Test (females only)	X	X			X		X
Drug Administration Record			X			X	
Meal Record			X			X	
Study Completion Information							X
Comments	*	*	*	*	*	*	*
Body Height	X						
Body Weight	X						
Body Temperature	X	X					
Blood Pressure, Pulse Pulse rate	X	X			X		X

Table 3.5-1 Evaluation and visit schedule (continued)

ECG Evaluation	X						
Hematology & Blood Chemistry Urinalysis	X						X
Adverse Events			X	X	X	X	X
Concomitant Meds/Therapies	X	X			X		X
PK Blood Collection			X			X	

* Comments as applicable

Safety and Tolerability

Safety and tolerability were assessed by physical examination, vital signs monitoring, ECGs, safety laboratory evaluations (hematology, serum chemistry, urinalysis) and adverse event recording.

Pharmacokinetic Profiling

Blood samples for the determination of the plasma concentrations of valsartan were collected at the following times: pre-dose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24 and 36 h after administration.

Bioassay

Valsartan plasma concentrations were measured by a HPLC method with detection that used an internal standard. Calibration curves were generated using 1/y weighted linear least squares regression and were presented as plots of the peak area ratios of valsartan to the internal standard versus the concentrations of the calibration standards. The concentration range of the calibration standards was 50-5000 ng/mL. QC samples with concentrations of 50, 100, 300, 1000 and 5000 ng/mL were used. Inter-day and intra-day accuracy and precision was determined using the QC samples that were analyzed in replicate on each of three analysis days. Sample stability was studied by analyzing duplicate sample aliquots of 50, 1000 and 5000 ng/mL immediately after preparation and then again after 6, 24, 48, and 72 h with the samples kept at room temperature and analyzing duplicate aliquots at time intervals of 7, 14 and 30 days after being frozen at -20°. After storage the samples were thawed and brought to room temperature before analysis. A freeze-thaw study was conducted with duplicate samples at each concentration. The samples that had been frozen for 30 days, were thawed and refrozen for three consecutive days, and then analyzed on the third day.

The correlation coefficient of the calibration curve fits were ≥ 0.9992. The inter-day accuracy of the QC samples ranged between -11.7% and 5.7%. The inter-day precision of the QC samples was ≤ 14.9%. The intra-day accuracy of the QC samples ranged between -11.8% and 14.9% and the intraday precision was ≤ 16.0%. Valsartan was stable in plasma kept at room temperature for 72 h, after storage for 4 weeks at -20° C and after going through a freeze-thaw cycle.
The assay was performed in the laboratories of the sponsor.

PK Data Analysis

The following PK parameters were estimated using non-compartmental methods: AUC0-tlast, AUC0-inf, Cmax, Tmax, Kel, t1/2. The AUC0-tlast was obtained by linear trapezoidal summation.

Statistical Methods

The PK parameters AUC0-tlast, AUC0-inf and Cmax of the test and reference treatments were compared using ANOVA based on the log transformed values. The analysis model contained sequence, formulation, and period as fixed factors and subject (nested in sequence) as random factor. The ratio of treatment means on the original scale was estimated, along with its 90% confidence interval, by the antilog of the difference in least square means on the log scale.

Sample Size

The sample size was calculated based on the criterion that, for an estimated ratio of formulation means (suspension versus tablet) for PK parameters AUC and Cmax there was at least an 80% probability that the 90% confidence interval was within 80%-125% of the true ratio value. In the calculation it was assumed that the true value of mean ratio was between 1 and 1.2, and the PK parameter coefficient of variation (CV) was 0.27 (source CVAL489 Studies 0603 and 0604 which suggested that the CVs for AUC and Cmax were 0.22 and 0.27, respectively).

Results

Thirty two (32) male subjects were enrolled in the study. Thirty (30) subjects completed both treatments. Subject 5110 only received Treatment A (oral suspension) and subject 5130 only received Treatment B (80 mg tablet). Subject 5110 had a positive drug screen at Period 2 check-in, and subject 5130 withdrew consent after the Period 1 dose. The 30 subjects who completed both treatments were included in the PK analysis. All 32 subjects were included in the safety evaluation.

The demographic of the subjects is shown in the table below:

Table 7.4-1 Demographics

Race (N)	
Black	17
Caucasian	9
Other	6
Age (years)	
Mean ± SD	33.8 ± 6.8
Range	21–45
Gender	
Male	32
Weight (kg)	
Mean ± SD	79.7 ± 10.2
Range	54.7–101.3
Height (cm)	
Mean ± SD	178.8 ± 6.1
Range	169–191

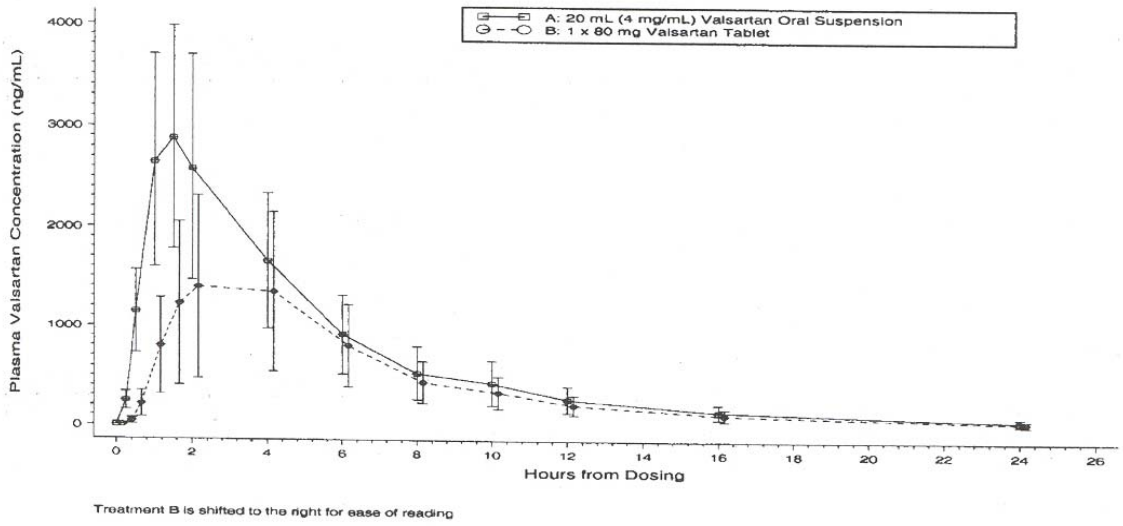
Tolerability

Two treatment emergent adverse events occurred in 2 subjects after administration of the valsartan oral suspension. One headache was moderate and occurred 1 h post-dose and was considered drug related by the investigator. The other headache was mild, occurred 15 h after drug administration and was considered unrelated to drug intake by the investigator. No serious adverse events or death occurred.

Pharmacokinetics

Plots of the mean plasma concentrations of valsartan after administration of the 20 mL (4mg/mL) oral suspension and 80 mg tablet are shown in the figure below:

Figure 8.1.3.1-1 Mean Plasma Valsartan Concentrations Versus Time



The plots indicate that the rate and extent of release of valsartan from the suspension is significantly greater than from the tablet.

The results of the arithmetic means, the geometric mean ratios and the 90% confidence intervals for the ratios of the treatments for Cmax, Tmax, AUC0-tlast, AUC0-inf, T1/2 and Kel listed in the table below confirm the visual impression from the plots:

Summary of the Pharmacokinetic Parameters of Plasma Valsartan for Treatments A and B

	--------- Plasma Valsartan ---------						
	Treatment A		Treatment B				
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	% Geometric Mean Ratio	p value	90% CI for True Ratio(A/B)
Cmax(ng/mL)	3128.0	1172.8	1764.3	960.07	192.8	0.0001	159.9- 232.5
Tmax(hr)	1.57	0.586	2.72	1.37	.	.	. - .
AUC(0-t)(ng*hr/mL)	16129	6287.3	10769	4933.8	158.0	0.0001	137.1- 182.2
AUC(0-inf)(ng*hr/mL)	16771	6605.1	11627	4985.3	155.7	0.0001	136.3- 178.0
T1/2(hr)	8.56	2.50	9.23	2.40	.	.	. - .
Kel(1/hr)	0.0865	0.0223	0.0805	0.0231	.	.	. - .

Treatment A = 20 mL (4 mg/mL) Valsartan Oral Suspension: test
Treatment B = 1 x 80 mg Valsartan Tablet: reference

Conclusions

The valsartan 20 mL (4mg/mL) oral suspension and 80 mg tablet are not bioequivalent. Cmax and AUC0-inf with the oral suspension is 1.93 and 1.56 times greater, respectively, than with the 80 mg tablet. Both treatments were tolerated well.

Comments

None

4.2 Study Report: VAL489J 2308 "An Open-Label, Single Dose, Two Period, Randomized Crossover Study to Determine the Relative Bioavailability of 80 mg Valsartan Pediatric Tablet (CSF) as Compared to a 80 mg Valsartan Marketed Tablet in Healthy Subjects"

Study Site and Investigator:

Objectives

The primary objective of this study was to determine the relative bioavailability of an 80 mg valsartan pediatric tablet (clinical service form, CSF) compared to an 80 mg valsartan marketed tablet final market image (FMI) in healthy subjects.

Investigational Drugs/Formulations

Valsartan pediatric (VAKL489A) 80 mg oral tablets (CSF), Lot No.:04-0110US, bulk number: AEUS/2004-0044

Valsartan marketed (VAL489A) 80 mg oral tablets (FMI), Lot No.:131J4422

Design

This study employed an open label, randomized, single dose, 2-period, crossover design. Twenty four subjects were randomly assigned to receive 1 of 2 treatments sequences. All subjects received a single 80 mg oral dose of valsartan pediatric tablet (CSF) (Treatment A) and a single 80 mg oral dose of valsartan marketed tablet (FMI) (Treatment B) under fasted conditions either as Treatment A followed by Treatment B or Treatment B followed by Treatment A during Periods 1 and 2. A seven day wash-out period was maintained between the Treatment periods.

Healthy male or female subjects in the age range between 18 and 45 years of age were eligible to participate in the study. Their good health was ascertained by medical history, physical examination, vital signs, ECG, and laboratory tests. Female subjects must not have been pregnant and must have been surgically sterilized at least 6 month before screening, using a double-barrier method of contraception, or be postmenopausal (defined as the absence of menstrual bleeding for 2 years before inclusion and confirmed by laboratory testing). Pregnancy tests were required of all women.
Participating subjects were confined to the study site for at least 12 h prior to dosing until 48 h after dosing. The subjects fasted for at least 10 h prior to dosing. The study drug was administered together with 240 mL of water.

Safety and Tolerability

Physical examination and hematology, chemistry and urinalysis was performed and vital signs, ECG, and adverse events recorded.

Pharmacokinetic Profiling

Blood samples for the determination of valsartan were collected at the following times: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after dosing.

Bioassay

A HPLC/MS/MS method using turbo ion spray positive ion mode with an [redacted] was employed. The LLOQ of the method is 20 ng/mL. The concentration range of the linear calibration curve ranged between 20 ng/mL and 10000 ng/mL. The coefficients of determination of the linear fits of the calibration curve were ≥ 0.9938. The data were weighted by $1/Y^2$. The QC samples exhibited concentrations of 50.0 ng/mL, 4000 ng/mL and 8000 ng/mL. The inter-day accuracy of the QC samples ranged between -0.4% and -3.6% and the precision was ≤ 7.3%. The measurements of the plasma concentrations of valsartan were performed in the laboratories of the sponsor.

Pharmacokinetic Data Analysis

The following parameters were determined using non-compartmental methods: AUC0-tlast, AUC0-∞, Cmax, tmax, t1/2 and λ.

Statistical Evaluation

For assessment of bioavailability AUC0-tlast, AUC0-∞, and Cmax were compared between the 80 mg valsartan oral tablet (CSF) (test drug Treatment A) and the 80 mg valsartan marketed oral tablet (FMI) (reference drug-Treatment B). A linear mixed effect model on log transformed PK parameters, with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The ratio of treatment means on the original scale was estimated, along with 90% confidence interval, by the

antilog of the difference in least squares means on the log scale for AUC0-tlast, AUC0-∞ and Cmax.

Sample Size

An estimated intra-subject coefficient of variation of 25% obtained from Study VAL489A Study 604 was used to determine the sample size. With a sample size of 24 subjects, there was 80% power that the 90% confidence interval for the treatment ratios of mean AUC0-t, AUC0-∞ and Cmax would be contained in the bioequivalence range of 80% to 125% assuming the true formulation means were equal.

Results

Twenty-four subjects were enrolled and completed the study. The below table lists the demographics of the subjects:

Table 7-1 Summary of demographic information

	Treatment		
	Sequence 1 N = 12	Sequence 2 N = 12	Overall N = 24
Race (N [%])			
Caucasian	2 (16.7%)	2 (16.7%)	4 (16.7%)
Other	10 (83.3%)	10 (83.3%)	20 (83.3%)
Age (years)			
Mean	40.4	37.9	39.2
SD	9.51	6.49	8.06
Median	44.5	40.0	41.5
Minimum, Maximum	24, 50	25, 47	24, 50
Sex			
Male	4 (33.3%)	6 (50.0%)	10 (41.7%)
Female	8 (66.7%)	6 (50.0%)	14 (58.3%)
Body Frame			
Small	3 (25.0%)	3 (25.0%)	6 (25.0%)
Medium	6 (50.0%)	7 (58.3%)	13 (54.2%)
Large	3 (25.0%)	2 (16.7%)	5 (20.8%)
Weight (kg)			
Mean	70.4	72.6	71.5
SD	8.62	7.92	8.18
Minimum, Maximum	59.5, 87.4	57.7, 84.4	57.7, 87.4
Height (cm)			
Mean	162.4	168.2	165.3
SD	9.47	8.67	9.36
Median	160.5	169.0	164.5
Minimum, Maximum	148, 184	153, 179	148, 184
Elbow breadth (cm)			
Mean	6.6	6.6	6.6
SD	0.72	0.42	0.57
Median	6.6	6.8	6.7
Minimum, Maximum	5.6, 8.1	5.9, 7.1	5.6, 8.1

Source: Appendix 3, Table 2.2.2
Categorical data are presented as N (%).
Sequence 1 = Single 80-mg oral dose of valsartan pediatric tablet (CSF) (test drug) during Period 1 and a single 80-mg oral dose of valsartan marketed tablet (FMI) (reference drug) during Period 2.
Sequence 2 = Single 80-mg oral dose of valsartan marketed tablet (FMI) (reference drug) during Period 1 and a single 80-mg oral dose of valsartan pediatric tablet (CSF) (test drug) during Period 2.

Tolerability/Safety

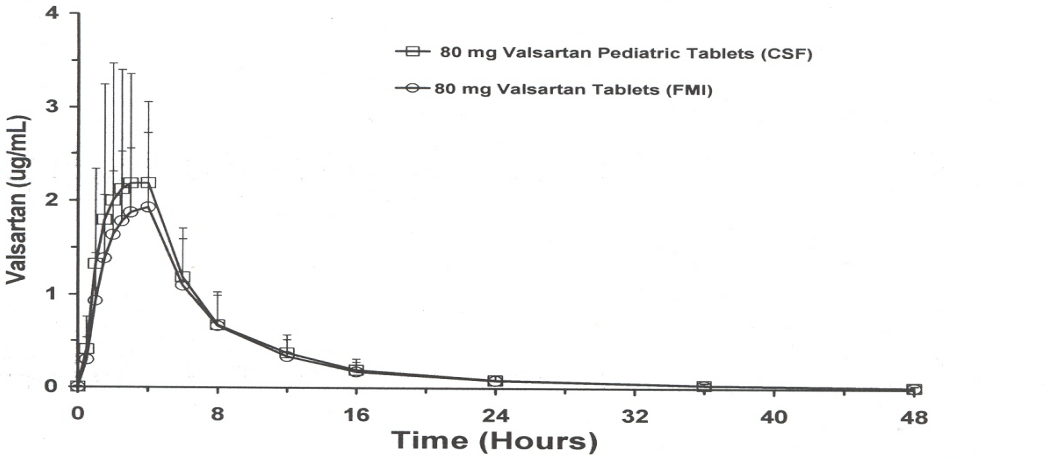
The treatments were tolerated well. One subject experienced a sore throat 25 h after receiving Treatment B. No serious adverse events or death occurred.

Pharmacokinetics

The estimates for AUC0-∞ and λz for subject 5106 were not included in the statistical analysis of the PK data, because the value for λz was unusually small in Treatment A. However, the corresponding Cmax and AUC0-tlast were inconspicuous and used in the statistical analysis.

The plasma concentration time profiles of valsartan following administration of the 80 mg valsartan pediatric tablet (CSF) and the 80 mg valsartan tablets (FMI) are shown in the plot below:

Figure 7-1 **Mean plasma valsartan concentration versus time profile following single-dose administration of 80-mg pediatric tablets (CSF) and 80-mg marketed tablets (FMI)**



It can be seen that the pediatric 80 mg tablets display slightly larger Cmax and AUC0-∞ values than the marketed 80 mg tablets.

The below two tables show the arithmetic means (SD) of AUC0-tlast, AUC0-∞, Cmax, tmax and t1/2 and the geometric means and 90% confidence intervals for the ratio of the geometric means:

Table 7-2 **Arithmetic mean plus or minus SD (CV%) pharmacokinetic parameters of valsartan following oral administration of 80-mg pediatric tablets (CSF) and 80-mg marketed tablets (FMI)**

Pharmacokinetic Parameter	Treatment A – test drug	Treatment B – reference drug
		(N = 24)
AUC_{0-t} (μg·h/mL)	17.04 ± 8.3 (48.5)	15.11 ± 5.4 (35.5)
$AUC_{0-\infty}$ (μg·h/mL)	17.46 ± 8.4 (48.1)	15.70 ± 5.4 (34.6)#
C_{max} (μg/mL)	2.6 ± 1.3 (50.3)	2.3 ± 0.7 (30.1)
$t_{1/2}$ (h)	8.26 ± 3.37 (40.8)	8.05 ± 3.24 (40.3)
t_{max} (h)*	3.17 (1.5, 6.0)	3.3 (1.5, 8.0)

Source: Appendix 4, Table 3, Appendix 4, Table 4 and Appendix 6, Table 6.1.1

* Median (minimum, maximum) values are presented.

\# N = 23

Treatment A = Single 80-mg oral dose of valsartan pediatric tablet (CSF).

Treatment B = Single 80-mg oral dose of valsartan marketed tablet (FMI).

Table 7-3 Assessment of relative bioavailability between 80-mg pediatric tablets (CSF) and 80-mg marketed tablets (FMI) for valsartan

Parameters	Treatment*	Geometric mean†	Ratio of geometric means†	90% CI for ratio†	*P* value†
AUC_{0-t} µg·h/mL (N=24)	A	15.4	1.09	(0.94, 1.28)	0.324
	B	14.1			
$AUC_{0-\infty}$ µg·h/mL (N=24)	A	15.8	1.08	(0.93, 1.26)	0.367
	B	14.6			
C_{max} µg/mL	A	2.3	1.06	(0.86, 1.31)	0.649
	B	2.2			

Source: Appendix 6, Table 6.1.1

* A = 80-mg pediatric tablet (test drug); B = 80-mg marketed tablet (reference drug)

† A mixed effect model analysis for the log-transformed values with treatment period and sequence as fixed effects and subject nested within sequence as a random effect.

The statistical evaluation of the data indicates that the geometric mean of Cmax and AUC with the 80 mg pediatric tablet is 1.06 and 1.08 times greater than with the commercial adult 80 mg tablet. The upper limits of the respective 90% confidence intervals for AUC0-tlast, AUC0-∞ and Cmax of the pediatric tablet with 1.28, 1.26 and 1.31 exceed the 1.25 margin, indicating that the pediatric tablet and the marketed tablet are bioinequivalent.

Conclusions

The bioavailability of the pediatric and the adult tablets are comparable, but are not equivalent. Both treatments were tolerated well.

Comments

None

4.3 Study Report: VAL489A 2304 " An Open Label, Single Dose, Two Period, Randomized Crossover Study To Determine the Relative Bioavailability of 4 x10 mg Valsartan Tablets (CSF) as Compared to a 40 mg Valsartan Tablet in Healthy Subjects"

Study Site and Investigator

Objectives

To determine the relative bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablets in healthy volunteers

Investigational Drugs

4 x 10 mg valsartan tablets (CSF) Lot No.: H-05994
40 mg commercial valsartan tablets Lot No.: 001E6956

Design

This was an open-label, randomized, two-period, crossover study. Treatment A was a single dose of 4 x 10 mg valsartan tablets (test) and Treatment B was 1 x 40 mg valsartan tablet (reference). A wash-out period of 7 days was maintained between the two treatment periods. Twenty-four healthy subjects in the age between 18 and 45 years were to be enrolled in the study. Female subjects of childbearing potential were using or agreed to use double-barrier local contraception. The subjects were admitted to the study site on the evening of dosing days and domiciled for at least 24 h after dosing. The treatments were administered together with 180 ml water after a 10 h fast.

Tolerability and Safety

The health of the enrolled subjects was ascertained by medical history, physical examination, ECG, laboratory tests (hematology, clinical chemistry and urinalysis).

Pharmacokinetic Profiling

Blood samples for the determination of valsartan plasma concentrations were obtained at the following times: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h post-dose.

Bioassay

A HPLC/MS/MS method using turbo ion spray positive ion mode with an [redacted] was employed. The LLOQ of the method is 2 ng/mL. The concentration range of the linear calibration curve ranged between 2 ng/mL and 5000 ng/mL. The coefficients of determination of the linear fits of the calibration curve were ≥ 0.9938. The data were weighted by $1/Y^2$. The QC samples exhibited concentrations of 4.0 ng/mL, 100 ng/mL and 4000 ng/mL. The inter-day accuracy of the QC samples ranged between -2% and 1% and the precision was ≤ 10.4%. The measurements of the plasma concentrations of valsartan were performed in the laboratories of the sponsor.

PK Data Analysis

The following parameters were determined: AUC0-t, AUC0-∞, Cmax, tmax, λz and t1/2. AUC0-tlast was determined by the linear trapezoidal rule. The other parameters were determined using non-compartmental standard methods.

Statistical Evaluation

The PK parameters AUC0-t, AUC0-∞ and Cmax were evaluated. For comparisons of means, parametric analyses were performed. A mixed effects model was fit to data

containing sequence, treatment, and period as fixed factors and subject within sequence as a random effect.
The 90% confidence limits for the difference between least squares means on the log scale were anti-logged to provide intervals for the ratios of the least squares means on the original scale.

Sample Size

Based on a previous bioequivalence study (VAL489Study 604), an estimated intra-subject CV of 0.25 was considered appropriate for sample size determination. Using this estimate and the normal approximation of the test statistic for the comparison between two means on the log–transformed scale, 24 subjects would provide approximately 80% power to have the 90% confidence intervals for the treatment ratios of mean AUC0-t, mean AUC0-∞, or mean Cmax to be contained entirely in the range 80%-125%, assuming the true ratio of the means of the formulations being 100%.

Results

Of the 24 subjects enrolled in the study 23 completed both treatments. Subject 05117 withdrew consent after Period 1. Mean weight and age of the subjects was 69 kg and 30 years, respectively.

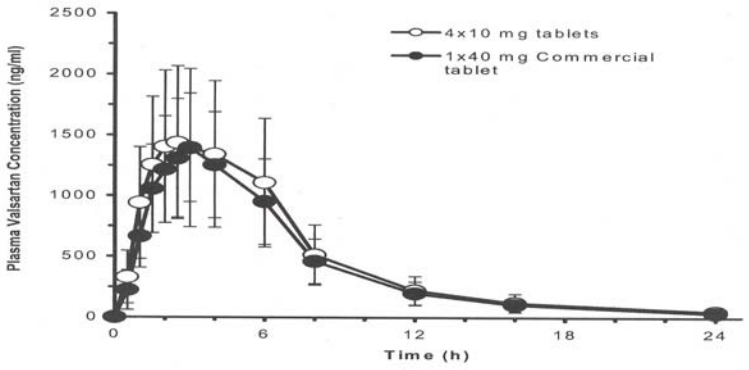
Tolerability and Safety

The two treatments were tolerated well. No serious adverse events of death were reported. Seven adverse events were recorded by 5 of 24 subjects. Six (6) of the adverse events were not suspected to be drug related by the investigator. Subject 5108 reported a headache which was suspected to be drug related by the investigator.

Pharmacokinetics

The mean plasma concentration time profiles of valsartan after administration of 4 x 10 mg tablets and 1 x 40 mg commercial tablet are shown below:

Figure 7-1 **Mean (±sd) plasma concentration vs time profiles of valsartan following single oral dose administration of 4x10 mg tablets of valsartan and 1x40 mg tablet of valsartan.**



The plots of the mean concentrations show that Cmax and AUC0-∞ after administration of 4 x10 mg tablets tend to be greater than after administration of the 40 mg commercial tablet.

Arithmetic means or medians of the bioavailability measures are shown in the below table:

Table 7-2 Summary of the pharmacokinetic parameters of valsartan after a single dose administration of 4x10 mg valsartan tablets vs 40 mg valsartan tablet (n=23, subject 5117 excluded due to drop out at period 2).

Treatment	Tmax (h) Median (min; max)	Cmax (ng/ml) Mean ± SD (CV%)	$AUC_{(0-t)}$ (ng.h/ml) Mean ± SD (CV%)	$AUC_{0-\infty}$ (ng.h/ml) Mean ± SD (CV%)
4x10 mg	2.5 (1.5; 6.0)	1766.5 ± 642.6 (36.4%)	11618.1 ± 4454.8 (38.3%)	11991.4 ± 4752.2 (39.6%)
40 mg	3.0 (1.07; 4.07)	1545.52 ± 426.4 (27.6%)	9925.3 ± 3104.8 (31.3%)	10227.7 ± 3309.9 (32.4%)

The geometric mean ratios and 90% confidence intervals are listed in the following two tables:

Table 7-3 Estimated ratios of means and 90% confidence intervals for AUC and C_{max} of valsartan (N=23)

PK parameter	Estimated ratio of means (4x10 mg / 40 mg)	90% confidence interval for the ratio
C_{max} (ng/mL)	1.08	(0.90, 1.29)
$AUC_{(0-t)}$ (ng.h/mL)	1.12	(0.96, 1.31)
$AUC_{(0-\infty)}$ (ng.h/mL)	1.12	(0.97, 1.31)

The results indicate that the bioavailability of the test 4 x 10 mg tablets and the reference 40 mg commercial tablet are comparable, but not equivalent. The geometric means of Cmax and AUC are 1.08 and 1.12 times greater, respectively, than with the commercial adult 40 mg tablet.

Conclusion

The bioavailability of valsartan from the test 4 x10 mg tablets and the reference 40 mg commercial tablets is comparable but not equivalent.

Comment

The plasma concentrations of valsartan should have been measured for more than 24 h in order to determine the true half-life of the terminal log linear disposition phase.

Overall Conclusion Regarding the Relative Bioavailability Studies

None of the test formulations was bioequivalent to the reference commercial adult tablets. The two solid test formulations, the pediatric 10 mg and 80 mg tablets, exhibited a marginally better bioavailability than the commercial adult 40 and 80 mg tablets. The third test formulation, the oral 4 mg/mL extemporaneous suspension, demonstrated a largely better bioavailability than the 80 mg adult tablet.

4.4 Study No. CVAL489A2305: A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Valsartan Given as an Oral Suspension in Pediatric and Adolescent Subjects 2 Months to 16 Years of Age with Hypertension

Objectives

Primary

To determine the single-dose pharmacokinetics of valsartan given as an oral suspension

Secondary

To determine the safety and tolerability of a single oral dose of valsartan in 1-16 year old children with hypertension

Investigational Drugs/Formulations

Valsartan extemporaneous oral suspension 4 mg/mL (Lot No.: 054H8641 and 580003)

Design

This was a multi-center, open label, single dose study. Twenty six children in the age between 2 months and 16 years received a single dose of valsartan oral suspension 4 mg/mL given as a dose of 2 mg/kg (maximum dose of 80 mg**).** A total of 26 subjects, males or females, were to be enrolled in the study with 6 subjects per age group were to complete the study. Subjects were to be stratified by age using the following age groups: Group 1: 1 year to < 4 years, Group 2: 4 years to < 6 years, Group 3: 6 years to < 12 years and Group 4: 12 years to 16 years. Each study site could enroll up to a maximum of 3 subjects in any one age group. All subjects were to have hypertension defined as a systolic or diastolic blood pressure $\geq$ 95th percentile for age, sex, and height, measured on at least 2 separate occasions prior to dosing.

On the morning of the study, the subjects' intake of food and beverages were to have been restricted as follows:

For subjects < 2 years of age, at 2.5 h prior to dosing these subjects were given 90 mL (3 oz) of one of the following: Breast milk, formula, 2% milk, or a suitable milk substitute. Subjects were allowed to have 2 ounces of rice cereal and Pedilyte, if necessary. The intake of water was allowed throughout the study and was not restricted.

For subjects ≥ 2 years of age, the intake of solid foods and beverages (except water) was not allowed from 2 h prior to dosing until 2 h after dosing. Approximately 2.5 h prior to dosing subjects could have a light, low fat breakfast type meal, which may, for example, have included dry cereal with milk, oatmeal, farina, grits, toast, roll, bagel, etc. The intake of foods that had a high fat content such as fried eggs, bacon, sausage, ham etc, was prohibited. The intake of water was allowed throughout the study and was not restricted. The valsartan suspension was administered to the subjects between 0600 and 1200.

The scheduled study activities are shown in the table below:

Table 3-1 Evaluation and visit schedule

Evaluation	Screening Day -7 to –1 (Visit 1)	Dosing and PK sampling Day 1 (Visit 2)									Day 2	
		Pre-dose	0.5 hr	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	24 hr	
Informed consent/assent	X											
Inclusion/exclusion criteria	X											
Concomitant medications	X											X [b]
Demographics/ medical history	X											
Physical examination	X											X [b]
Hepatitis screen	X											
Urine alcohol, drug & cotinine screen (subjects ≥6 yrs)	X	X										
Pregnancy test (post menarchal females only)	X [a]	X [a]										
Vital signs: BP, HR	X	X	X	X	X	X	X	X	X	X		X [b]
Body temperature	X	X										X [b]
Clinical laboratory tests (blood & urine)	X											X [b]
ECG	X				X							X [b]
Collect blood samples for PK evaluations (subjects 1 to <6 yrs)	X		X	X	X		X			X	X	
Collect blood samples for PK evaluations (subjects 6 to 16 yrs)		X	X	X	X	X	X	X	X	X	X	
Adverse event assessment		X	X	X	X	X	X	X	X	X		X [b]
Study completion												X

[a] Pregnancy test at screening performed using serum sample and pregnancy test at Visit 2 performed using urine sample; both pregnancy test results had to be negative prior to dosing with valsartan.

[b] To be done after 24-hour PK sample was collected.

Note: BP = blood pressure, HR = heart rate, hr = hour, yrs = years.

The inclusion and exclusion criteria were the following:

3.2.2 Inclusion and exclusion criteria

Inclusion criteria

Subjects meeting all of the following criteria were considered for admission into the study:

1. Female or male subject from 1 year to 16 years of age;
2. If post-menarchal female, serum pregnancy test result at screening was negative and urine pregnancy test result at Visit 2 (prior to receiving single-dose of oral valsartan) was negative;
3. Subject exhibited hypertension as defined by a sitting systolic or diastolic blood pressure measuring at or above the 95th percentile for age, gender, and height on at least two separate occasions at least one day apart (unless the subject was currently taking anti-hypertensive therapy) (see Protocol Section 7.1 – BP tables for children and Section 7.2 – Height tables);
4. Informed consent form (approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)) signed by the parent/legal guardian (plus approved pediatric assent signed by the subject if applicable);
5. Physical examination demonstrated no abnormalities that would make this study medically hazardous to the subject;
6. Subject (of the appropriate age) and/or parent/guardian was able to follow verbal and/or written instructions in the local language;
7. Subject demonstrated no clinically significant abnormalities or clinically noteworthy abnormal laboratory values (other than those relating to renal function);
8. Subject demonstrated no clinically significant ECG abnormalities other than those associated with left ventricular hypertrophy;
9. If subject ≥6 years of age, urine tests at screening and Visit 2 were negative for alcohol, drugs of abuse, and cotinine.

Exclusion criteria

Subjects meeting any of the following criteria were **not** to be included in the study:

1. Subject had any clinically significant unstable medical condition or chronic disease other than those associated with hypertension;
2. Subject who could not safely tolerate the temporary discontinuation of concomitant anti-hypertensive medications for 24 hours prior to valsartan dosing or whose blood pressure was not able to be controlled with only amlodipine or atenolol during the 24 hours prior to valsartan dosing.
3. Subject had experienced a significant clinical illness within 10 days prior to receiving the single-dose of study medication;
4. Subject tested positive at screening for the hepatitis B surface antigen or hepatitis C antibody, or had a history of a positive result for one of these tests;
5. Subject was known to have tested seropositive for the human immunodeficiency virus (HIV) or subject was concomitantly receiving anti-retroviral therapy;
6. Subject had a clinically significant abnormality of the hepatic system, or a history of malabsorption or previous gastrointestinal surgery that could effect drug absorption or metabolism;
7. Subject had a disorder or history of a condition that could interfere with drug absorption, distribution, metabolism, or excretion;
8. Subject had used any drug known or suspected to effect hepatic or renal clearance capacity within 30 days prior to start of study (this included drugs that are known to cause induction or inhibition of liver enzymes, see Protocol Section 7.5 for cytochrome P450 inducers and inhibitors);
9. Subject had any of the following clinical laboratory abnormalities:
   - AST/SGOT or ALT/SGPT >2 times the upper limit of the reference range;

- Total bilirubin or direct bilirubin >2 times the upper limit of the reference range;
- Creatinine clearance <40 ml/min/1.73m^2 (calculated using Modified Schwartz formula to estimate glomerular filtration rate (GFR), see Protocol Section 7.4 for formula)
- Hemoglobin <9 gm/dL;
- WBC count <3000/mm^3;
- Platelet count <100,000/mm^3;
- Serum potassium >upper limit of the reference range.

10. Subject had a known hypersensitivity to valsartan;
11. Subject had sustained a significant blood volume loss (>3% of calculated blood volume) in the past 30 days;
12. Subject had taken an investigational drug or participated in an investigational study within 30 days prior to study drug administration;
13. Subject consumed more than 180 mg of caffeine per day (see Protocol Section 7.3 – Caffeine content of beverages) and/or was unable/unwilling to refrain from ingesting caffeine or xanthine containing beverages from 24 hours prior to dosing through study completion.

Tolerability/Safety

The subjects' safety/tolerability was ascertained by monitoring adverse event, clinical vital signs, and ECG and by performing clinical laboratory evaluations.

Pharmacokinetic Profiling

Blood samples were collected for the determination of valsartan in plasma at the following times:
Children 2 months to < 6 years of age: pre-dose, 0.5, 1, 2, 4, 8, 12, and 24 h after dosing
Children 6 years to 16 years of age: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after dosing

Bioassay

The plasma concentrations of valsartan were measured by a HPLC-MS/MS method using turbo ion spray positive ion mode. The method used an [redacted] procedure. The LLOQ of the method is 2.0 ng/mL. The range of the linear calibration curve is from 2.0 ng/mL to 5000 ng/mL. The coefficient of determination of the fits of the calibration curves to the data was ≥ 0.9925. The concentrations of the QC samples were 4.0 ng/mL 1000 ng/mL and 4000 ng/mL. The inter-day accuracy of the QC samples ranged between -7.8% and 2.3% and the precision was ≤ 8.7%.

PK Data Analysis

The following parameters were determined: AUC0-tlast, AUC0-tlast*(similar to AUC0-tlast, but using selected time points for estimation), AUC0-∞, Cmax, tmax, tlag, CL/F, λz and t1/2. The parameters were derived from non-compartmental methods using WinNonlin® Professional, version 3.1 or higher. AUC0-tlast was computed using the linear trapezoidal rule. λz was obtained from linear regressions of the natural log transformed concentration versus time data in the terminal phase (if estimable). A minimum of 3 points clearly visible in the terminal phase were required to calculate λz. All the parameters with the exception of tmax, tlag, λz and t1/2 were dose or body weight adjusted.

Statistical Evaluation

Descriptive statistics are reported by age group for the following dose unadjusted and dose adjusted (DA: adjusted to a dose of 2 mg/kg dose) valsartan parameters: AUC0-tlast, DA-AUC0-tlast, AUC0-tlast*, DA-AUC0-tlast*, AUC0-∞, DA-AUC0-∞, Cmax, DA-Cmax and body weight unadjusted and adjusted CL/F and body weight unadjusted t1/2. Regression analyses were performed to study the effect of age on the PK parameters DA-AUC0-tlast, DA-AUC0-tlast*, DA-AUC0-∞, DA-Cmax and body weight adjusted CL/F. The natural log-transformed parameter was the response variable (denoted as value in the model equation below), and age in years as continuous variable) was the predictor variable in accordance with Value = $\alpha + \beta \bullet AGE + \varepsilon$, where α is the intercept and β the slope of the straight line and ε is a random error. The point estimate and 90% confidence interval estimates of the slope and intercept and the p-vales for the test of the slope equal to zero were obtained for each parameter as well as the coefficient of determination of the linear fit.
The lack of fit of the regression model was also checked for quadratic curvature by including the term squared age variable to the above equation as follows:

$$Value = \alpha + \beta \bullet AGE + \gamma \bullet AGE^2 + \varepsilon$$

A test for $\gamma = 0$ was performed at 0.05 significance level. Non-rejection of this hypothesis ($P < 0.05$) showed the absence of a quadratic curvature.

Sample Size

The sample size of 6 subjects per age group was based on clinical judgment and common practices for pharmacokinetic studies in pediatric subjects, and was not based on statistical consideration.

Results

All 26 subjects enrolled completed the study. All subjects were included in the PK and tolerability/safety analyses.

The demographic characteristics of the study subjects by age group are shown in the table below:

Table 7-3 Demographic characteristics summary by age group

	Valsartan				
	1 year to <4 years (N = 6)	4 years to <6 years (N = 6)	6 years to <12 years (N = 7)	12 years to 16 years (N = 7)	Total (N = 26)
Age (year)					
Mean ± SD	2.3 (1.03)	4.2 (0.41)	8.1 (1.95)	13.6 (0.79)	7.3 (4.56)
Median	3.0	4.0	8.0	13.0	6.0
Sex – n (%)					
Male	4 (66.7)	3 (50.0)	2 (28.6)	4 (57.1)	13 (50.0)
Female	2 (33.3)	3 (50.0)	5 (71.4)	3 (42.9)	13 (50.0)
Race – n (%)					
Black	1 (16.7)	3 (50.0)	1 (14.3)	3 (42.9)	8 (30.8)
Caucasian	2 (33.3)	-	3 (42.9)	3 (42.9)	8 (30.8)
Oriental	-	-	-	-	-
Other	3 (50.0)	3 (50.0)	3 (42.9)	1 (14.3)	10 (38.5)
Weight (kg)					
Mean ± SD	15.1 (5.67)	20.5 (5.20)	42.0 (15.71)	92.0 (27.43)	44.3 (35.09)
Median	14.9	19.4	49.7	88.0	27.5
Height (cm)					
Mean ± SD	92.6 (13.34)	107.7 (4.76)	134.4 (14.08)	170.3 (12.62)	128.3 (32.22)
Median	96.8	108.3	140.0	166.0	116.8

N = number, SD = standard deviation.
Source: Appendix 3, Table 2.2.2.

A subject listing of relevant medical history and current medical conditions can be found in Appendix 3-Table 2.3.

The mean doses unadjusted and adjusted for body weight of the subjects in the 4 age groups are summarized in the following table:

Table 7-4 Demographic characteristics and dosing by age group

Group	Age [years]	Pts enrolled	Mean age	Mean body weight [kg]	Mean dose [mg]	Mean dose [mg/kg]
1	1-<4	6	2.3	15.1	30.5	2.0
2	4-<6	6	4.2	20.5	40.7	2.0
3	6-<12	7	8.1	42.0	68.4	1.6
4	12-16	7	13.6	92.0	80	0.9

It can be seen that the mean dose increased from about 30 mg in Group 1 (1- < 4 years of age) to 80 mg in Group 4 (12-16 years old). The weight normalized mean dose in Groups 1, 2, 3 and 4 was 2.0 mg/kg, 2.0 mg/kg, 1.6 mg/kg, and 0.9 mg/kg, respectively.

Tolerability/Safety

Changes in blood pressure were observed after administration of valsartan as follows:

Table 7-6 **Mean (plus minus SD) change from Day 1 pre-dose in systolic and diastolic blood pressure**

	SBP		DBP	
Day 1 pre-dose (hours)	**N**	**Mean (±SD)**	**N**	**Mean (±SD)**
0	25	113.0 (17.33)	25	69.7 (10.77)
Day 1 post-dose (hours)	**N**	**Mean change (±SD)**	**N**	**Mean change (±SD)**
0.5	25	-5.5 (18.90)	25	-5.9 (10.77)
1	25	-7.3 (13.05)	25	-6.8 (10.53)
2	25	-6.1 (12.71)	25	-8.5 (13.36)
3	24	-5.8 (15.84)	24	-8.7 (10.09)
4	25	-7.1 (15.95)	25	-10.0 (10.95)
6	24	-9.6 (17.43)	24	-9.2 (12.23)
8	24	-7.5 (15.02)	24	-6.5 (11.85)
12	25	-0.2 (16.02)	25	-4.8 (12.90)

DBP = diastolic blood pressure, N = number, SBP = systolic blood pressure, SD = standard deviation.
Source: Appendix 3-Table 3.4.3. (Note: Subject 0003/00303 missed baseline blood pressure reading/assessment)

The treatment was tolerated well by the subjects. There were no serious adverse events or death noted. Three of the subjects experienced an adverse event: ventricular hypertrophy in a 1 year old subject, injection site pain in an 8 year old subject and headache in a 14 year old subject. They were not suspected to be drug related.

Bioassay:

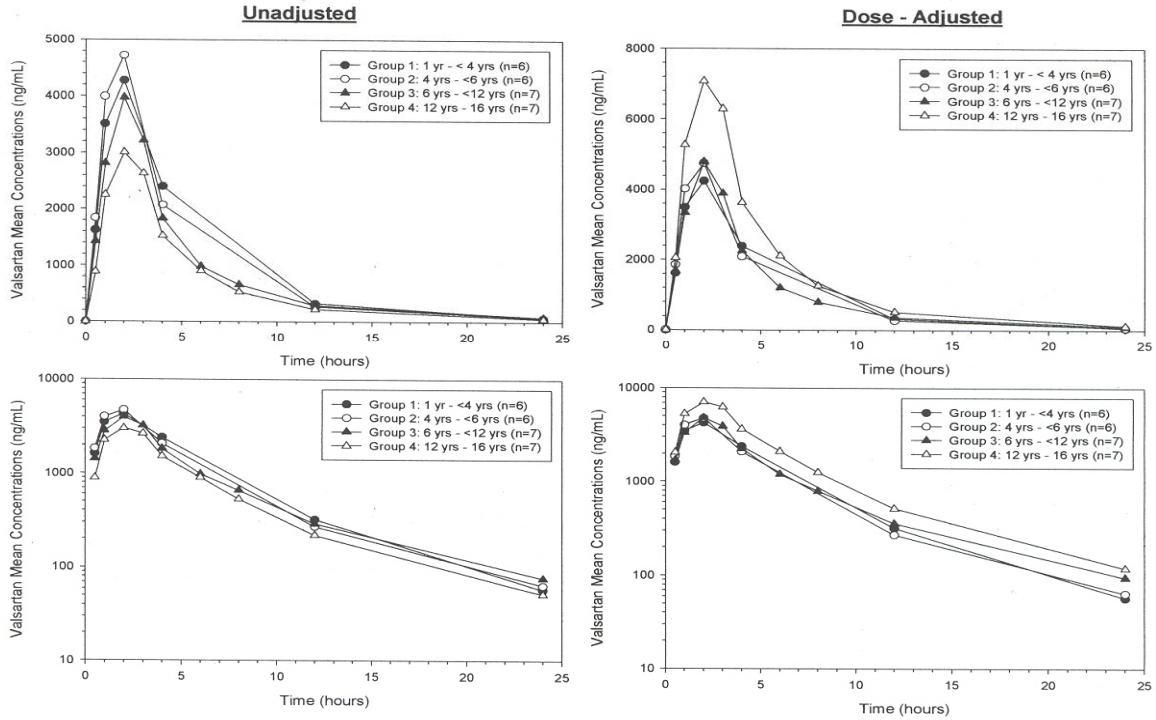
The plasma concentrations of valsartan were measured by an [redacted] procedure and analysis of the extract by HPLC-MS/MS using turbo ion spray positive ion mode. The calibration curve ranged between 2.0 ng/mL and 5000 ng/mL. The LLOQ was 2.0 ng/mL. QC samples were measured along samples with unknown concentrations of valsartan. The coefficient of determination of the linear function to the data was ≥ 0.9782. The data were weighted by $1/Y^2$. The QC samples had nominal concentrations of 4.0 ng/mL, 100 ng/mL and 4000 ng/mL. The inter-day accuracy of the QC samples ranged between 2.3% - (-)7.8 % and the precision was ≤ 8.7%.

Samples from subjects 02-0201, 02-0202, and 02-203 were thawed due to power interruption at the clinical site. The samples of the 3 subjects were in a 0 °C -15 °C environment for approximately 36 h. They were subsequently refrozen. In accordance with the results of the stability report ([redacted] Report 93027) valsartan does not degrade when exposed to room temperature for 72 h or during a freeze-thaw cycle.

Pharmacokinetics

Linear and semi-logarithmic plots of the arithmetic mean plasma concentrations of valsartan unadjusted and adjusted for dose are shown below:

Figure 7-1 **Linear and semi-log plots of mean unadjusted and dose-adjusted valsartan plasma concentration-time profiles by age group following single dosing with valsartan**



Note: Dose-adjusted concentrations are adjusted to a 2 mg/kg dose.
Source: Appendix 4, Table 1, and Appendix 4, Figure 1 and Appendix 4, Figure 2.

The dose unadjusted plasma concentrations time profiles indicate that the exposure to valsartan increases in the order Group 4 (adolescents), Group 3 (6-<12 years old), Group 2 (4 - < 6 years old) and Group 1 (1-< 4 years old). The plots of the dose adjusted arithmetic mean plasma concentrations indicate that the subjects in Group 4 (12-16 years of age) incur a slightly greater exposure to valsartan than the subjects of Groups 1-3 (1- < 12 years of age).

A summary of the dose unadjusted and dose adjusted mean Cmax and AUC, dose unadjusted tlag and t1/2 and body weight unadjusted and adjusted CL/F, are listed below:

Table 7-7 Summary of unadjusted and dose-adjusted valsartan pharmacokinetic parameters by age group

Pharmacokinetic Parameters	Arithmetic Mean (CV%) [Geometric Mean] Group 1: 1 year to <4 years (N = 6)	Group 2: 4 years to <6 years (N = 6)	Group 3: 6 years to <12 years (N = 7)	Group 4: 12 years to 16 years (N = 7)
Unadjusted				
C_{max} (ng/mL)	4307 (43) [3832]	4818 (39) [4500]	4254 (27) [4112]	3069 (41) [2835]
$AUC_{(0-t)}$ (ng*hr/mL)	25505 (43) [23203]	24500 (31) [23497]	19600 (36) [18447]	15560 (34) [14619]
$AUC_{(0-t)}$* (ng*hr/mL)	25505 (43) [23203]	24500 (31) [23497]	21414 (36) [20089]	16764 (39) [15564]
$AUC_{(0-\infty)}$ (ng*hr/mL)	25823 (43) [23517]	26800 (26) [26071]	20214 (36) [18994]	15944 (35) [14988]

Pharmacokinetic Parameters	Arithmetic Mean (CV%) [Geometric Mean] Group 1: 1 year to <4 years (N = 6)	Group 2: 4 years to <6 years (N = 6)	Group 3: 6 years to <12 years (N = 7)	Group 4: 12 years to 16 years (N = 7)
CL/F (L/hr)	1.50 (67) [1.23]	1.63 (21) [1.60]	3.80 (43) [3.45]	5.75 (45) [5.34]
$t_{1/2}$ (hr)	3.79 (10) [3.77]	3.95 (13) [3.92]	5.33 (12) [5.30]	4.97 (15) [4.92]
t_{max} (hr) [a]	2.00 (1.00, 2.02)	2.00 (1.00, 2.00)	2.00 (1.02, 3.00)	2.00 (1.00, 3.02)
Adjusted [b]				
DA-C_{max} (ng/mL)	4275 (43) [3796]	4848 (38) [4536]	5113 (30) [4882]	7214 (46) [6237]
DA-$AUC_{(0-t)}$ (ng*hr/mL)	25288 (42) [22983]	24667 (30) [23696]	23771 (40) [21919]	36806 (43) [32185]
DA-$AUC_{(0-t)}$* (ng*hr/mL)	25288 (42) [22983]	24667 (30) [23696]	26057 (42) [23856]	39703 (46) [34256]
DA-$AUC_{(0-\infty)}$ (ng*hr/mL)	25605 (42) [23294]	2700 (24) [26333]	24514 (40) [22544]	37667 (43) [32997]
CL/F (L/hr/kg)	0.097 (64) [0.086]	0.078 (26) [0.076]	0.098 (49) [0.089]	0.076 (94) [0.061]

N = number; DA = Dose-adjusted.
$AUC_{(0-t)}$* - $AUC_{(0-t)}$ which is calculated using only the time points that are common to all age groups.
[a] Median (min, max).
[b] C_{max} and AUC values are dose-adjusted to a 2 mg/kg dose. CL/F is adjusted to a unit body weight.
Source: Appendix 4-Table 2.

Table 1. Summary values of volume of distribution (Vd/F) by age group uncorrected and corrected for body weight.

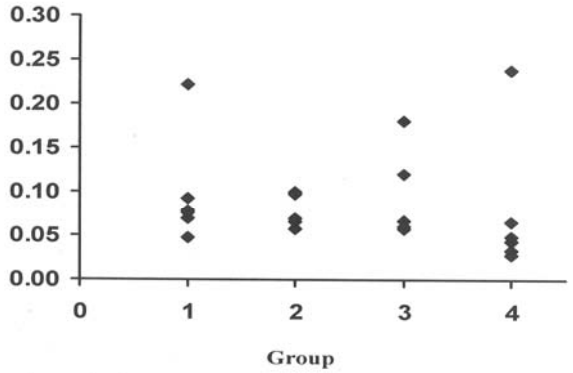
Pharmacokinetic Parameters	Arithmetic Mean ± SD (CV%) [Geometric Mean]			
	Group 1: 1 year to <4 years (N = 6)	Group 2: 4 years to <6 years (N = 6)[a]	Group 3: 6 years to <12 years (N = 7)	Group 4: 12 years to 16 years (N = 7)
Uncorrected				
Vd/F (L)	8.52 ± 6.40 (75.1%) [6.69]	9.22 ± 1.81 (19.6%) [9.08]	28.94 ± 12.27 (42.4%) [26.32]	41.56 ± 22.30 (53.7%) [37.93]
Corrected [b]				
Vd/F (L/Kg)	0.548 ± 0.412 (75%) [0.465]	0.436 ± 0.07 (16%) [0.432]	0.737 ± 0.334 (45.4%) [0.678]	0.571 ± 0.612 (107%) [0.429]

N = number; [a] For one subject, estimation of terminal half life was not possible. Thus, the summary parameters are for N=5 only; [b] is adjusted to a unit body weight.
Erratum: A reporting error was noticed in the derived Vd/F values for Group 3 and Group 4 in the CTD 2.7.2 document, Page 7, Table 2-2. The Vd/F values presented in this document are accurate and were generated from the source CL/F and elimination rate constant values. Please refer to the Appendix 4 of the study report for individual PK parameters.

Maximum plasma concentrations of valsartan are attained in all four groups 2 h after administration. The t1/2 of the terminal disposition phase in the four groups is comparable and ranges between 3.79 h and 5.33 h. The oral clearance increases with age from 1.50 L/h in Group 1 to 5.75 L/h in Group 4 indicating an age or body weight dependency. The oral volume of distribution increases with bodyweight and/or age as well. The coefficient of variation about Cmax and AUC ranges between 26% to 43% in the different age groups.

The dose adjusted arithmetic and geometric mean parameters Cmax and AUC0-∞ confirm that peak and average exposure to valsartan appears to be slightly greater in Group 4 (12- 16 year old subjects) than in the three younger 3 age groups, but the small number of subjects in the four age groups should be considered. The body weight unadjusted oral clearance of valsartan is greater in the adolescents than in the children in the age between 1- < 12 years. After adjusting oral clearance for body weight the CL/F values among the four age groups become more comparable as shown in the below figure:

Figure 7-2 **Body weight-adjusted clearance (Cl/F) of valsartan versus age**

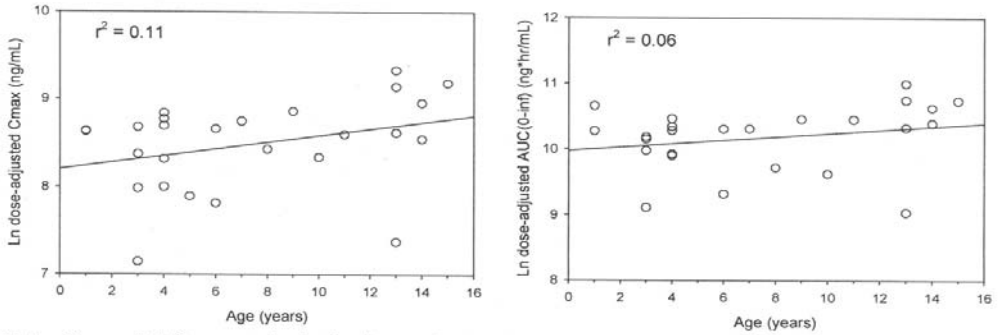


Results of regressions of valsartan parameters versus age showed that when C_{max} and AUC values were standardized to a uniform dose per unit body weight (i.e., 2 mg/kg), no significant age effect was observed ($p>0.05$, $r^2 \geq 0.11$; Figure 7-3, Appendix 6-Table 1, and Appendix 4-, Figure 9 to Appendix 4, Figure 12).

The geometric mean CL/F values (range: 0.06 -0.09 L/h/kg) and arithmetic mean CL/F values (range: 0.08-0.10 L/h/kg) are comparable in the 4 investigated pediatric age groups. There is considerable inter-subject variation. The report states that in adults receiving the suspension a mean value for CL/F of approximately 0.06 L/h/kg was obtained (Study CVA4892301). These results appear to provide a rationale for using a body weight normalized dose regimen for valsartan in the pediatric population. The body weight corrected oral volume of distribution is also comparable among the four age groups.

The figure below shows no important dependency for the natural log transformed and dose adjusted Cmax and AUC0-∞ on age.

Figure 7-3 **Linear regression plots of dose-adjusted valsartan C_{max} and $AUC_{(0-\infty)}$ versus age**



Note: C_{max} and $AUC_{(0-\infty)}$ are standardized to a valsartan dose of 2 mg/kg across all subjects.
Source: Appendix 3-Table 2.2.1, Appendix 4-Listing 2, and Appendix 6-Table 1.

Conclusions

The mean peak and average exposure to valsartan when normalized for dose appear not to be importantly different among the four pediatric age groups. The body weight adjusted oral clearance of valsartan after administration of a single dose of an extemporaneous suspension formulation in the four pediatric age groups ranges between 0.06-0.09 L/h/kg. The body weight adjusted clearance in adults receiving the same formulation of valsartan is 0.06 L/h/kg and comparable. These results provide a rationale for using body weight adjusted dose of valsartan in children.

Comments

1. The plasma concentrations of valsartan should have been measured for more than 24 h after administration in order to determine true half-life of the terminal log linear disposition phase.

2. There is a typographical error in table 7-7: The arithmetic mean of the dose adjusted mean AUC0-∞ is given as 2700 ng●h/mL.
   There is typographical error in Table 1.1: The dose of valsartan was normalized for body weight not age.

4.5 Bioanalytical Cross-Check between a HPLC and a LC/MS/MS Method for the Analysis of Valsartan in Human Plasma

The objective of the study was to cross-validate the LC/MS/MS method developed for the measurement of valsartan in plasma with a previously reported HPLC method with [redacted] detection. Six spiked QC samples and 14 actual samples obtained after administration of a 160 mg valsartan tablet daily for 7 days under fasting conditions from study CVAS489A2303 were used. All spiked QC samples at each level had to be within 15% of the theoretical concentration.

The individual and mean accuracy of valsartan in the spiked samples and the results of the actual samples when measured by the HPLC [redacted] method and the LC-MS/MS assay are shown in the two tables below:

Table 10-1 Individual and mean accuracy of valsartan in spiked samples (QCS)

Analytical method	Date of analysis	Nominal concentrations (µg/mL) 0.0300	1.00	7.50	Mean accuracy (%)	CV %
HPLC	20-Sep-02	[redacted]			**97.0**	**6.1**
LC/MS/MS	27-Feb-02	[redacted]			**104**	**5.6**

Table 10-2 Valsartan concentrations of human plasma samples analyzed with HPLC and LC/MS/MS

The comparison of the two bioanalytical methods was performed with 16 values of valsartan concentrations in actual plasma samples.

Study CVAS489A2303		Time (h)	HPLC Ref.	LC/MS/MS Test	Diff. Test-Ref.	% Diff.	Test/ref
SUBJECT 5112/A	Day 5	0	[redacted]				
	Day 6	0					
	Day 7	0					
		0.25					
		0.5					
		1					
		2					
		3					
		4					
		6					
		8					
		12					
		16					
		24					
N					14	14	14
Mean					0.10	7.6	1.08
SD					0.21	8.5	0.09
CV (%)							8.3

The data indicate that both assays exhibit the required accuracy in measuring the concentrations of the QC samples. The average % difference between LC (test) and HPLC (reference) in measuring the plasma concentrations of valsartan was 7.6 (8.5) %. The difference between the two methods with individual samples ranged between [redacted].

Conclusion

Plasma concentrations of valsartan measured by the HPLC and LC/MS/MS methods are comparable.

Comment

None

4.6. Publication Yamashiro W, Maeda K, Hirouchi M, Adachi Y, Hu Z, Sugiyama Y. Involvement of Transporters in the Hepatic Uptake and Biliary Excretion of Valsartan, a Selective Antagonist of the Angiotensin II AT1-Receptor, in Humans. Drug Metab Dispos 2006;34: 1247-1254

Valsartan is excreted in the bile. It is hydrophilic and has an anionic carboxyl group and could have difficulty in crossing plasma membranes. Therefore, anionic transporters could be involved in the hepatic transport of valsartan. OATP is involved in hepatic uptake and MDR1, MRP2 and BCRP are involved in hepatic efflux of organic anions.

This in vitro study examined the involvement and relative contribution of OATP1B1 and OATP1B3 to the hepatic uptake of valsartan using human cryopreserved hepatocytes and transporter expressing cells and identified the transporters responsible for the biliary excretion of valsartan using double transfectants and transporter expressing vesicles. The involvement of MRP2 in the pharmacokinetics of valsartan in vivo using Eisai hyperbilirubinenic (EHBR) rats, in which mrp2 is deficient was also investigated.

Materials and Methods

Materials and Methods

Materials. [^{3}H]Valsartan (80.9 Ci/mmol) and unlabeled valsartan were kindly donated by Novartis Pharma K.K. (Basel, Switzerland). [^{3}H]Estradiol-17β-glucuronide ($E_2$17βG) (45 Ci/mmol) and [^{3}H]estrone-3-sulfate (46 Ci/mmol) were purchased from PerkinElmer Life and Analytical Sciences (Boston, MA), and [^{3}H]cholecystokinin octapeptide (CCK-8) (77 Ci/mmol) was purchased from GE Healthcare Bio-Sciences (Buckinghamshire, UK). Unlabeled $E_2$17βG, estrone-3-sulfate, and CCK-8 were purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals were of analytical grade and commercially available.

Cell Culture. Transporter-expressing or vector-transfected HEK293 cells and MDCKII cells were grown in Dulbecco's modified Eagle's medium low glucose (Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum (Sigma, St. Louis, MO), 100 U/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml amphotericin B at 37°C with 5% CO_2 and 95% humidity. LLC-PK1 cells were cultured in Medium 199 (Invitrogen) supplemented with 10% fetal bovine serum (Sigma), 100 U/ml penicillin, and 100 μg/ml streptomycin.

Transport Study Using Human Cryopreserved Hepatocytes. This experiment was performed as described previously (Hirano et al., 2004). Cryopreserved human hepatocytes were purchased from In Vitro Technologies (Baltimore, MD) (lot 094 and OCF) and from the Research Institute for Liver Disease (Shanghai, China) (lot 03-013). Immediately before the study, the hepatocytes (1-ml suspension) were thawed at 37°C, then quickly suspended in 10 ml of ice-cold Krebs-Henseleit buffer and centrifuged (50*g*) for 2 min at 4°C, followed by removal of the supernatant. This procedure was repeated once more to remove cryopreservation buffer, and then the cells were resuspended in the same buffer to give a cell density of 1.0×10^6 viable cells/ml for the uptake study. The number of viable cells was determined by trypan blue staining. Before the uptake studies, the cell suspensions were prewarmed in an incubator at 37°C for 3 min. The uptake studies were initiated by adding an equal volume of buffer containing labeled and unlabeled substrates to the cell suspension. After incubation at 37°C for 0.5, 2, or 5 min, the reaction was terminated by separating the cells from the substrate solution. For this purpose, an aliquot of 80-μl incubation mixture was collected and placed in a centrifuge tube (450 μl) containing 50 μl of 2 N NaOH under a layer of 100 μl of oil (density, 1.015; a mixture of silicone oil and mineral oil; Sigma-Aldrich), and subsequently, the sample tube was centrifuged for 10 s using a tabletop centrifuge (10,000*g*; Beckman Microfuge E; Beckman Coulter, Inc.). During this process, hepatocytes passed through the oil layer into the alkaline solution. After an overnight incubation in alkali to dissolve the hepatocytes, the centrifuge tube was cut and each compartment was transferred to a scintillation vial. The compartment containing the dissolved cells was neutralized with 50 μl of 2 N HCl and mixed with scintillation cocktail, and the radioactivity was measured in a liquid scintillation counter.

Transcellular Transport Study Using Double Transfected Cells. The protocol has been described in detail previously (Matsushima et al., 2005). In brief, transfected MDCKII cells were seeded in a Transwell membrane insert (6.5-mm diameter, 0.4-μm pore size; Corning Costar, Cambridge, MA) at a density of 1.4×10^5 cells per well 96 h before the transport study. Among a series of cell lines we used in this experiment, human MDR1, MRP2, and OATP1B1 were stably transfected into MDCKII cells as shown previously (Evers et al., 1998; Matsushima et al., 2005). Human BCRP cDNA was transduced into MDCKII cells by the infection of recombinant adenovirus 48 h before the transport study. The cell culture medium was replaced with culture medium supplemented with 5 mM sodium butyrate 24 h before the transport assay. For uptake studies, cells were washed three times and preincubated with Krebs-Henseleit buffer. The experiment was initiated by replacing the medium at either the apical or the basal side of the cell layer with complete medium containing ^{3}H-labeled and unlabeled valsartan or $E_2$17βG (0.1 μM). The cells were incubated at 37°C and aliquots of medium were taken from each compartment at several time points. Radioactivity in 100 μl of medium was measured in a liquid scintillation counter after addition of 2 ml of scintillation

fluid. At the end of the experiments, the cells were washed three times with 1.5 ml of ice-cold Krebs-Henseleit buffer and solubilized in 500 μl of 0.2 N NaOH. After addition of 100 μl of 1 N HCl, 400-μl aliquots were transferred to scintillation vials. Then, 50-μl aliquots of cell lysate were used to determine protein concentrations by the method of Lowry et al. (1951) with bovine serum albumin as a standard.

Vesicle Transport Assay. The preparation procedure of the membrane vesicles expressing human MRP2 was described previously (Hirouchi et al., 2004). The transport medium (10 mM Tris, 250 mM sucrose, and 10 mM $MgCl_2$, pH 7.4) contained the labeled and unlabeled valsartan, 5 mM ATP, and an ATP-regenerating system (10 mM creatine phosphate and 100 μg/μl creatine phosphokinase). An aliquot of transport medium (15 μl) was mixed rapidly with the vesicle suspension (5 μg of protein in 5 μl). The transport reaction was stopped by the addition of 1 ml of ice-cold buffer containing 250 mM sucrose, 0.1 M NaCl, and 10 mM Tris-HCl buffer (pH 7.4). The stopped reaction mixture was passed through a 0.45-μm HA filter (Millipore Corp., Billerica, MA) and then washed twice with 5 ml of stop solution. The radioactivity retained on the filter was measured in a liquid scintillation counter after the addition of scintillation cocktail. Ligand uptake was normalized in terms of the amount of membrane protein.

In Vivo Pharmacokinetic Study. Male Sprague-Dawley (SD) rats and EHBRs (7–8 weeks old) were purchased from Nippon SLC (Shizuoka, Japan). All animals were maintained under standard conditions with a reverse dark-light cycle and were treated humanely. Food and water were available ad libitum. This study was carried out in accordance with the guidelines provided by the Institutional Animal Care Committee (Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan). SD rats and EHBRs were anesthetized by inhalation of diethyl ether. The abdomen was opened with a midline incision and the common bile duct was cannulated with a polyethylene tube (Becton Dickinson Primary Care Diagnostics, Sparks, MD). The phosphate-buffered saline containing [^{3}H]valsartan (8 μCi/ml) and unlabeled valsartan (1 mg/ml) was injected into a femoral vein (1 ml/kg body weight). Blood samples were collected from a femoral artery and bile samples were collected in preweighed tubes at designated times. The total radioactivity in plasma and bile samples was measured in a liquid scintillation counter.

Kinetic Analyses of Uptake Transporters. Ligand uptake was expressed as the uptake volume [μl/mg protein], given as the amount of radioactivity associated with the cells [dpm/mg protein] divided by its concentration in the incubation medium [dpm/μl]. Specific uptake was obtained by subtracting the uptake into vector-transfected cells from the uptake into cDNA-transfected cells. Kinetic parameters were obtained using the following equation:

$$v = \frac{V_{max} \cdot S}{K_m + S} + P_{dif} \cdot S \quad (1)$$

where v is the uptake velocity of the substrate (pmol/min/mg protein), S is the substrate concentration in the medium (μM), K_m is the Michaelis constant (μM), V_{max} is the maximum uptake rate (pmol/min/mg protein), and P_{dif} is the nonsaturable uptake clearance (μl/min/mg protein). Fitting was performed by the nonlinear least-squares method using a MULTI program (Yamaoka et al., 1981), and the Damping Gauss-Newton Method algorithm was used for curve fitting. The input data were weighted as the reciprocal of the observed values.

To determine the saturable hepatic uptake clearance in human hepatocytes, we first determined the hepatic uptake clearance ($CL_{(2\ min-0.5\ min)}$) (μl/min/10^6 cells) by calculating the slope of the uptake volume (V_d) (μl/10^6 cells) between 0.5 and 2 min (eq. 2). The saturable component of the hepatic uptake clearance (CL_{hep}) was determined by subtracting $CL_{(2\ min-0.5\ min)}$ in the presence of 100 μM substrate (excess) from that in the presence of 1 μM substrate (tracer quantity) (eq. 3).

$$CL_{(2\ min-0.5\ min)} = \frac{V_{d,2\ min} - V_{d,0.5\ min}}{2 - 0.5} \quad (2)$$

$$CL_{hep} = CL_{(2\ min-0.5\ min),tracer} - CL_{(2\ min-0.5\ min),excess} \quad (3)$$

where $CL_{(2\ min-0.5\ min),\ tracer}$ and $CL_{(2\ min-0.5\ min),\ excess}$ represent the $CL_{(2\ min-0.5\ min)}$ values estimated in the presence of 1 and 100 μM substrate, respectively.

Estimation of the Relative Contribution of Each Transporter to the Hepatic Uptake. This method for estimating the contribution of OATP1B1 and OATP1B3 to the overall hepatic uptake has been used previously (Hirano et al., 2004). In this analysis, estrone-3-sulfate and CCK-8 were chosen as transporter-selective substrates of OATP1B1 and OATP1B3, respectively. The ratio of the uptake clearance of the reference compounds in human hepatocytes to that in the expression system was calculated and defined as $R_{act,\ OATP1B1}$ and $R_{act,\ OATP1B3}$. The uptake clearance mediated by OATP1B1 and OATP1B3 in human hepatocytes was separately calculated by multiplying the uptake clearance of valsartan in transporter-expressing cells ($CL_{OATP1B1,\ test}$ and $CL_{OATP1B3,\ test}$) by $R_{act,\ OATP1B1}$ and $R_{act,\ OATP1B3}$, respectively, as described in the following equations:

$$R_{act,OATP1B1} = \frac{CL_{Hep,E_3S}}{CL_{OATP1B1,E_3S}} \quad (4)$$

$$R_{act,OATP1B3} = \frac{CL_{Hep,CCK\text{-}8}}{CL_{OATP1B3,CCK\text{-}8}} \quad (5)$$

$$CL_{hep,test,OATP1B1} = CL_{OATP1B1,test} \cdot R_{act,OATP1B1} \quad (6)$$

$$CL_{hep,test,OATP1B3} = CL_{OATP1B3,test} \cdot R_{act,OATP1B3} \quad (7)$$

Kinetic Analyses of Efflux Transporters. The basal-to-apical transcellular clearance (CL_{trans}) was calculated by dividing the steady-state efflux velocity for the transcellular transport (V_{apical}) by the ligand concentration in the incubation buffer on the basal side, whereas the efflux clearance across the apical membrane (PS_{apical}) in double transfected cells was obtained by dividing V_{apical} by the intracellular concentration of ligand at 120 min. In the vesicle transport assay, ATP-dependent transporter-specific uptake was calculated by subtracting the uptake in the presence of AMP from that in the presence of ATP. The saturation kinetics of CL_{trans}, PS_{apical}, and ATP-dependent uptake into vesicles were calculated using eq. 1 by the curve-fitting procedure described above.

Pharmacokinetic Analysis. The plasma concentration-time profile was fitted to a biexponential equation and the $AUC_{0-\infty}$ was estimated by integration up to infinity. The initial distribution volume (V_1) was calculated by dividing the dose by the initial plasma concentration estimated from the fitted biexponential equation. The plasma clearance (CL_p) was calculated as Dose/$AUC_{0-\infty}$. The biliary clearance (CL_{bile}) was calculated as the ratio of the cumulative excreted amount in bile over 120 min to the AUC over 120 min ($AUC_{0-120\ min}$).

Results

Uptake of Valsartan by OATP Transporter Expressing Cells

Valsartan is significantly taken up by OATP1B1 and OATP1B3 expressing HEK 293 cells compared with vector transfected cells as shown in the below Figure 1:

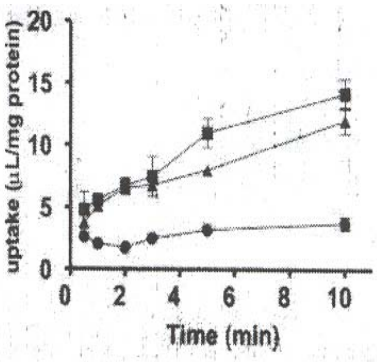


FIG. 1. Time profiles of the uptake of valsartan by OATP1B1- and OATP1B3-expressing HEK293 cells. Squares, triangles, and circles represent the uptake in OATP1B1- and OATP1B3-expressing cells and vector-control cells, respectively. Each point represents the mean ± S.E. (n = 3).

The process is time-dependent. The saturation kinetics of the valsartan uptake by OATP1B1 and OATP1B3-expressing cells and vector-transfected cells was evaluated for 5 min, over which time the uptake of valsartan remained linear. The Eadie-Hofstee plots are shown by Figure 2 and the kinetic parameters in Table 1:

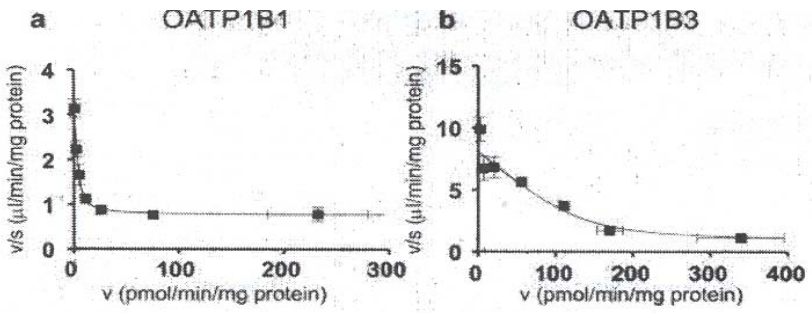


FIG. 2. Eadie-Hofstee plots of the uptake of valsartan by OATP1B1- and OATP1B3-expressing HEK293 cells. The concentration dependence of OATP1B1 (a)- and OATP1B3 (b)-mediated uptake of valsartan is shown as Eadie-Hofstee plots. The uptake of valsartan for 5 min was determined at various concentrations (0.1–300 μM). Each point represents the mean ± S.E. (n = 3).

TABLE 1

Kinetic parameters of the uptake of valsartan by OATP1B1- and OATP1B3-expressing HEK293 cells

Data shown in Fig. 2 were used to determine these parameters calculated by nonlinear regression analysis as described under *Materials and Methods*. Each parameter represents the mean ± computer-calculated S.D.

	K_m	V_{max}	P_{dif}
	µM	*pmol/min/mg protein*	*ml/min/mg protein*
OATP1B1	1.39 ± 0.24	3.85 ± 0.46	0.747 ± 0.022
OATP1B3	18.2 ± 5.9	135 ± 40	0.680 ± 0.223

There was not significant transport of valsartan by OATP2B1.

Uptake of Estrone-3 Sulfate, CCK-8, and Valsartan in Human Cryopreserved Hepatocytes

The uptake of Estrone-3-sulfate (E1S) a substrate of OATPB1B1, CCK-8, a substrate of OATP1B3 and valsartan by human hepatocytes is shown in Figure 3:

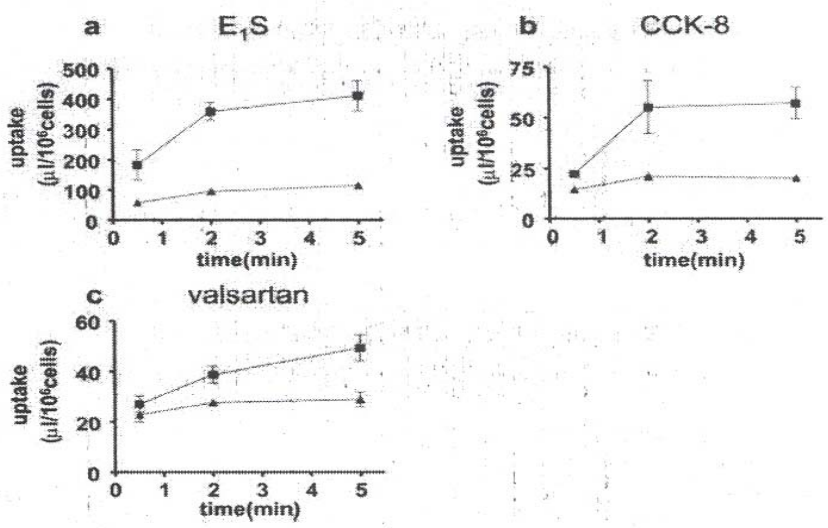


FIG. 3. Typical time profiles of the uptake of estrone-3-sulfate, CCK-8, and valsartan by human hepatocytes (lot OCF). The uptake of estrone-3-sulfate (a), CCK-8 (b), and valsartan (c) for 0.5, 2, and 5 min was determined at two concentrations (squares, 1 μM; triangles, 100 μM) at 37°C. Each point represents the mean ± S.E. (n = 3).

The uptake clearance of E1S, CCK-8 and valsartan are listed in Table 2 and the relative contributions of OATP1B1 and OATP1B3 in different batches of hepatocytes is shown in Table 3:

TABLE 2

Uptake clearance of reference compounds (E_1S and CCK-8) and valsartan in expression systems and human hepatocytes

	Transporter-Expressing Cells		Human Hepatocytes		
	$CL_{OATP1B1}$	$CL_{OATP1B3}$	OCF	094	03-013
	µl/min/mg protein		*µl/min/10^6 cells*		
E_1S	84.6		93.0	98.7	45.2
CCK-8		10.3	17.7	71.6	3.65
valsartan	1.56	0.96	3.55	17.1	6.15

TABLE 3

Contribution of OATP1B1 and OATP1B3 to the hepatic uptake of valsartan in each batch of human hepatocytes

In the column 'Estimated Clearance of Valsartan,' the lower row shows the percentage of OATP1B1- or OATP1B3-mediated uptake clearance relative to the sum of the estimated clearance mediated by OATP1B1 and OATP1B3. The details of this estimation are described under *Materials and Methods*.

Lot	Ratio of Uptake Clearance $CL_{-hep}/CL_{-transporter}$		Estimated Clearance of Valsartan	
	$R_{act,OATP1B1}$	$R_{act,OATP1B3}$	OATP1B1	OATP1B3
			µl/min/10^6 cells	
OCF	1.10	1.72	1.72	1.65
			51.0%	49.0%
094	1.17	6.95	1.83	6.67
			21.5%	78.5%
03–013	0.53	0.35	0.827	0.336
			71.1%	28.9%

Valsartan is less avidly taken up by OATP1B1 than E1S and also less avidly taken up by OAT1B3 than CKK-8. The results for valsartan vary dependent on the batch of hepatocytes used. The relative contribution of the uptake of valsartan by OATP1B1 and OATP1B3 varies also dependent on the batch of hepatocytes used.

Transcellular Transport of Valsartan across MDCKII Monolayers

The MDCKII monolayers express uptake and efflux transporters. No significant vectorial transport of valsartan was observed in single transfected cells expressing OATP1B1, MDR1, MRP2 and BCRP, and vector transfected control cells. However as shown in Figure 5 below the basal to apical transcellular transport of valsartan in OATP1B1/MRP2 double transfected cells is largest among the doubled transfected cells expressing OATP1B1/MRP2, OATP1B1/MDR1, and OATP1B1/BCRP:

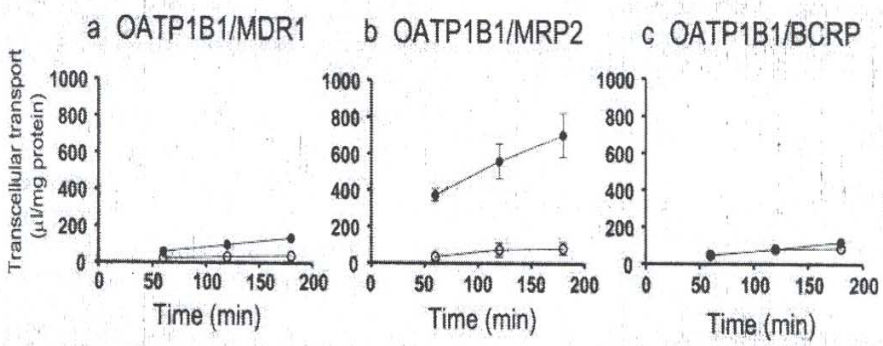


FIG. 5. Time profiles of the transcellular transport of valsartan across MDCKII monolayers expressing transporters. Transcellular transport of valsartan (0.1 μM) across MDCKII monolayers expressing OATP1B1/MDR1 (a), OATP1B1/MRP2 (b), and OATP1B1/BCRP (c) was observed. Open circles and closed circles represent the transcellular transport in the apical-to-basal and basal-to-apical directions, respectively. Each point represents the mean ± S.E. (n = 3).

The basal to apical transport of the control E2-17βG was 36, 8.9 and 6.1 time greater than that in the opposite direction.

ATP dependent Uptake of Valsartan in Human MRP2 Expressing Membrane Vesicles

To confirm that valsartan is a substrate of MRP2, the time dependent uptake of valsartan membrane vesicles prepared from MRP2-expressing LLC-PK1 cells was examined. As shown by Figure 7 valsartan is significantly and ATP dependently taken up into the membrane vesicles:

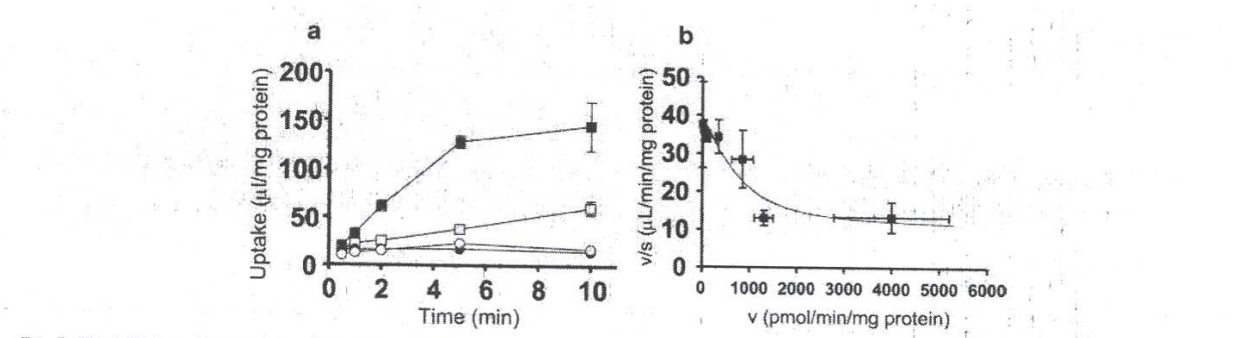


FIG. 7. The ATP-dependent transport of valsartan in MRP2-expressing LLC-PK1 cells. Time profiles for the uptake of valsartan were measured in isolated membrane vesicles prepared from LLC-PK1 cells expressing MRP2 (a). Membrane vesicles were incubated at 37°C with valsartan (0.1 μM) in the medium in the presence of ATP (closed symbols) or AMP (open symbols) for designated periods (0.5, 1, 2, 5, or 10 min). Squares and circles represent the uptake of membrane vesicles expressing MRP2 and control vesicles infected only with adenovirus containing tetracycline-responsive transcriptional activator, respectively. The concentration dependence of MRP2-mediated uptake of valsartan is shown as Eadie-Hofstee plots (b). The uptake of valsartan for 2 min was determined at various concentrations (0.3–300 μM). Each point represents the mean ± S.E. (n = 3).

The process is saturable.

Pharmacokinetics of Valsartan in Sprague-Dawley and EHBR Rats

The plasma concentrations of valsartan in the EHBR rats were significantly larger than in normal rats as shown in Figure 8a:

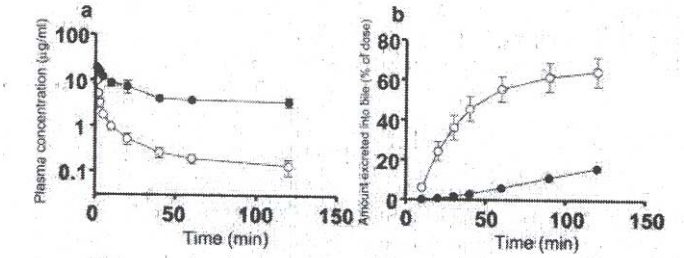


FIG. 8. Biliary elimination of valsartan in male SD rats and EHBRs. Rats were injected with valsartan (1 mg/kg body weight dissolved in phosphate-buffered saline) into a femoral vein after cannulation of the bile duct. The time profiles of the plasma concentration (a) and cumulative biliary excretion (b) of valsartan in SD rats (open circles) and EHBRs (closed circles) are shown. Each point represents the mean ± S.E. (n = 3).

Two hours after administration 70% of the total radioactivity injected was excreted into the bile in normal rats whereas only 15% was excreted by the EHBR rats. The AUC in EHBR rats was 17 times greater than in normal rats.

Conclusion

The data of the in vitro study suggest that valsartan is a substrate of OATP1B1 and OATP1B3 and MRP2. The in vivo study in EHBR rats deficient in mrp2 indicates that valsartan is a substrate of mrp2. The relevance of this finding is that drug interactions of valsartan and inhibitors of OATP including cyclosporine, rifampicin and other drugs could occur under clinical conditions. This potential liability should be noted in the labeling of valsartan.

Comments

1. mrp2 in rats and MRP2 in humans may not be orthologous.

5. BIOPHARMACEUTICS

Of the three tested clinical service formulations, the oral extemporaneous suspension and the pediatric 10 mg and 80 mg tablets, only the oral suspension is proposed for marketing in children in the age of 2- < 6 years old and adults who cannot swallow the tablet.

5.1. Valsartan 4 mg/mL Extemporaneous Suspension

Preparation and Composition of 4 mg/mL Oral Suspension of Valsartan

The commercially available Diovan 80 mg film coated tablets were used for the extemporaneous preparation of the oral suspension. The diluents used for the 4 mg/mL suspension are Ora-Plus oral suspending vehicle and Ora-Sweet SF oral syrup vehicle. These are commercially available vehicles from Paddock Laboratories, Inc., and contain compendial components. The composition of the Diovan® oral suspension is shown in the below table:

Table 2-1 Representative composition of Diovan 4 mg/mL suspension

Component	Quality
Diovan 80 mg tablets	8 tablets (640 mg of valsartan)
Ora-Plus oral suspending vehicle	80 mL
Ora-Sweet SF oral suspending vehicle	80 mL
Total volume of suspension	160 mL

The extemporaneous preparation of the 640 mg/160 mL (4mg/mL) suspension is as follows: 80 mL of Ora-Plus are added to the dispensing bottle containing eight 80 mg Diovan tablets. After shaking for at least 2 minutes, the suspension is allowed to stand for a minimum of one hour. Subsequently, the suspension is shaken for an additional one minute. Eighty (80) mL of Ora-Sweet SF is added to the bottle and the suspension is shaken for 10 seconds to disperse the ingredients.

6. REVIEW OF SPONSOR'S RESPONSES TO REVIEWER'S COMMENTS Submitted September 20, 2007

FDA Comment 1: Failure to consider impact of difference in relative bioavailability among pediatric clinical service formulations used in the clinical trials. Cmax (1.8 times) and AUC (1.4 times) were greater with the extemporaneous suspension administered to

children < 6 years of age than with the clinical service formulations administered to children ≥6 years of age.
Sponsor's Response: The sponsor's response does not address FDA Comment 1.

FDA Comment 2: Label does not consider impact of difference in relative bioavailability between the extemporaneous suspension and the commercial adult 40, 80 and 160 mg tablets (Cmax (1.9 times) and AUC (1.6 times) greater with the suspension than with the commercial adult tablets. The label does not state that the dose of the adult tablets should be increased by a factor of 1.6 to 1.9 when in a pre-school age child the extemporaneous suspension is changed to an adult tablet.

Sponsor's Response: The sponsor proposes to add the following statement to the CLINICAL PHARMACOLOGY section of the label: "The exposure (measured as AUC) of valsartan with the suspension formulation is 56% higher when compared to the tablet formulation in normal healthy adult volunteers." This Reviewer proposes that the label should state that "When the extemporaneous suspension is replaced by a tablet in a child the dose may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablets. "

FDA Comment 3: Failure to include in the label results from a published study (Yamashiro et al. 2006) showing evidence for valsartan to be a substrate of OATP and MRP2. Valsartan may be susceptible to interactions when co-administered with OATP inhibitors (e.g. rifampin, cyclosporine) or drugs interfering with the activity of MRP2 (e.g. ritonavir or probenecid).
Sponsor's Response: The sponsor believes that a label change is not required based on the following rationale:

- The absolute oral bioavailability of valsartan administered as solution is about 40%. The first-pass hepatic clearance is low and is lower than the hepatic blood flow.
- The mean estimated Km values observed in vitro studies are about 1.4, 18.2 and 27.5 µM with OATP1B1, 1B3 and MRP2, respectively, which are significantly higher than the free plasma concentrations of valsartan that are generally achieved with the maximum clinical dose of 320 mg about 1 µM.
- It has been shown that valsartan exhibits dose proportional and dose linear pharmacokinetics in the available clinical doses (20 to 320 mg) [CTD 2.7.1, VALIANT NDA 21-283, S-011].
- Pharmacokinetic drug interaction studies involving digoxin (OATP1B3 substrate) and simvastatin (OATP substrate) have shown that pharmacokinetics of valsartan were not affected to a significant extent [Protocol 39 (digoxin)*; Sunkara et al, 2007 (simvastatin)**]. *: this report was submitted with original NDA 20-665 submission of valsartan; ** Sunkara et al, 2007- Evaluation of a pharmacokinetic interaction between valsartan and simvastatin in healthy subjects, Curr Med Res Opin. 2007 Mar;23(3):631-40.
- Valsartan has been shown to be safe and effective in post-transplant patients who were on cyclosporine (Andres et al., 2006*). Cyclosporine is an inhibitor of MRP2 and OATPB1. *Efficacy and safety of valsartan, an angiotensin II receptor antagonist, in hypertension after renal transplantation: a randomized multicenter study, Transplant Proc. 2006 Oct;38(8):2419-23
- The current label of valsartan (Diovan) indicates that no dose adjustments are required with mild to moderate hepatic failure.

Among these arguments the most relevant is that valsartan was found to be safe and effective in patients who were on cyclosporine (Andres et al. submitted earlier).

This Reviewer believes that the findings by Yamashiro et al. should be mentioned in the labeling. The study by Andres et al. did not measure exposure to valsartan in the presence of cyclosporine. Even if cyclosporine were found not to increase exposure to valsartan extrapolations from one inhibitor to another should not be made. There is not enough experience with inhibitors of transporters.

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/s/

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11/20/2007 08:39:17 AM
BIOPHARMACEUTICS

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