EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report for DIOVAN and associated names

International Non-proprietary Name: Valsartan

Procedure No. EMEA/H/A-29 PAD/1220

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 29 of Regulation (EC) No 1901/2006, as amended, and Annex II (point 2 iv) of Regulation 1084/2003, Novartis Pharma AG submitted to the EMEA on 20 August 2009 an application for a new pharmaceutical form associated with a new strength for the above mentioned medicinal product.

The application concerns oral solution 3 mg/ml.

Licensing status:
Diovan and associated names are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom as well as in Iceland and Norway.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Alan Irs Co-Rapporteur: Liv Mathiesen

Pursuant to Article 8 of Regulation (EC) No 1901/2006 as amended, the application included an EMEA Decision (P/125/2009) for the following conditions:

- On the agreement of a Paediatric Investigation Plan (PIP) for hypertension
- On the granting of a waiver for heart failure and heart failure following recent myocardial infarction

The PIP is completed. The PDCO issued an Opinion on compliance.

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 20 August 2009.
- The procedure started on 25 August 2009.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 14 September 2009 . The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 14 September 2009.
- During the meeting on 24 September 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 November 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 November 2009.
- During the meeting on 15 December 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion recommending the granting of the Marketing Authorisations for Diovan and associated names, oral solution. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2009.

2. Scientific discussion

2.1. Introduction

Hypertension in children is defined as a persistent systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥ 95th percentile for age, gender, and height. Obesity, insulin resistance, inactivity, ethnic predisposition to essential hypertension, and family history of hypertension are the common causes of hypertension in older children and adolescents. However, in children younger than 10 years of age, secondary causes of hypertension, including renal and reno-vascular disease, are more commonly observed. Current epidemiologic data indicate that the prevalence of persistent hypertension in school-age children or above is approximately 1-2 percent, and in younger age

children (< 6 years old) is extremely low (0.017%). Most children found to be hypertensive in the < 6 year old age group present with severe, symptomatic hypertension due to underlying diseases (secondary hypertension). These patients often require pharmacological therapy to control blood pressure controlled. There is a paucity of data regarding the efficacy and pharmacokinetics of antihypertensive drugs in children. Antihypertensive medications have been extensively studied in adults, and most of them have been used commonly in hypertensive children, though few of them had been studied systematically in children until recently.

Valsartan (Diovan) is an angiotensin II receptor blocker (ARB), approved in adults for the treatment of hypertension. It has been marketed in Europe in adults in doses of 80-160 mg since 1996 and in the highest dose of 320 mg since 2006. In the United States and other countries, valsartan 320 mg has been available for use in adults since 2001.

Valsartan has been approved and marketed for the treatment of hypertension in children 6-17 years of age in the United States since 2007. Valsartan has also been approved for the treatment of heart failure and treatment of recent myocardial infarction in adults in many countries worldwide.

Valsartan exerts its antihypertensive effect mainly by blocking the vasoconstriction, aldosterone secretion and sodium retention mediated by angiotensin II via selectively blocking the binding of angiotensin II to the AT1 receptor in tissues such as vascular smooth muscle and the adrenal gland. Valsartan has been shown to be effective in reducing both systolic and diastolic blood pressure in adults when used as monotherapy or in combination with other antihypertensive agents and is relatively well-tolerated.

2.2. Quality aspects

Introduction

Diovan – and associated names – oral solution contains 3 mg/ml of valsartan as active substance. Other ingredients in the oral solution formulation are: sucrose, methyl parahydroxybenzoate (E218), potassium sorbate, poloxamer (188), citric acid, anhydrous, sodium citrate, artificial blueberry flavour (538926 C), propylene glycol (E1520), sodium hydroxide, hydrochloric acid and purified water.

The oral solution is packed in amber glass bottle (type III) with a child-resistant screw-cap and a yellow tamper evident ring. An oral dosing syringe and a bottle adapter are included in the secondary packaging.

Drug Substance

Valsartan is a well known drug substance. Full documentation for the drug substance has been submitted. The applicant states that the valsartan drug substance used in the 3 mg/ml oral solution is identical to the drug substance used for the registered Diovan 40 mg, 80 mg, 160 mg and 320 mg film coated tablets.

Valsartan which has the chemical name (S)-2-{*N*-(1-oxopentyl)-*N*-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid is a is a white to practically white fine powder. It is practically insoluble in water and freely soluble in ethanol and methanol.

Polymorphic forms have not been encountered for valsartan. There is one chiral center in the valine moiety of the molecule. Valsartan is essentially the pure (S)-enantiomer.

- Manufacture

The manufacturing route comprises four consecutive chemical steps and one auxiliary step for reagent preparation.
Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- Specification

The active substance specification includes tests for appearance, clarity of solution, identification (IR, HPLC), assay (HPLC), impurities (HPLC), enantiomer (HPLC), residual solvents (GC), water content (KF), sulphated ashes, heavy metals, and particle size.
The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.
Batch analysis data of a number of batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

The stability of valsartan was studied under normal and accelerated storage ICH conditions (25 °C/60% RH/36 months, 30 °C/60% RH/9 months, 40 °C/75% RH/6 months). Furthermore, studies were performed under stress conditions in solid state (heat, light) and in aqueous solution/suspension (heat, varying pH). The active substance was stored in the proposed commercial container/closure system.
Results from accelerated long-term and stress storage conditions, show that valsartan is a very stable substance.

Drug Product

- Pharmaceutical Development

The aim of the formulation development was to produce an industrially prepared, formulation targeted for 6 months to 5 years old patients. The preference was to develop a liquid preparation for oral use allowing individual dosing by volumetric measures.

The formulation has initially been developed for age group of 6 months to 5 years old; ultimately, the clinical development program covered the paediatric subsets from 1 to 18 year old and no clear dose response, nor efficacy, could be established from the clinical data in the younger age group below 6 years. Development of an oral solution was continued to provide a dosage form for young patients with difficulties in swallowing tablets.

In early development different formulations were investigated. The oral solution formulation for multidose use was found to be an acceptable formulation balancing age-appropriateness, pharmaceutical characteristics and stability of the drug product.

For the choice of excipients, special consideration was made with regard to the paediatric use of the dosage form. The chosen excipients were sucrose (sweetener), methyl parahydroxybenzoate (E218) (preservative), potassium sorbate (preservative), poloxamer (188) (solubilizing agent), citric acid, anhydrous (pH buffering agent), sodium citrate (pH buffering agent), artificial blueberry flavour (538926 C) (flavoring agent), propylene glycol (E1520), sodium hydroxide and hydrochloric acid (pH adjustment) and purified water.

All of the excipients in the capsule filling solution except blueberry flavour are compendial excipients controlled according to the current monograph in the Ph.Eur. The blueberry flavour 538926 C is commercially available and consists of propylene glycol and various flavouring ingredients.

For this multidose formulation, the preservative system of methyl parahydroxybenzoate and potassium sorbate was chosen. The concentrations are within normally used amounts, and they were decided based on studies on antimicrobial efficacy at different concentration levels at worst case pH, and was found to secure the antimicrobial preservatives efficacy according to the Ph.Eur. 5.1.3. The amount of methyl parahydroxybenzoate included is within the Acceptable Daily Intake (ADI) of 10 mg/kg for the sum of methyl and ethyl esters of 4–hydroxybenzoic acid and their sodium salts according to the European Commission, Scientific Committee on Consumer Products (SCCP) (2005) "Extended opinion on the safety evaluation of parabens").

To optimise the drug product stability and the antimicrobial efficacy of the preservatives it was found necessary to buffer the solution to maintain the desired pH.

The usage of a flavouring agent (along with a sweetener) is justified by the slightly bitter and metallic taste of valsartan. Sucrose was selected as the sweetener for the oral solution based on its wide use in pharmaceutical products.

The container closure system proposed for the drug product consists of a standard amber type III glass bottle closed with a child resistant polypropylene screw cap, including a polyethylene sealing disk and a yellow tamper evident ring. Compatibility of the primary packaging materials with the product solution is documented through the ongoing stability studies. The solution is to be dispensed with a 5 ml polypropylene oral dosing syringe and a bottle adapter, which are included in the secondary packaging. The functionality of the administration device has been tested with regard to insertion of the bottle adaptor into the bottle, insertion of the syringe into the bottle adapter and usage of the syringe. The dosing accuracy has been demonstrated by compliance with Ph.Eur. 2.9.27 Uniformity of mass of delivered doses from multi-dose containers. Compatibility with drug product was found acceptable based on results of a study where the syringe and bottle adapter components were soaked into the product solution followed by analyses of assay valsartan and preservatives and unknown peaks.

- Manufacture of the Product

The manufacturing process for the drug product consists of the main steps of ingredient dissolution, pH adjustment, adjustment to final volume, filtration and filling.

The manufacturing process has been adequately validated by a number of studies for the major steps of the manufacturing process in three consecutive commercial batches.
The batch analysis data show that the oral solution can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The specification includes tests by validated methods for appearance (container and solution), identity (HPLC, TLC), pH value, deliverable volume, degradation products (HPLC), microbial enumeration (Ph Eur), and assay (HPLC).

The tests and limits of the release and shelf life specifications for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.
The batch analysis results show that the finished product can be manufactured reproducibly in accordance with the finished product specifications.

- Stability of the Product

In general the stability studies have been carried out in accordance with the ICH requirements; the only exception is the intermediate conditions: instead of the ICH recommended 30°C/65%RH, the applicant used 30°C/75% RH. The stability studies on the three pilot scale batches cover 9 months at the long term and intermediate conditions and 6 months at accelerated conditions. The in use stability of the product has also investigated. Based on the photostability results the drug product can be considered photostable.

The proposed shelf life for the unopened and in use product is acceptable, however the results of the ongoing stability studies of the closed bottles should be provided. The proposed storage conditions are acceptable at the present; however, the temperature restriction should be revised based on the further results stability investigations.

Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant provided a Letter of Undertaking and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

2.3. Non-clinical aspects

The non-clinical dossier comprises of six reports (two sub-acute toxicity studies in neonatal/juvenile animals, and four pharmacokinetic studies) from recently performed studies considered relevant for the paediatric indication, and an Environmental Risk Assessment. The previously submitted studies are adequately addressed in the non-clinical overview, and this overview will therefore mainly address the submitted original studies that were performed to support a paediatric indication.

Pharmacokinetics

In mice, rats, and marmosets valsartan was rapidly absorbed. In dogs absorption was slow. The absolute oral bioavailability of valsartan was variably high in mice, rats and dogs (10-73% of dose) and low (< 10%) in marmosets. Exposure to valsartan increased dose-dependently and partly dose-proportionally. There was no unexpected accumulation in blood or plasma following daily oral treatment.

Valsartan is metabolized to a minor degree only. It is eliminated largely via biliary/fecal route. In human, it is suggested that the organic anion-transporting polypeptides OATP1B1 and OATP1B3 as uptake transporters and the multi-drug resistance-associated protein-2 (MRP2) as the efflux transporter are responsible for the efficient hepatobiliary transport of valsartan.

Valsartan did not inhibit CYP activities to any significant extent, and is very unlikely to alter the CYP-mediated metabolic clearance of co-medications. Conversely, CYP inhibitors or inducers are unlikely to alter the clearance of valsartan. The drug interaction potential of valsartan has been shown to be very low.

The site and the qualitative extent of the absorption of valsartan were investigated in the rat at neutral and acidic pH in order to support the development of a pH modified formulation of valsartan. After injection of 230 µM [14C]VAL489 at neutral pH (6.8), the highest average absorption was observed for duodenum (28.9%) followed by ileum (15.6%) and colon (14.9%). Under acidic conditions (pH 4.8), a trend for an increased absorption of [14C]VAL489 from each segment was observed with mean values of 33.6%, 23.1% and 21.4% for duodenum, ileum and colon, respectively. This is in accordance with what has been previously seen for valsartan. The pH levels tested in the study cover the pH range specified for the applied Diovan 3 mg/ml oral solution (pH 5.7-6.2).

Toxicology

The Applicant has performed subacute oral toxicity studies in neonatal and juvenile albino rats on *post partum* Days 7 to 34 at doses of 20 to 300 mg/kg/day, and on *post partum* Days 7 to 70 at doses of 1 to 150 mg/kg/day to support the paediatric indication in hypertension.

These studies have demonstrated irreversible renal toxicity at all valsartan dose levels (1-300 mg/kg/day in animals dosed from post partum day 7 to day 34 (study 0380101) or day 70 (study 0680270)), with a NOAEL < 1 mg/kg/day. Overall, although similar effects are observed in both juvenile and adult rats, existing data do indicate that young rats (up to post partum day 70) are more sensitive to adverse renal effects than adult rats.

In humans, functional and anatomical renal development occurs from gestation week 5. All nephronic units are formed within gestation week 36, while postnatal maturation and elongation of tubuli continues during first year of life. In rats, formation of nephronic units is completed by postnatal day 11, while tubular differentiation continues until weaning. Angiotensin converting enzyme (ACE) is related to anatomical development and functional maturation of the kidneys, and the use of ACE inhibitors and AIIR blockers is contraindicated in the second and third trimester of pregnancy due to a risk of fetal renal toxicity. According to Zoetis and Hurtt (2003, Birth Def Res (Part B), 68:111-120), treatment of newborn rats with ACE inhibitors for the first 12 postnatal days resulted in irreversible morphological changes, including few and immature glomeruli, tubular dilatation, abnomal arterioles and arrested maturation. When rats were treated with the ACE inhibitor enalapril on postnatal days 3-

13 (Guron et al 1999, J Am Soc Nephrol 10:1550-1560) or with the AIIR blocker losartan on postnatal days 3-21 (McCausland et al. 1997, Exp Nephrol 5(3):201-209), similar morphological and functional abnormalities were seen. In contrast, when treatment was initiated at postnatal day 14 (enalapril) or 21 (losartan), no morphological changes were observed. These data indicate that the rat is susceptible to angiotensin related altered renal morphology and function throughout the first two postnatal weeks, corresponding to the period of nephrogenesis, which in humans is completed within gestation week 36 (Matsusaka et al. 2002, Annu Rev Physiol 64:551-561).

The valsartan related renal findings in neonatal/juvenile rats included juxtaglomerular hypertrophy/hyperplasia, tubular nephropathy and pelvic dilatation, with non-existing margins of safety. Some of these findings appear to be class related effects on nephrogenesis. However, because the rats were dosed with valsartan up to postnatal day 34 in the dose range study, and up to postnatal day 70 in the pivotal study, one cannot exclude additional renal effects throughout the period of functional maturation, which in rats continues until postnatal week 4-6 (Zoetis and Hurtt 2003, Birth Def Res (Part B) 68:111-120). Although nephrogenesis in humans is completed within gestational week 36, functional maturation is an ongoing process within the first year of life. The indication sought for both formulations are children and adolescents ≥ 6 years of age, and the increased sensitivity in young, normotensive rats with immature renal system is likely not relevant to hypertensive children and adolescents ≥ 6 years of age. However, potential effects on functional maturation of the human renal system can not be excluded in children ≤ 1 year of age. This needs to be reflected in Section 5.3 of the SPC.

Toxicokinetic data for valsartan were evaluated in both repeat dose toxicity studies in neonatal/juvenile rats submitted in support of a paediatric indication in children. In both studies, all animals of all compound-related dose groups were systemically exposed to valsartan. There was no measurable concentration of valsartan from any sample in the control groups. In general, exposure levels increased in a dose-proportional manner after repeated dosing. No systematic difference between male and female rats was observed.

In the GLP compliant Study no 0680270, the exposure to valsartan was much higher in neonatal rats on postnatal day 7 than in adult rats on postnatal day 70 (range, 7- to 33-fold). Based on the mean dose-normalized AUC0-24h values, the exposure to valsartan decreased between Day 7 and Day 70 by a factor of 32-33 (male-female), 18-21 and 7-9 for the dose 1, 20 and 150 mg/kg/day, respectively. According to the applicant, the differences in exposure between the animals of Day 7 and Day 70 may be explained by the fact that the drug metabolizing enzymes in the liver of postnatal Day 7 animals are not yet fully expressed, and/or gastric permeability is greater at postnatal Day 7 in the developing animal when compared to adults (deZwart et al. 2004, Reg Toxicol Pharmacol 39:282-309).

The reduction in valsartan exposure on day 70 compared to day 7 is remarkable. It is known that the expression/activity of drug metabolising enzymes increases in both rats and humans after birth, but in view of the limited oxidative in vivo biotransformation of valsartan normally seen in rats; this does not seem like a plausible explanation. Increased absorption of valsartan in very young animals compared to adults is possible, but it is difficult to assess to what extent this may affect exposure levels.

The compiled data show that mean dose-normalized valsartan exposure in neonatal male and female rats 7 days after birth is much higher than in adult rats, across studies. Thus, methodological problems in the toxicokinetic part of Study 0680270 can be excluded.
Published literature data suggest a role for the organic aniontransporting polypeptides OATP1B1 and OATP1B3, and the multidrug resistance-associated protein-2 (MRP2) in the efficient hepatobiliary transport of valsartan (Yamashiro, et al 2006). Gradual postnatal expression and maturation of these transporters in rat liver, in addition to increased absorption of valsartan in very young animals, could contribute to the considerably higher valsartan exposure observed in neonatal rats, compared to adult rats (Gao, et al 2004) (deZwart, et al 2004).

The proposed Diovan 3 mg/ml oral solution contains methyl parahydroxybenzoate (methyl paraben). The proposed posology for Diovan is up to 80 mg valsartan administered as oral solution, corresponding to a daily intake adequately below the acceptable daily intake (ADI) level of 10 mg/kg for the sum of methyl and ethyl paraben and their sodium salts determined by the European Food safety Authority (EFSA Journal 83:1-26) and the Scientific Committee on Consumer Products (SCCP/0873/05, SCCP/1017/06).

An environmental risk assessment has been submitted in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). Based on a refined $PEC_{surface\ water}$ level = 1,053 µg/L, relevant PEC/PNEC ratios are well below accepted

risk ratios. Even if a $PEC_{surface\ water}$ level = 1.6 µg/L is anticipated (based on maximum daily dose and the formula in the CHMP guidance document) risk ratios would be satisfactory. Valsartan is not readily biodegradable, but base data does not suggest any potential for bioaccumulation, significant adsorption to sludge in sewage treatment plants, or significant shifting of the drug substance to the sediment. The use of valsartan as either tablets or solution does not appear to contribute to any significant environmental risk.

2.4. Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The development program consisted of five clinical pharmacology studies as provided below.

Table 1. Clinical pharmacology studies

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan
CVAL489 A2301-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.
CVAL489 A2304	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
CVAL489 J2308	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
CVAL489 A2305	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
CVAL489 K2101	Healthy volunteers 18 to 55 years of age	PK of valsartan pediatric FMI formulation (oral solution) vs. valsartan CSF extemporaneous suspension; safety and tolerability	86	Single-dose, valsartan pediatric FMI formulation (3 mg/mL oral solution) and valsartan CSF extemporaneous suspension (16 mg/mL oral suspension)

The proposed formulations for paediatric use are commercially available valsartan tablets and a new solution formulation to fulfil the requirements described in the PIP.

One study investigated the PK of valsartan in children aged 1 to 16 years. Following oral administration, valsartan exposure (C_{max} and AUC) normalized to a standard dose/body weight did not vary significantly with age 1-16 year range. The body weight-adjusted CL/F values were comparable across the 1-16 year old children and similar to those observed in adult subjects.

10 mg 80 mg clinical service form (CSF) tablets were developed exclusively for the use in efficacy studies. Two comparative bioavailability studies conducted with the new tablets and commercial tablets confirmed that the data collected from the efficacy studies could be abridged to the commercial tablets.

In phase II/III studies, in children ≤ 6 years of age valsartan was administered as an extemporaneous suspension. The bioavailability of valsartan from the extemporaneous suspension was 1.5-fold higher than that of the tablets. Hence, children ≤ 6 years of age received 1.5-fold higher dose than older children. The applicant has demonstrated that the data collected in this subgroup of children using the suspension could be abridged to the commercial tablets.

The bioavailability of valsartan from the Diovan 3 mg/ml oral solution (FMI) was compared with an extemporaneous suspension formulation (made from 160 mg commercial tablets) used in the efficacy and safety studies. Study results indicated that the mean Cmax of valsartan was 32% higher (90%CI 1.27¸ 1.38) with the solution formulation comparing to that of the extemporaneous suspension formulation, whereas the extent of absorption (AUC) of valsartan was equivalent (90%CI 1.05; 1.13).

One study was conducted to compare valsartan bioavailability between 80 mg commercially available tablets and an extemporaneous suspension made from 80 mg tablets at the clinical trial site. Study results indicated that the Cmax and $AUC_{0\text{-}inf}$ of the valsartan suspension formulation were 1.93-fold (90%CI 1.60; 2.32) and 1.56-fold (90%CI 1.36; 1.78), respectively, higher than that of the valsartan tablet.

Based on the differences in the bioavailability between tablet and solution formulation, dose reduction by 2-fold is recommended when switching from tablet to solution.

The comparative bioavailability study with the commercial tablet and oral solution FMI has not been performed. Based on the results from two bioequivalence studies, it could be expected that the oral solution FMI will result in AUC 1.5-fold higher than commercial tablet (solution versus suspension AUC was equivalent; suspension versus tablet AUC was 1.5 fold higher). Hence, the proposed 2-fold dose reduction may lead to the systemic exposure lower than received with the tablets. The lack of a bioequivalence study between the 3 mg/mL solution intended for marketing with a marketed tablet formulation results in uncertainty in the appropriate dose level of the oral solution. Food effect with the new formulation oral solution has not been investigated.

Therefore, it seems appropriate that the clinical development plan should have included a direct comparison between the two formulations, even at an earlier stage when the primary use was anticipated to be in children below 6 years of age, as at the point in time where the child is able to use tablets, a switch between the two formulations will occur.
The results of a comparative bioavailability study between the oral solution and the tablet formulation is not expected to show bioequivalence, but to provide specific data on the appropriate ratio for dose adjustment between the two formulations.

The applicant has committed to conduct a post authorization comparative bioavailability study confirming the relative dosing of the tablets and oral solution to support the dosing recommendations.

Clinical efficacy

Four studies were submitted which evaluate the efficacy and safety of valsartan in the treatment of hypertension in children aged 6 months to 17 years. Although the applied indication covers children 6 years and older only, there is possibly even greater need for new treatment options in children < 6 years of age.

Table 2. Studies in the valsartan pediatric clinical development program

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan[1]
Efficacy/safety studies in this submission			**726**	
CVAL489A2302	Children 6 to 16 years of age with hypertension	Efficacy, dose response, safety, tolerability	**261** 245 235	Period 1: dose-response; Period 2: placebo withdrawal; Valsartan 10, 20, 40, 80, and 160 mg tablets Open-label: dose titration by response. Valsartan 40, 80, 160 mg and 160 mg + HCTZ 12.5 mg tablets
CVAL489K2302	Children 6 to 17 years of age with hypertension	Efficacy, safety, tolerability	**300**	Valsartan 80, 160 and 320 mg tablets Enalapril 10, 20 and 40 mg tablets Open-label extension to this study is ongoing
CVAL489A2307	Children 1 to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	**90** 87 88	Period 1: dose-response; Period 2: placebo withdrawal; Valsartan 5, 10, 20, 40 and 80 mg oral extemporaneous suspension Open-label: dose titration by response. Valsartan 20, 40, 80 mg and 80 mg + HCTZ 12.5 mg Oral extemporaneous suspension
CVAL489K2303	Children 6 months to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	**75**	Period 1: dose-response; Period 2: placebo withdrawal; Valsartan 0.25, 1 and 4 mg/kg Oral extemporaneous suspension Open-label extension to this study is ongoing

As seen in table 3-2, two studies are directly relevant for the population addressed by the application, but also 2 other studies, performed in younger children (1-5 years of age) provide relevant information particularly on safety.

Important differences in study designs included the different study treatment duration (4 weeks is necessary to see near maximum effect of valsartan) and dosing strategies (fixed dosing per weight category as opposed to mg per kg of body weight, the latter is more common in paediatric practice and arguably allows for more individualised dosing and more sensitive dose-response detection).

A2302 Results

322 patients were enrolled to the placebo wash-out period of whom 261 were subsequently randomized into phase 1; 245 of them (93.9%) completed the study. All patients who completed Phase 1 were re-randomized (1:1 ratio) to either valsartan or placebo for Phase 2. 13 patients (5.3%) discontinued phase 2.
235 patients entered open label (OL) phase, of whom 177 (75.3) completed the OL phase.
The treatment groups were generally comparable with respect to demography and baseline characteristics. The overall mean age of randomized patients was 11.4 years. Patients with weight < 35 kg accounted for only 17.2% of all randomized patients. Mean BMI was 27.0 kg/m2. More than 50% of patients (54%) had a BMI ≥95th percentile for gender and age at baseline. There were 4

patients with baseline weight < 20 kg (range: 18.0-19.8 kg). Overall, there were more males (60.5%) than females (39.5%); 48.7% of patients were black and 46.0% Caucasian. The mean average BP was 132.4/77.6 mmHg.

Primary efficacy evaluation

At the end of Phase 1, there was a significant decrease from baseline in systolic blood pressure (SSBP) in all 3 dose groups. There was a greater SSBP reduction with increasing valsartan dose: -7.9 mmHg for the low dose group, -9.6 mmHg for the medium dose group, and -11.5 mmHg for the high dose group. The primary efficacy slope analysis was statistically different from zero (p=0.0256), which demonstrated a dose-response for change from baseline to the end of Phase 1 in SSBP. Similar results were found for PP1 population. A statistically significant difference was observed between the low and high doses (p=0.0270) in ITT1 and PP1 populations.

Table 3. Changes in SSBP (mmHg) from baseline to end of Phase 1 by treatment (ITT1 population)

	Low Dose (N = 102)	Medium Dose (N = 52)	High Dose (N = 105)
Baseline/Visit 2			
Mean (SD)	131.4 (10.54)	133.3 (9.91)	133.2 (9.70)
End of Phase 1			
Mean (SD)	123.4 (11.43)	123.7 (11.92)	121.7 (12.53)
Change from baseline to end of Phase 1			
Mean (SD)	-7.9 (10.41)	-9.6 (9.12)	-11.5 (11.16)
95% CI [1]	(-9.98,-5.89)	(-12.16,-7.08)	(-13.66,-9.34)
p-value [1]	< 0.0001*	< 0.0001*	< 0.0001*

[1] p-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.

* indicates statistical significance at the 0.05 level.

At the end of Phase 2, there was a minimal change in SSBP in the pooled valsartan group (1.2 mmHg; p=0.1758) and a greater, statistically significant mean increase in SSBP in the pooled placebo group (3.9 mmHg; p<0.0001).

K2302 Results

348 patients were enrolled to the placebo wash-out period of whom 300 were subsequently randomized to valsartan or enalapril, 281 of them (93.7%) completed the study. Nineteen patients (6.3%) discontinued.

The treatment groups were generally comparable with respect to demography and baseline characteristics. However, there were more patients in the age group 13-17 years (59%) than in the age group 6-12 years (41%). There majority of population were males (63.7%) and Caucasians (82.7%), black patients accounted only for 6.7%. The overall mean age of randomized patients was 12.9 years. The mean weight was 66.3kg and BMI was 25.5 kg/m2. Most of the patients originated from Europe. The mean average BP was 134.2/79.1 mmHg. 17.3% of patient had chronic kidney disease (CKD).

Primary efficacy evaluation

Statistically significant reductions from baseline in mean SSBP (MSSBP) were achieved with valsartan and enalapril in the ITT as well as in PP populations, the between-treatment LS mean difference was -1.3 (95% CI -3.80, 1.17) demonstrating that valsartan is not inferior to enalapril in reducing MSSBP.

Table 4. Within treatment change from baseline at endpoint in MSSBP (mmHg) by treatment group (ITT population)

Visit	Statistics	Valsartan (N=148)	Enalapril (N=148)
Baseline	n	148	148
	Mean (SD)	134.0 (9.83)	134.6 (9.28)
	Min, Max	109.7, 161.0	105.3, 164.7
Endpoint	n	148	148
	Mean (SD)	121.0 (13.96)	122.8 (13.38)
	Min, Max	88.7, 172.7	83.0, 155.0
Change from baseline	n	148	148
	Mean (SD)	-13.0 (11.86)	-11.8 (10.39)
	Min, Max	-40.7, 34.0	-37.7, 21.7
	95% CI [1]	(-14.94, -11.09)	(-13.49, -10.12)
	P-value [1]	<0.0001 *	<0.0001 *

- Baseline is the week 0 (visit 2) value; endpoint is the week 12 (visit 7) or last observation carried forward value.

- Only patients who had both baseline and endpoint values are included.

[1] P-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.

* Indicates statistical significance at 0.05 level.

The proportions of patients achieving systolic BP control (MSSBP<95th percentile for gender, age and height) at endpoint were comparable for valsartan (66.9%) and enalapril (70.3%) [OR 0.838 (95%CI 0.51; 1.38)].

A2307 Results

130 patients were enrolled to the placebo wash-out period of whom 90 were subsequently randomized into phase 1; 87 of them (96.7%) completed the study.
All patients who completed phase 1 were re-randomized (1:1 ratio) to either valsartan or placebo for phase 2. Four patients (4.6%) discontinued phase 2. No patients were discontinued from phase 1 or phase 2 due to adverse events. A total of 88 entered OL phase. One patient discontinued from phase 1 entered directly the OL phase without being re-randomized into phase 2 (as specified by the protocol). Eighty two patients (93.2%) completed the OL phase.
The treatment groups were generally comparable with respect to demography and baseline characteristics, with the exception that mild disease was more prevalent in the medium dose group. The overall mean age of randomized patients was 3.2 years. Most patients (64.4%) were in the <18 kg weight category, and the mean weight for the overall population was 16.8 kg. Most patients were Caucasian (41.1%) or Black (30%). Overall, there were more males (60%) than females. Valsartan was used as an add-on therapy in 17 patients (18.9%).

Primary efficacy evaluation

At the end of phase 1, statistically significant reductions from baseline values in sitting SBP (primary efficacy variable) of approximately 8.5 mmHg was observed in all 3 treatment groups (low, medium and high dose) in ITT1 population. However, higher dose was not associated with greater reduction of MSSBP values and the dose response trend (primary endpoint) did not achieve statistical significance in the ITT1 population as well as in PP1 population.

At the end of phase 2 in ITT2 population, patients in the pooled valsartan group exhibited a mean reduction in SSBP compared to values at the end of Phase 1, whereas patients in the pooled placebo group exhibited a mean increase in sitting SBP from the end of Phase 1, The mean difference between the two pooled groups (-3.9 mmHg) was statistically significant (p=0.0217) in favour of greater SSBP reduction in the pooled valsartan group. The trend was similar in PP2 population, however, the comparison between placebo and valsartan groups was not statistically significant (22 patients excluded from analysis).

Table 5. Changes in SSBP (mmHg) from baseline to end of Phase 1 by treatment (ITT1 population)

	Low Dose N = 37	Medium Dose N = 18	High Dose N = 35
Baseline/Visit 2			
n	37	18	35
Mean (SD)	116.8 (6.88)	112.1 (8.56)	115.1 (6.34)
End of Phase 1			
n	37	18	35
Mean (SD)	108 (11.04)	103.7 (7.40)	106.5 (8.67)
Change from baseline to End of Phase 1			
n	37	18	35
Mean (SD)	-8.4 (8.44)	-8.3 (7.63)	-8.6 (7.55)
95% CI [1]	-11.18, -5.55	-12.13, -4.54	-11.18, -6.00
p-value [1]	<0.0001*	0.0002*	<0.0001*

[1] p-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
*indicates statistical significance at the 0.05 level

K2303 Results

Eighty-one patients were enrolled for the study of which 75 were randomized to period 1 (30 patients to low dose, 15 to medium dose and 30 to high dose groups), all randomized patients completed period 1.
75 patients were randomized to period 2 (37 to valsartan and 38 to placebo group) of which all patients in placebo group completed the study, while 35 patients (94.6%) in valsartan group completed period 2.
The treatment groups were generally comparable with respect to demography and baseline characteristics. Fifty-six percent of randomized patients in the study were Caucasian and 64% were males. The mean age was 3.3 years, mean weight was 16.2 kg and BMI 16.7 kg/m2. No patient < 1 years old or > 5 years old was enrolled. However, MSSBP was higher in the high dose group (117mmHg) than in the low (113 mmHg) and medium (112 mmHg) dose groups. Valsartan was used as an add-on therapy in 14 patients (18.7%).

Primary efficacy evaluation

At the end of period 1, statistically significant reductions from baseline in MSSBP of 8.3, 10.3 and 14.4 mmHg, respectively, were observed in the 3 treatment groups in the ITT1 as well as in PP1 population. Greater reductions was associated with higher doses, however, the dose response trend (primary endpoint) did not achieve statistical significance in the ITT1 as well as in PP1 populations. The treatment difference between the low and high doses was 4.3 mmHg.

Table 6. Changes from baseline in MSSBP (mmHg) at end of Period 1 by treatment (ITT1 population)

	Low N=30	Medium N=14	High N=30
Baseline			
n	30	14	30
Mean (SD)	113.3 (8.45)	112.0 (5.97)	117.2 (9.88)
Median	114.7	112.7	118.7
Min, Max	85.3, 129.7	101.0,121.3	97.3, 138.7
End of period 1			
n	30	14	30
Mean (SD)	105.0 (9.52)	101.8 (13.16)	102.8 (9.08)
Median	104.0	101.5	102.0
Min, Max	90.0, 123.3	77.0, 122.7	87.7, 123.3
Change from baseline to End of Period 1			
n	30	14	30
Mean (SD)	-8.3 (10.44)	-10.3 (9.83)	-14.4 (10.93)
Median	-8.3	-8.2	-12.5
Min, Max	-33.7, 14.0	-29.7, 4.0	-46.7, 2.7
95% CI[1]	(-12.2, -4.4)	(-15.9, -4.6)	(-18.4, -10.3)
P-value[1]	0.0002 *	0.0018 *	<0.0001 *

[1]P-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
* Indicates statistical significance at 0.05 level.
-Baseline is the Visit 2 value, and endpoint of Period 1 is the value at Visit 5 or LOCF.
-Only patients who had both baseline and Period 1 endpoint values are included.
- 'Low'= Valsartan 0.25 mg/kg; 'Medium' = Valsartan 1.0 mg/kg; 'High' = Valsartan 4.0 mg/kg

Slight increases from the end of Period 1 were observed in both treatment groups (valsartan and placebo) at the end of Period 2 in MSSBP.

No pooled analyses were conducted due to differences in study designs and populations, as well as for interpretation reasons of the BP changes in children of different age, gender and height. Based on these differences, no pooling for efficacy data for subgroups was performed. Safety data was pooled for the two studies in older children and the two studies in younger children, but not for the overall population of all four studies.

To support the long-term efficacy and safety of valsartan, both studies A2302 (children 6-16 years old) and A2307 (children 1-5 years old) included an optional one year open-label period. Patients were titrated to the dose of valsartan according to their mean trough SSBP. The initial valsartan dose in the open-label period was 40 mg o.d. in Study A2302 and 20 mg o.d. in Study A2307. If the mean of three SSBP measurements was ≥ 95th percentile for age, gender, and height, the investigator could up-titrate the dose of valsartan every 2 weeks to the next higher dose. If the highest valsartan dose was not efficacious (160 mg o.d. in study A2302, and 80 mg o.d. in study A2307), then 12.5 mg hydrochlorothiazide (HCTZ) could be added to valsartan for patients able to tolerate HCTZ.

The primary population analyzed was the open-label population, which consisted of all patients who entered the open-label period, and had at least one dose of open-label study medication. The MSSBP achieved during the double-blind periods were maintained during the OL treatment periods of both studies for one year.

Preliminary data from the extension study in younger children, K2303E1, was submitted as part of this application. This was an optional 18 week open label extension to the core study. The starting dose of open label valsartan was 1 mg/kg for all patients. This dose was taken for the first 2 weeks of the extension. Extemporaneous liquid suspension of valsartan was used. Patients were seen at 2 week intervals during the first 6 weeks of the study, and at 4 week intervals thereafter. If the MSSBP (mean of 3 measurements) was ≥ 95th percentile for age, gender and height, the investigator could increase the dose to 2 mg/kg. The dose could be further increased to 4 mg/kg after two weeks at the next

scheduled visit to control MSSBP (<95th percentile). If the patient's MSSBP remained ≥ 95th percentile after 2 weeks on valsartan 4 mg/kg, HCTZ or amlodipine could be added at the discretion of the investigator. The efficacy assessments consisted of mean sitting systolic and diastolic blood pressure (MSSBP and MSDBP), standard safety monitoring was applied.

The extension population was comprised of 66 patients. There were more males (43 patients; 65.2%) than females (23 patients; 34.8%), and more than half of the patients were Caucasian (36 patients, 54.5%). The mean age of the enrolled patient population was 3.4 years and mean sitting blood pressure was 114.7/70.7 mmHg.

At endpoint (week 26), reductions in MSSBP of 11.2 mmHg were observed compared to baseline in the extension study population. This decrease in systolic blood pressure was comparable to the reduction observed at the end of the dose-ranging period of the core study and superior to that observed at the end of the placebo withdrawal period of the core study.

A decrease of 6.6 mmHg in MSDBP was observed at study endpoint compared to baseline, which was similar to the reduction in diastolic blood pressure at visit 5, and superior to that observed at visit 7. The systolic BP control rate for all patients who continued into the extension was 63.6%. At the end of the extension period, when all patients were taking valsartan (with or without adding amlodipine or HCTZ), the systolic control rate increased to 75.8%.

In summary, the efficacy of valsartan in older children and adolescents was shown in two clinical trials, study A2302 (a placebo-controlled study in patients aged 6-16 years old, and study K2302 (an active-controlled study in patients aged 6-17 years old):

- dose-dependent reductions in MSSBP and MSDBP were achieved with valsartan in study A2302;
- statistically significant differences in MSSBP and MSDBP were achieved with valsartan compared to placebo during the withdrawal period in study A2302;
- valsartan was as effective as enalapril in reducing MSSBP and MSDBP in study K2302;
- the proportions of patients achieving systolic BP control (MSSBP <95th percentile for age, gender and height) were comparable for valsartan and enalapril in study K2302;
- no major differences in valsartan effect between subgroups studied were seen in studies A2302 and K2302;
- efficacy of valsartan alone or in combination with HCTZ seemed to persist for a period of one year in study A2302.

The efficacy of valsartan in younger children has not been consistently established and needs to be further studied. Inconsistent results were observed in two placebo-controlled trials (study A2307 in patients aged 1-5 years old and study K2303 in patients aged 6 months-5 years). In study A2307, valsartan was effective compared to placebo during the placebo withdrawal period, but a dose response was not demonstrated. In study K2303, a dose response trend was observed; however, a significant treatment difference compared to placebo was not demonstrated. It is not entirely clear to which extent this is a study design and dosing issue, but in the CHMP's view there is no plausible biological explanation for an inherent inefficacy of the drug in this sub-population.

Clinical safety

Patient exposure

The safety has been evaluated in 410 patients 6-17 years of age and in 164 children 1-5 years (the total safety population is 574 children). Data from 2 studies with each age group have been pooled. The third safety analysis population was compiled of the patients from the long term extension studies. This provides a minimally acceptable safety database.

Valsartan has been approved for the treatment of hypertension in the pediatric population 6 - 16 years of age by the FDA in November 2007. Since in 2004, more than 17900 patients between 6 and 18 years old have received valsartan in the United States, with cumulative exposure of 17923 patient years.

Adverse events

The adverse events (AE) seen in the studies were in general expected in the paediatric patients. The three safety populations (including long-term safety population), showed a similar pattern of AEs. In

general, the most frequently reported AEs were headache, pyrexia, nasopharyngitis, cough, upper respiratory tract infection, diarrhea, and dizziness.

In the older age group, the most frequently reported AEs were headache, cough, nasopharyngitis, and dizziness. In the younger children, the most frequently reported AEs were pyrexia, upper respiratory tract infection, cough, nasopharyngistis, and diarrhea.

Gastrointestinal adverse events were seen more frequently in the valsartan group vs. the active comparator/placebo group. GI events were also a reason to discontinue the study treatment in the active controlled trial. Therefore GI adverse events need to be reflected in the Product Information.

The incidence of study drug-related AEs was low and did not seem to be dose-dependent. Headache (2.9%) in older and hyperkalemia (2.4%) in younger patients were the most commonly reported AEs suspected to be study drug-related. The total of reported AEs suspected to be study drug related was 11.2% in older and 6.1% in younger age group.

No AEs were observed that had not previously been reported in adults treated with valsartan, with the exception of pyrexia. No significant new AEs were observed with long-term treatment compared to short-term treatment.

AEs related to mechanism of action for valsartan

Overall, few adverse events related to the mechanism of action were reported. Dizziness seems to be more frequent in the valsartan groups, and this AE should be included in the SPC. In children below the age of 6, no AE related to hypotension were seen. As expected, due to the underlying co-morbidities in this age group, the frequency of hyperkalemia was higher in children < 6 years.

Serious adverse events and death, discontinuation due to AES

The incidence of serious AEs and discontinuations due to AEs was low. Serious AEs were reported more frequently in children <6 years old compared to children ≥6 years old consistent with the co-morbidities in this population.

No major clinically relevant differences in the safety profiles of valsartan and enalapril were observed, other than a higher discontinuation rate in the valsartan arm.

Laboratory findings

In laboratory parameters a slightly increased incidence of elevated creatinine, BUN, and potassium was observed. Incidence of hyperkalemia (potassium >5.3 mmol/L) was low and mainly observed in patients with CKD.

Isolated elevations of liver function tests (LFT) were observed. Four cases of clinically important increases (>10xULN) in LFTs were observed in children younger than 6 years old during long-term treatment. Only 1 case was considered drug-related by the investigator.

Evaluations of vital signs, ECGs, and neurocognitive assessments did not indicate any clinically meaningful adverse effects of valsartan treatment in children 1–17 years of age.

K2303E1 extension study

Safety data from extension study K2303E1 in younger children were made available during the procedure. This was an optional 18 week open label extension to the core study.

Adverse events occurred in 57.6% of the patients. The most common AEs were pyrexia (16.7%) and nasopharyngitis (10.6%). There were no deaths during the study. Four patients (6.1%) experienced a total of 5 serious AEs, including a viral infection, forehead contusion/forehead wound, head injury, and nephrotic syndrome relapse. All of the serious AEs resulted in hospitalization, but none were considered to be related to study medication. One case of moderate hyperkalemia commenced during the extension; this event was suspected to be study drug related and led to discontinuation from the study but was not a serious AE. Two patients (3.0%) were discontinued due to an AE with an onset during the extension; these included hyperkalemia and nephrotic syndrome relapse. In addition, one patient had discontinued due to hyperkalemia that began during the core study. Both hyperkalemia cases (one mild and one moderate) were suspected to be study drug related; in this regard, the former

was continuing while the latter case resolved upon study completion. The case of nephrotic syndrome was a serious AE but not suspected to be study drug related. Changes in BUN, creatinine, potassium, GFR, and uric acid were consistent with the concomitant medical disorders in the patient population and the pharmacology of an ARB. Evaluation of laboratory values, vital signs, and ECG findings did not give evidence of any clinically relevant or unexpected adverse trends in patients receiving valsartan.

Safety in special populations

Children with GFR < 30ml/min were excluded from the studies and AEs seemed to be more common in patients with CKD. Long-term renal effects cannot be reliably assessed based on the existing data. The mild and moderate intensity of the hyperkalaemia reported may have been due to the close monitoring to which clinical trial patients are subjected to.
Valsartan is not expected to be less safe in patients with CKD than other Renin-Angiotensin-Aldosterone-System (RAAS) acting agents. However the lack of data should be reflected in the product information, the product should be contraindicated to patients with GFR < 30ml/min and the issue should be further studied during the post marketing phase.

2.5. Pharmacovigilance

- **Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

- **Risk Management Plan**

The applicant has submitted a consolidated version of a Risk Management Plan (RMP) for valsartan.

There are potential safety issues which should be discussed further in the safety specification:
- results of juvenile safety studies regarding the risk of nephrotoxicity and its relevance for the use in the different paediatric groups
- paediatric exposure in clinical trials and in post marketing use by age group, indication (including off label use), dose, duration of use, gender and ethnicity.

Two important identified risks (hyperkalemia, hypotension) and four important potential risks (renal impairment, elevation of liver function values, hypersensitivity including angioedema and serum sickness, hemoglobin/hematocrit decreased) have been identified for valsartan in the pediatric hypertensive population aged 6 – 17 years.

Table 7. Ongoing Safety Concerns

Important identified risks	Hyperkalemia
	Hypotension
Important potential risks	Elevation of liver function values
	Renal impairment (including proteinuria)
	Hypersensitivity including angioedema and serum sickness
	Decrease in hemoglobin and/or hematocrit
	Medication error including overdose
Important missing information	Clinical management and use of pharmacotherapy in paediatric heart failure
	Clinical management and use of pharmacotherapy in paediatric recent myocardial infarction
	Clinical management and use of pharmacotherapy in paediatric hypertension with renal impairment (GFR < 30 mL/min)
	Clinical management and use of pharmacotherapy in paediatric hypertension with mild to moderate hepatic impairment

The risks are proposed to be addressed mainly by routine measures, with the exception of renal impairment, which is proposed to be further studied in post-approval setting.

Table 8. Safety Concerns and Planned Pharmacovigilance Actions

Safety Concern	Planned action(s)
Important Identified risks	
Hyperkalemia	Routine pharmacovigilance
Hypotension	Routine pharmacovigilance
Important potential risks	
Elevation of liver function values	Routine pharmacovigilance
	Targeted follow up with the use of an event-specific checklist for postmarketing reports in patients under 18 years of age
Renal impairment	Routine pharmacovigilance
	Targeted follow up with the use of an event-specific checklist for postmarketing reports in patients under 18 years of age
	Study CVAL489K2305 including safety assessments on renal function, hyperkalemia and proteinuria
Hypersensitivity including angioedema and serum sickness	Routine pharmacovigilance
	Targeted follow up with the use of an event-specific checklist for postmarketing reports in patients under 18 years of age
Decrease in hemoglobin and/or hematocrit	Routine pharmacovigilance
	Targeted follow up with the use of an event-specific checklist for postmarketing reports in patients under 18 years of age
Medication error including overdose	Routine pharmacovigilance
Important missing information	
Clinical management and use of pharmacotherapy in pediatric heart failure	Routine pharmacovigilance
	Physician survey of clinical management and uses of medicinal products in pediatric patients with heart
Clinical management and use of pharmacotherapy in paediatric recent myocardial infarction	Routine pharmacovigilance
Clinical management and use of pharmacotherapy in paediatric hypertension with renal impairment (GFR < 30 mL/min)	Routine pharmacovigilance
Clinical management and use of pharmacotherapy in paediatric hypertension with mild to moderate hepatic impairment	Routine pharmacovigilance

The relevant changes to the Risk Management Plan should be submitted to the Competent Authorities of the Member States.

2.6. Benefit-Risk Balance

Benefits

The paediatric program has established that valsartan reduces the systolic and diastolic blood pressure in 6-17 year old children in a dose dependent manner and to a clinically relevant extent (study A2302). It has also been established that the effect is comparable to that of enalapril, another agent affecting

the RAAS and already widely used in paediatric patients (study K2302). The open-label longer term follow up of 52 weeks did not show cessation of effect or increased safety concerns.

Valsartan was well tolerated in the patient population studied and the well-known adverse effects of the medicines affecting the RAAS (including hyperkalemia and hypotensive effects) were manageable in paediatric patients. Growth and neurocognitive developmental assessments performed indicated that long-term (12 months) valsartan treatment has no negative impact on growth or development in children 1–17 years old.

The applicant has developed an age-appropriate formulation (oral solution) for patients not able to swallow the tablets.

Risks

The studies in the age range 1-5 years did not provide robust proof of efficacy of valsartan. The study population in older age group has excluded more severe forms of hypertension, thus there is a lack of information of the safety and efficacy of valsartan in these patients. The studies had extensive exclusion criteria which have resulted in identified missing information about several sub-populations.

Considering the lack of experience in children with GFR< 30ml/min, the use of valsartan cannot be recommended in this population.

In older children, the most frequently reported AEs were headache, cough, nasopharyngitis and dizziness. In younger children, the most frequently reported AEs were pyrexia, upper respiratory tract infection, cough, nasopharyngitis, and diarrhea. These AEs are not unexpected in a paediatric population. In both older and younger children, the incidence of study drug-related AEs was low and was in general not dose-dependent. Headache and hyperkalemia were the most commonly reported AEs suspected to be study drug-related in older and younger patients, respectively. As expected, due to the underlying co-morbidities in this age group, the frequency of SAEs was higher in children < 6 years. Even though only one out of three cases of hepatitis was considered by investigator to be drug related, marked elevated transaminases were seen in two patients in the age group < 6 years. This is considered a potential safety issue in this age group. Elevated liver function values were also seen in a few cases for children > 6 years.

The duration of the studies is limited, as is the number of participants, so rare and unexpected side-effects may still occur.

The long-term effects on target organs of hypertensive damage have not been studied and the renal patients have been under-represented in the studies - no firm conclusions on the use of valsartan can be drawn in this sub-population. An acceptable study proposal has been submitted by the applicant.

The applicant has developed an age-appropriate formulation (oral solution) for patients not able to swallow the tablets and proposes 2-fold reduction when switching from oral solution to tablets. However this has not been formally addressed in a comparative bioavailability study.

Off-label use of the oral solution in the younger age-group, not yet adequately studied and not covered by this application, is possible.

Benefit-Risk Balance

Hypertension in children is an increasing health problem, where well-studied therapeutic options are scarce. The clinical problem encompasses 2 relatively different populations – young children with mainly secondary hypertension, often moderate to severe, and adolescents, for whom the essential hypertension is more frequent and less severe. The current product satisfies the need for effective and reasonably safe treatment of hypertension mainly of the second sub-population.
The blood-pressure lowering effect demonstrated in the studies was clinically meaningful and the safety profile was relatively benign. In an active comparator trial, both the short-term efficacy and safety stood up well when compared to an authorised agent. However, no consistent results were seen in the 1-5 year old population. Further development of the product in this population is considered very important.

During the assessment process, the CHMP consulted the PDCO on the following issues:

- The lack of understanding of the reasons behind the results of the studies in children aged 1 to 5 years, and the possible need for a further study in this age group
- If a further study in this age group was to be considered as needed, input on main principles of the design and methodology

The PDCO's response indicated that the reasons behind the inconsistent results seen in the two clinical trials involving patient from 1 to 5 years old are not entirely understood. It should be noted that no clear and well-established approach exists as to how to design clinical trials for antihypertensive agents in the paediatric population. However the clinical need in this age group exists and therefore it would be relevant to conduct a new study as valsartan has shown efficacy in the older age group and there is a pharmacological rationale for its use in secondary hypertension.

The methodology for such a study cannot be clearly defined at this point, as the reasons behind the inconsistent results of the previous studies are not entirely understood. However it is suggested that the CHMP, together with the PDCO, SAWP and other relevant parties could initiate a dialogue in order to study the problem and create a sound design for antihypertensive agents in the paediatric population.

The applicant has agreed to undertake the necessary commitments for post authorisation studies aimed at clarifying both the efficacy in children aged 1 to 5 years old, and the safety in CKD patients.

The applicant has developed an age-appropriate formulation (oral solution) for patients not able to swallow the tablets and proposes 2-fold reduction when switching from oral solution to tablets. While this has not been formally addressed in a comparative bioavailability study, the age-appropriate formulation is much needed and therefore the study will be conducted as a post authorisation commitment.

3. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Diovan oral solution 3 mg/ml in the treatment of hypertension in children and adolescents 6 to 17 years of age is favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the agreed Paediatric Investigation Plan is fully completed. Paediatric data of studies subject to this plan are reflected in the Summary of Product Characteristics (SPC) and, as appropriate, the Package Leaflet.

The CHMP recommends specific wording to be introduced in the sections concerned by the assessment during this procedure: 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3 and 6 of the Summary of Product Characteristics. The labelling and Package Leaflet are updated accordingly. However, given that Diovan film-coated tablets has been the object of a recent harmonization throughout Europe (including the 27 Member States, Norway and Iceland) and is currently part of the Mutual Recognition System, a full SPC is included.

A post-approval study of long-term effects in CKD and non-CKD patients needs to be carried out and the efficacy of valsartan in younger age group (having potential impact also to the older children with secondary hypertension) has to be clarified in an additional randomised trial.