15 November 2012
EMA/CHMP/549534/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Micardis, Pritor, Kinzalmono

Procedure No. EMEA/H/C/xxxx/WS/0254

Worksharing applicant (WSA): Boehringer Ingelheim International GmbH

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 9 March 2012 an application for a variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal products:

Medicinal product:	International non-proprietary nameCommon name:	Presentations:
Micardis, EMEA/H/C/000209/WS/0254	telmisartan	See Annex A
Kinzalmono, EMEA/H/C/000211/WS/0254	telmisartan	See Annex A
Pritor, EMEA/H/C/000210/WS/0254	telmisartan	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

In accordance with Article 46 of regulation EC No 1901/2006, the WSA proposed the update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include the results of study 0502-0403, a study conducted to evaluate the safety, efficacy and pharmacokinetics of telmisartan in the paediatric population. Furthermore, the Product Information is being brought in line with the latest QRD template version and minor editorial corrections were implemented in section 4 of the Package Leaflet of Micardis, Pritor and Kinzalmono, in section 6.4 of the SmPC of Pritor and Kinzalmono, and in section 9 of the outer labelling of Kinzalmono and Pritor.

The requested worksharing procedure proposed amendments to the SmPC, Labelling and Package Leaflet.

Rapporteur: Daniela Melchiorri

1.2. Steps taken for the assessment

Submission date:	9 March 2012
Start of procedure:	22 April 2012
Rapporteur's preliminary assessment report circulated on:	25 May 2012
Rapporteur's updated assessment report circulated on:	15 June 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 June 2012
MAH's responses submitted to the CHMP on:	15 August 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	05 September 2012
Rapporteur's updated assessment report on the MAH's responses circulated on:	20 September 2012
2nd Request for supplementary information adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	03 October 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 October 2012
Rapporteur's updated assessment report on the MAH's responses circulated on:	9 November 2012
CHMP opinion:	15 November 2012

2. Scientific discussion

2.1. Introduction

Telmisartan is an angiotensin II receptor antagonist that lowers blood pressure. The antihypertensive effect of the once-daily dosing in patients with mild-to-moderate hypertension results in a significant reduction of sitting, supine and standing systolic and diastolic blood pressure, usually with a small or no orthostatic change. The usual starting dose of telmisartan is 40 mg once-daily. This dosage reduces the SBP/DBP by an average of 11.3/7.3 mmHg, with 80 mg this average is 13.7/8.1 mmHg. The antihypertensive activity occurs within two hours after single-dose administration and is maintained for the full 24-hour dosing interval.

The proposed type II variation was submitted in compliance with Article 46 of Regulation EC No 1901/2006 and proposed updates for sections 4.2, 5.1 and 5.2 of the SmPC to include information on paediatric use of the products. To support the proposed amendments to the SmPC with regard to use in children and adolescents, the MAH conducted a prospective, randomized, double-blind, placebo-controlled, four weeks of treatment trial (study 502.403) in order to evaluate the safety and efficacy of telmisartan in children and adolescents (6 to <18 years of age) with hypertension.

The study further aimed to characterise the steady-state pharmacokinetics (PK) of telmisartan in paediatric patients treated over four weeks with single, daily doses of telmisartan in order to detect possible differences in its pharmacokinetics between children/adolescents and adults, as well as between children (6 to <12) and adolescents (12 to <18).

The proposed amendments of the Product Information are identical for all three telmisartan containing medicinal products (Micardis, Pritor, Kinzalmono) and therefore are submitted through a worksharing procedure:

4.2 Posology and method of administration

Paediatric population

The safety and efficacy of Kinzalmono in children and adolescents aged below 18 years have not been established.
Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.
~~The safety and efficacy of Kinzalmono in children and adolescents aged below 18 have not been established. No data are available.~~

5.1 Pharmacodynamic properties

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Paediatric population
The safety and efficacy of Kinzalmono in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in hypertensive patients aged 6 to < 18 years (n = 76) after taking telmisartan 1 mg/kg (n = 30 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. After adjustment for age group effects and baseline SBP values an average placebo-corrected SBP change from baseline (primary objective) of 8.5 mm Hg was observed in the telmisartan 2 mg/kg group, and a -3.6 mm Hg SBP change was found in the telmisartan 1 mg/kg group. The adjusted and placebo-corrected DBP changes from baseline were 4.5 mm Hg and -4.8 mm Hg in the telmisartan 1 mg/kg and 2 mg/kg groups, respectively. The change was dose dependent. The safety profile appeared generally comparable to that observed in adults.

5.2 Pharmacokinetic properties

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Special Populations

Paediatric population
The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age-related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max}.

2.2. Clinical Pharmacology aspects

2.2.1. Methods – analysis of data submitted

The pharmacokinetics of two doses of telmisartan was assessed as a secondary objective in a prospective, randomized, double-blind, placebo-controlled trial study 502.403 in hypertensive patients

aged 6 to <18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. The aim of this study was to characterise the steady-state PK of telmisartan in paediatric patients treated over 4 weeks with single, daily doses of telmisartan to detect possible differences in the PK of telmisartan between children/adolescents and adults, as well as between children (6 to <12) and adolescents (12 to <18). The PK set comprised a total of 60 patients; in 57 of these PK parameters could be derived. The following table describe the distribution of these patients within each dose group:

Number of patients by age group assigned to each treatment of either 1 mg/kg or 2 mg/kg Micardis included in the pharmacokinetic parameter analysis (out of total completed patient number)

1 mg/kg		2 mg/kg	
6- < 12 years	12- < 18 years	6- < 12 years	12- < 18 years
7	20	7	23

Pharmacokinetic parameters:

- Cmax,ss (maximum concentration of the analyte in plasma at steady state over a uniform dosing interval);
- Cmin,ss (minimum measured concentration of the analyte in plasma at steady state over a uniform dosing interval);
- Cpre,ss (predose concentration of the analyte in plasma at steady state immediately before administration of the next dose);
- Cavg (Average concentration of the analyte in plasma at steady state);
- tmax,ss (time from dosing to maximum concentration at steady state);
- AUCtau,ss (area under the concentration time curve of the analyte in plasma at steady state over a uniform dosing interval);
- t1/2,ss (terminal half-life of the analyte in plasma at steady state);
- MRTpo,ss (mean residence time of the analyte in the body at steady state);
- CL/F,ss (apparent clearance of the analyte in the plasma after extravascular administration at steady state);
- Vz/F,ss (apparent volume of distribution during the terminal phase λz following an extravascular dose at steady state);
- PTF (peak trough fluctuation).

2.2.2. Results

The pharmacokinetic parameters for both dose strengths (1 and 2 mg/kg) are summarised in table below.

Comparison of the pharmacokinetic parameters (N, gMean and gCV%) of telmisartan after multiple oral administration of 1 mg/kg or 2 mg/kg Micardis® for 4 weeks in children (6 to < 12 years) and adolescents (12 to < 18 years) with hypertension

telmisartan		1 mg/kg (N = 24)		2 mg/kg (N = 24)	
		gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$	[ng·h/mL]	1650	130	3730	98.5
$AUC_{\tau,ss,norm}$	[(ng·h/mL)/mg]	22.4	99.6	27.4	94.2
$C_{max,ss}$	[ng/mL]	269[1]	140	1110	98.4
$C_{max,ss,norm}$	[(ng/mL)/mg]	3.68[1]	115	8.19	99.3
$C_{pre,ss,mean}$	[ng/mL]	33.0[4]	160	55.6[3]	142
CL/F_{ss}	[mL/min]	745	99.6	608	94.2
Vz/F_{ss}	[L]	1770	122	1340	101
$t_{1/2,ss}$	[h]	28.1[4]	56.4	27.2[2]	46.2
$t_{max,ss}$[5]	[h]	1.50[3]	0.500-6.07	1.0[3]	0.5 - 2.24

High inter-individual variability and considerable overlap between the 1 and 2 mg/kg dose groups were seen i hypertensive children and adolescents for the two main exposure parameters AUCT,ss and Cmax,ss. The median time to reach peak concentrations was short for both dose strengths. Steady state t1/2 was on average 28.1 h for 1 mg/kg and 27.2 h for 2 mg/kg. There was a trend to non-linearity with the increase in dose resulting in higher then dose proportional Cmax and AUC and at the same time a decrease in CL/F,ss from 745 to 608 mL/min. Comparison of PK parameters of telmisartan after multiple oral administration of 1 mg/kg or 2 mg/kg telmisartan for 4 weeks among the two different groups of patients with hypertension (children (6 to <12 years) and adolescents (12 to <18 years)) was also performed. Children (6 to <12 years) could not be distinguished from adolescent patients (>12 to <18 years) regarding dose normalised AUCT,ss,norm and Cmax,ss,norm at the low dose of 1 mg/kg. At the dose of 2 mg/kg, children had a higher AUCT,ss,norm and Cmax,ss,norm than adolescent patients. At the 2 mg/kg dose CL/F,ss and Vz/F,ss was lower in hypertensive children but there was no difference found within the age groups. However, in general, none of these younger patients (age 6 - <12) had AUCT,ss and Cmax,ss levels exceeding those of the adolescent group.

The non-linearity in PK seemed more pronounced for the younger aged group (6 to <12 years), especially for Cmax,ss, while for the adolescent hypertensive patients group, Cmax,ss increased nearly in a dose proportional manner. There is a trend to non-linearity for AUCt,ss when the dose was doubled from 1 mg/kg to 2 mg/kg, for both groups, but is more evident for adolescents. The CL/F,ss seemed to be less affected by the increase in dose in the adolescent patient group. However, in previous reports dosages in adults were not weight adjusted. Looking at the absolute dosages, four paediatric patients at the high dose strength of 2 mg/kg had a body weight of ≥90 kg. Since the 2 mg/kg dose was limited to an absolute dose of 120 and 160 mg for younger aged patients and patients aged between 12 and <18 years, respectively, patients, with a body weight of ≥90 kg did in some case not receive the full 2 mg/kg dose. The non-linearity might have been, therefore, slightly underestimated. This could also explain the fact that for adolescent patients the non-linearity almost diminished for the dose normalized AUCT,ss (AUCT,ss, norm). No significant correlation between age and the PK parameters AUCT,ss or Cmax,ss was found. The conducted study 502.403 confirmed the non-linearity in the pharmacokinetics of telmisartan, especially for Cmax,ss. This observation is consistent with findings in adults where the non-linearity in telmisartan PK was mainly related to Cmax and thus absorption/first-pass processes. The difference in the telmisartan PK between the two age groups in this pediatric patient population was modest, mostly limited to Cmax,ss (referred to dose normalized Cmax,ss,norm) and the high dose of 2 mg/kg.

Comparison with historical data in the adult population: Results obtained from the study 502.403 were compared with historical adult PK data from trials 502.202 and 502.203. In trial 502.202, PK analysis was conducted in 114 male and female adult hypertensive patients who were treated with doses of 40 mg/day, 80 mg/day, or 120 mg/day over 28 days. A dose of 160 mg/day was administered to adult hypertensive patients in trial 502.203 and plasma concentrations (pre-dose ($C_{pre,ss}$) and one hour after drug administration (C1h,ss) were assessed after several treatment intervals. The $C_{1h,ss}$ and $C_{pre,ss}$ at Day 28 of continuous dosing from the actual trial in adolescents receiving 2 mg/kg were, thus, comparable to the historical data in adults. The comparison of PK parameters among the two different dose groups (1mg/kg or 2 mg/kg) in paediatric patients and adults is summarised in the following tables:

gMean (gCV) non-compartmental pharmacokinetic parameters of telmisartan after multiple (N= 28 days) oral administration of either 2 mg/kg to hypertensive pediatric patients at the age of 6 -<18 years, or 120 mg (502.202) or 160 mg (502.203) to hypertensive adult patients

		2 mg/kg[1]		120 mg/day (approx. 1.5 mg/kg)		160 mg/day (approx. 2 mg/kg)	
		6- < 18 years (N = 24)		trial 502.202 (N = 38)		trial 502.203 (N = 43)	
		gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$	[ng·h/mL]	3730	98.5	4213	91.3	---	----
$AUC_{\tau,ss,norm}$	[(ng·h/mL)/mg]	27.4	94.2	35.08	91.3	---	---
$C_{max,ss}$	[ng/mL]	1110	98.4	1046	145.8	---	---
$C_{max,ss,norm}$	[(ng/mL)/mg]	8.29	99.3	8.72	145.8	---	---
$C_{pre,ss,28}$	[ng/mL]	45.5	211	---	---	98.99	---

gMean (gCV) non-compartmental pharmacokinetic parameters of telmisartan after multiple (N= 28 days) oral administration of either 1 mg/kg to hypertensive children and adolescents, or 80 mg (502.202 & 502.203) to hypertensive adult patients

		1 mg/kg[1]		80 mg/day (approx. 1 mg/kg)		80 mg/day (approx. 1 mg/kg)	
		6 - < 18 years (N =25)		trial 502.202 (N = 37)		trial 502.203 (N = 40)	
		gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$	[ng·h/mL]	1650[1]	130	2651	99.5	---	----
$AUC_{\tau,ss,norm}$	[(ng·h/mL)/mg]	22.4[1]	99.6	33.14	99.5	---	---
$C_{max,ss}$	[ng/mL]	269	140	465	125	---	---
$C_{max,ss,norm}$	[(ng/mL)/mg]	3.68	115	5.81	125	---	---
$C_{pre,ss,28}$	[ng/mL]	31.2	266	---	---	46.29	---

[1] N = 24

On the basis of the results shown above, the MAH stated that, taken into account the known high inter-individual variability in PK parameters, the exposure in the paediatric hypertensive patient population in this study was comparable to exposure in an adult patient population. The MAH also

stated that, although the study was small for a meaningful assessment of the PK of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for Cmax.

2.2.3. Discussion

Although the MAH concluded that considering the high inter-individual variability in PK parameters, the exposure in the paediatric hypertensive patient population was comparable with that in adults, the number of patients in the younger age group (6 to <12 years) is smaller than that in the adolescent group, making the comparison between the two age group not completely reliable. In addition, due to this difference in group size, the pooling of data in the 6 to <12 group for the comparison with the adult population is not considered adequate for a correct evaluation of the differences between the paediatric and adult populations. Study population is largely overweight/obese. The influence of overweight/obesity on PK parameters has not been investigated. Thus, conclusion on the transferability of PK data obtained in this patient population to the general European hypertensive paediatric patient population in the normal weight range is not considered possible.

2.3. Clinical Efficacy aspects

2.3.1. Methods – analysis of data submitted

The primary objective of study 502.403 was to assess the blood pressure lowering effects of two doses of telmisartan (1 mg/kg and 2 mg/kg) over a four-week treatment period, to assess the safety and tolerability of the two doses of telmisartan and to determine potentially effective doses for paediatric patients for future studies. The secondary objectives included determination of the steady state PK of telmisartan in children aged 6 to <18 years; comparison of plasma PK parameters for telmisartan among children in two age groups (6 to <12 years, and 12 to <18 years); and determine if age-related differences. The main inclusion criteria were: Male or female, ages 6 to <18 years; hypertensive patients: systolic blood pressure (SBP) ≥ 95th percentile for age, height, and gender based on the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; weight ≥ 20 kg and ≤ 120 kg.

The study consisted of a two-week washout period followed by a four-week double-blind phase. Dosing was determined by body weight, after the patient was stratified by age and randomised to a specific dose level (1 mg/kg or 2 mg/kg) or to receive placebo. The maximum dose in the telmisartan “low dose” group was 60 mg for children (6 to <12 years old) and 120 mg for adolescents (12 to <18 years old). In the telmisartan high dose group the maximum dose was 120 mg in children and 160 mg in adolescents.

The CHMP noted that study investigated two dosages of telmisartan (TEL) per kg of body weight: 1 mg/kg and 2 mg/kg, defined as low and high, respectively. Considering that mean weight was above 70 kg in all arms, both dosages were substantially higher than the usual dosage in adults (40 mg/day). Thus, the reasons underlying the choice of these dosages in the paediatric age are not clear. The MAH should justify the dose in the paediatric patients. Given that even the low dosage was actually high, the conclusions of the study could be reliable for the safety (AEs incidence should be lower with lower doses) but are of limited value for efficacy. This view shared by the MAH who concluded that data are not sufficient to recommend the treatment of hypertension with TEL in individuals with age <18 years and do not represent a reliable basis for dosage regimen.

The primary endpoint was change from baseline in seated systolic blood pressure (SBP) at the end of four weeks of treatment. Secondary efficacy endpoints included change from baseline in seated diastolic blood pressure (DBP) at the end of four weeks of treatment and blood pressure response defined as < 95th percentile at the patient's final visit based on age, height, and gender. Safety was assessed by monitoring adverse events (AEs), ECG, changes from baseline in pulse rate, changes in laboratory parameters. However, the study did not include the list of laboratory parameters which were monitored. This is an important point; the lack of information preclude a complete safety evaluation. The CHMP believes the calculation of power and sample size was adequate. Furthermore, the applied statistical analysis appears acceptable because the report includes non-adjusted result. A total of 77 patients were randomized to one of three treatment groups (Placebo, telmisartan 1 mg/kg, or telmisartan 2 mg/kg). There were two protocol amendments.

The CHMP noted that the rate of discontinuation was slightly higher in the Telm 2mg/kg group (22.6% of patients), compared to patients in the placebo group (12.5%). The study was conducted in Brazil, Mexico and US. A large majority of the study population consists of overweight/obese patients enrolled in Brazil, Mexico and US. It is questionable if these patients represent the current European population of hypertensive children and adolescent. No information is given about the selection criteria with regard to possible causes of high blood pressure and possible co-morbidities. The lack of this information precludes the possibility to assess if efficacy and safety differed by and/or were dependent on the clinical characteristics of the patients.

2.3.2. Results

The primary finding from this trial is the effectiveness of telmisartan "high dose" (i.e. telmisartan 2 mg/kg) on lowering systolic blood pressure (SBP) at the end of four week treatment period. After adjusting the age group effect and baseline SBP values in the ANCOVA model, the average change of SBP from baseline in the telmisartan "high dose" group was -14 mmHg. In comparison with the placebo group, the difference was -8.5 mmHg with the confidence interval of (-14, -3) mmHg. It is statistically significant at alpha=0.05 with p-value of 0.0027. The average change of SBP from baseline in the telmisartan "low dose" group was -9.7 mmHg. The difference between telmisartan "low dose" group and placebo group was -3.6 mmHg, which is statistically insignificant with the confidence interval of (-9.2, 1.9) mmHg and p-value of 0.193, but clinically significant. With the hierarchical testing procedure, statistical significance was achieved for the telmisartan "high dose" group only for SBP.

ANCOVA for SBP (mmHg) change from baseline at final visit (Week 4) - FAS (LOCF)

Systolic BP	Placebo	Telm 1 mg/kg	Telm 2 mg/kg
Number of Patients	14	28	31
Baseline			
Mean (SD)	130 (7.5)	132 (7.5)	131 (6.3)
Week 4			
Mean (SD)	126 (10.0)	123 (9.9)	117 (9.0)
Change from Baseline			
Mean (SD)	-4.7 (10.7)	-9.0 (7.8)	-13 (8.7)
Adjusted Mean (SE)	-6.0 (2.4)	-9.7 (1.7)	-14 (1.7)
Difference from Placebo			
Adjusted Mean (SE)		-3.6 (2.8)	-8.5 (2.7)
95% confidence interval		[-9.2, 1.9]	[-14,-3.0]
p-value		0.1930	0.0027

Adjustment for age group and baseline SBP

Both age by treatment and gender by treatment interaction effects were insignificant in the analyses of covariance models. However, relatively significant reduction in SBP among the age 12 to 18 years old patients was observed in the telmisartan “high dose” group. In this age group, the average difference of the change from baseline in SBP between telmisartan “high dose” group and placebo group was -10.28 mmHg in contrast to the younger age group of -1.99 mmHg.

Secondary efficacy endpoints included: change from baseline in seated diastolic blood pressure (DBP) at the end of week 4, and blood pressure response defined as both SBP and DBP <95th percentile at the patient’s final visit based on age, height and gender. There was no statistical significance in either the telmisartan “high dose” or “low dose” groups at the alpha level of 0.05 (p value= 0.0511, 0.0725) for the change from baseline in DBP at the end of Week 4.

The reduction in the telmisartan “high dose” group was -8.4 mmHg and -8.1 mmHg in the “low dose” group (p-values less than 0.1), after adjusting the age group effect and the baseline DBP value. However, for both the 1 mg/kg and 2 mg/kg doses, both effects were clinically highly significant. This tendency was confirmed by the longitudinal analyses using all available DBP data. It is of note that contrary to SBP, there was no dose related difference in DBP effect which can be explained by the pathophysiology of hypertension in children.

ANCOVA for DBP (mmHg) change from baseline at final visit (Week 4) - FAS (LOCF)

Diastolic BP	Placebo	Telm 1 mg/kg	Telm 2 mg/kg
Number of Patients	14	28	31
Baseline			
Mean (SD)	78.4 (10.8)	79.0 (9.7)	78.4 (7.4)
Week 4			
Mean (SD)	75.5 (9.3)	71.3 (9.2)	70.6 (8.5)
Change from Baseline			
Mean (SD)	-2.9 (7.6)	-7.7 (9.6)	-7.8 (8.1)
Adjusted Mean (SE)	-3.5 (2.1)	-8.1 (1.6)	-8.4 (1.5)
Difference from Placebo			
Adjusted Mean (SE)		-4.5 (2.5)	-4.8 (2.4)
95% confidence interval		[-9.5, 0.4]	[-9.7, 0.0]
p-value		0.0725	0.0511

Adjustment for age group and baseline DBP

2.3.3. Discussion

The 4-week treatment with TEL induced a blood pressure reduction of 9-13 mmHg in msSBP and of 8-8 mmHg in msDBP (1 and 2 mg/kg, respectively). A statistical significant and clinically relevant decrease in msSBP (- 14 mmHG) in the Telm2 mg/kg dose group at 4w was observed vs placebo; whereas no statistical significant difference was observed for the 1mg/kg dose, albeit there was an average reduction of 9.7 mmHg vs placebo. No statistical significant effects were recorded for longitudinal analyses and clinical secondary endpoints. No treatment interaction effect for age, gender or weight resulted from analyses of covariance models. However, relatively significant reduction in SBP among the age 12 to 18 years old patients was observed in the telmisartan “high dose” group: -10.28 mmHg compared to placebo vs -1.99 mmHg compared to placebo in the younger age group.

Overall, the effect of both dosages on blood pressure levels is substantially similar. These results are weakly significant due to limited sample size and large variability of blood pressure in paediatric age. The lack of a dose-response curve in blood pressure reduction precludes any reliable conclusion about

the appropriate dosage of TEL in the paediatric age. In summary, no definite findings on efficacy and posology in the studied population are available.

2.4. Clinical Safety aspects

2.4.1. Methods – analysis of data submitted

All randomised patients who took at least one dose of randomised trial medication were included in the safety analysis evaluating primarily adverse events, vital signs and laboratory tests. Overall 61 patients were randomized to active treatment; 16 to placebo. The mean duration of overall treatment exposure was comparable for all three groups (20.6 days for telmisartan 1 mg/kg; 20.9 days for telmisartan 2 mg/kg; and 18.4 days for placebo). The overall treatment exposure ranged from one to 25 days.

2.4.2. Results

The mean duration of treatment was comparable across treatment groups (18.4, 20.6 and 20.9 days for placebo, telmisartan 1 mg/kg and telmisartan 2 mg/kg, respectively).

According to the MAH, the overall occurrence of AEs during the four-week treatment phase was similar for the two active treatment groups and consistent with the prescribing information for telmisartan in adults. Adverse events were reported in 37 (48.7%) of the 76 patients who received at least one dose of study medication; 25 (41.7%) patients during telmisartan 1 mg/kg treatment (initial and target doses), 13 (41.9%) patients during telmisartan 2 mg/kg treatment (target dose), and five (31.3%) patients during placebo treatment (initial and target doses). The below table shows the frequency of adverse events by treatment, primary system organ class and preferred terms.

Table on Frequency [N (%)] of subjects with AEs by treatment, primary SOC and PTtreated set

System organ class/ Preferred term	Placebo N (%)	Telm 1 N (%)	Telm 2 N (%)	Total N (%)
Number of subjects	16 (100.0)	60 (100.0)	31 (100.0)	76 (100.0)
Total with adverse events	5 (31.3)	25 (41.7)	13 (41.9)	37 (48.7)
Infections and infestations	1 (6.3)	3 (5.0)	2 (6.5)	6 (7.9)
Influenza	1 (6.3)	2 (3.3)	1 (3.2)	4 (5.3)
Pharyngitis streptococcal	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Tonsillitis	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Immune system disorders	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Drug hypersensitivity	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Metabolism and nutrition disorders	1 (6.3)	2 (3.3)	0 (0.0)	3 (3.9)
Anorexia	1 (6.3)	2 (3.3)	0 (0.0)	3 (3.9)
Psychiatric disorders	1 (6.3)	1 (1.7)	0 (0.0)	2 (2.6)
Stress	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.3)
Depression	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Nervous system disorders	2 (12.5)	12 (20.0)	5 (16.1)	19 (25.0)
Headache	0 (0.0)	7 (11.7)	3 (9.7)	10 (13.2)
Dizziness	1 (6.3)	4 (6.7)	2 (6.5)	7 (9.2)
Tension headache	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.3)
Presyncope	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Syncope	0 (0.0)	1 (1.7)	1 (3.2)	2 (2.6)
Respiratory, thoracic and mediastinal disorders	1 (6.3)	6 (10.0)	0 (0.0)	7 (9.2)
Cough	0 (0.0)	4 (6.7)	0 (0.0)	4 (5.3)
Epistaxis	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.3)
Nasal congestion	0 (0.0)	2 (3.3)	0 (0.0)	2 (2.6)
Pharyngolaryngeal pain	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Rhinorrhoea	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Sinus congestion	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Gastrointestinal disorders	0 (0.0)	9 (15.0)	4 (12.9)	12 (15.8)
Odynophagia	0 (0.0)	1 (1.7)	2 (6.5)	3 (3.9)
Abdominal pain	0 (0.0)	3 (5.0)	0 (0.0)	3 (3.9)
Vomiting	0 (0.0)	2 (3.3)	1 (3.2)	3 (3.9)
Abdominal discomfort	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Nausea	0 (0.0)	1 (1.7)	1 (3.2)	2 (2.6)
Abdominal pain upper	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Constipation	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Gingivitis	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (1.7)	1 (3.2)	2 (2.6)
Dermatitis	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Acne	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (3.3)	2 (6.5)	3 (3.9)
Back pain	0 (0.0)	1 (1.7)	1 (3.2)	1 (1.3)
Musculoskeletal chest pain	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Pain in jaw	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Renal and urinary disorders	0 (0.0)	1 (1.7)	1 (3.2)	2 (2.6)
Nephrolithiasis	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Polyuria	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
General disorders and administration site conditions	2 (12.5)	4 (6.7)	1 (3.2)	7 (9.2)
Face oedema	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.3)
Fatigue	1 (6.3)	1 (1.7)	0 (0.0)	2 (2.6)
Asthenia	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Malaise	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Pyrexia	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Thirst	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Investigations	1 (6.3)	0 (0.0)	1 (3.2)	2 (2.6)
Blood pressure increased	1 (6.3)	0 (0.0)	0 (0.0)	1 (1.3)
Blood creatinine increased	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Blood urea increased	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Traumatic haematoma	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)

Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 10.1

Adverse events (AEs) experienced during the trial were primarily mild or moderate across all treatment groups. There were a total of five (8.3%) patients who experienced AEs of severe intensity, all during

the telmisartan 1 mg/kg treatment. The AE pattern was similar between both active treatment groups. Events of headache and dizziness were reported at a frequency greater than 5% in both the telmisartan 1 mg/kg and telmisartan 2 mg/kg treatment groups. Events of cough were seen only in greater then 5% of patients while on telmisartan 1mg/kg and only odynophagia was seen in greater than 5% of patients while in the telmisartan 2 mg/kg group. Drug related events were similar between the two active treatments, with events of headache and dizziness reported as related in both active treatments, and asthenia, increased blood creatinine and increased blood urea reported only in the telmisartan 2 mg/kg treatment.

With respect to serious adverse events and deaths, primarily, the AEs in each treatment group were of mild or moderate intensity. No fatal AEs were reported during study 502.403. Discontinuation due to AEs was noted only in two (6.5%) patients; both in the telmisartan 2 mg/kg treatment group, but the subjects recovered from all events. Possible clinically significant abnormalities were infrequent. Four (16.7%) patients in the telmisartan 2 mg/kg treatment experienced an increase in eosinophils in the differential. One (6.3%) patient experienced a decrease in glucose while on telmisartan 1 mg/kg treatment and one (4.5%) patient experienced an increase while on telmisartan 2 mg/kg in glucose values. One (4.5%) patient experienced an increase in blood urea nitrogen.

A physical exam and ECG were performed at screening and at conclusion of patient participation. Any vital signs, physical or ECG findings constituting a worsening from baseline were reported as adverse events. No significant changes in pulse rate were observed over the course of the trial. However, the study does not include the list of laboratory parameters which were monitored. The lack of this information precludes a complete safety evaluation and the CHMP requested this to be provided.

2.4.3. Discussion

High percentage of patients treated with telmisartan experience AEs. The small number of patients (n=57) and the short period of follow-up (4 weeks) preclude any sound evaluation on the safety of telmisartan in the paediatric population. Overall, the proportions of patients complaining of at least one AE were high: 31.3%, 41.7% and 41.9% in the placebo, telmisartan 1 mg/kg and telmisartan 2 mg/kg, groups, respectively. Due to the relatively small sample size, particularly in the placebo group, any event experienced in at least one patient in placebo, three patients in telmisartan 1 mg/kg and two patients in telmisartan 2 mg/kg resulted in a frequency greater than or equal to 5%.

Of particular concern is the observation that the already high frequency of the AEs of the Nervous system disorders SOC in the 1 mg/kg dose telmisartan group rised exponentially. The most common adverse events observed in the telmisartan groups were headache and dizziness. The lack of information on important characteristics of the patients included in the study (primary hypertension, secondary hypertension) affects the evaluation of the safety profile.

2.5. Changes to the Product Information

The MAH proposed the changes to the Product Information (PI), as described in section below.

During the procedure, the CHMP requested further amendments to the PI and the following changes to the Product Information of Micardis, Kinzalmono and Pritor have been agreed:

4.2 Posology and method of administration

Paediatric population

The safety and efficacy of Kinzalmono in children and adolescents aged below 18 years have not been established.

Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.
~~The safety and efficacy of Kinzalmono in children and adolescents aged below 18 have not been established. No data are available.~~

5.1 Pharmacodynamic properties

Paediatric population
The safety and efficacy of Kinzalmono in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n = 29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and -3.5 (2.1) mm Hg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.
An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown. These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

5.2 Pharmacokinetic properties

Paediatric population
The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age-related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max}.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed and accepted by the CHMP.

3. Overall conclusion and impact on the benefit/risk balance

The proposed type II variation was submitted to comply with Article 46 of Regulation EC No 1901/2006 and to provide text updates for sections 4.2, 5.1 and 5.2 of the SmPC to include information on paediatric use of the products. To support the proposed amendments to the SmPC with regards to the use of the medicinal product in children and adolescents, the MAH conducted the study 502.403, a prospective, randomized, double-blind, placebo-controlled trial with a total duration of up to 6 weeks (4 weeks of active treatment) in male and female hypertensive patients aged 6 to <18 years of age. The study investigated two dosages of telmisartan (TEL) per kg of body weight: 1 mg/kg and 2 mg/kg, defined as low and high, respectively. The reasons underlying the choice of these dosages in the paediatric age are not clear and need to be justified. Furthermore, the CHMP noted that no information was given about the selection criteria with regard to possible causes of high blood pressure and

possible co-morbidities. Thus, based on the initially submitted data it was difficult to assess if efficacy and safety differed by the clinical characteristics of the patients.

The 4-week treatment with telmisartan induced a blood pressure reduction of 9-13 mmHg in msSBP and of 8-8 mmHg in msDBP (1 and 2 mg/kg, respectively), however, a statistically significant decrease in msSBP (- 14 mmHG) was observed only in the telmisartan 2 mg/kg dose group vs placebo; whereas no statistical significant difference was observed for the 1mg/kg dose, albeit an average reduction of 9.7 mmHg vs placebo. No statistical significant effects were recorded for clinical secondary endpoints.

Furthermore, no statistically significant difference from placebo was observed in either the telmisartan "high dose" or "low dose" groups for the secondary endpoint. Similar gains over placebo were achieved by both TEL doses. No relevant differences in the effects of the two doses on blood pressure levels were observed. This observation further supports the CHMP's concerns that too high dosages were used in this study. The lack of a dose-response curve in blood pressure reduction precludes any reliable conclusion about the appropriate dosage of telmisartan in the paediatric population. In summary, the information on the blood pressure lowering effect of doses of telmisartan highly exceeding both the recommended and the highest dose of the drug in adult patients is not considered relevant to be included in the SmPC section 5.1 as proposed by the MAH.

The exposure in the paediatric hypertensive patient population was comparable to the exposure in an adult patient population receiving approximately the same per kilogram doses, 80 and 160 mg/day. It is noted that the recommended dose of telmisartan in the adult population is 40 mg/kg and that further increases up to 80 mg/kg are possible. Thus, the doses administered to the paediatric study population largely exceed both the recommended as well as the maximal dose in the adult patient.

The number of children included in the group 6-<18 years is smaller than that included in the adolescent group and the CHMP concluded that the two age groups cannot be directly compared. The study population is also largely obese. The influence of overweight/obesity on PK parameters has not been investigated. Thus, a conclusion on the transferability of PK data obtained in this population to the European hypertensive paediatric population in the normal weight range cannot be made. The study also confirmed that the non-linearity in the pharmacokinetics of telmisartan observed in the adult population occurs in the paediatric population. The non-linearity for Cmax is more evident for the younger group (6 to <12 years) while, the non-linearity for AUCtau,ss, seems to be more moderate. A significant decrease in the CL/F ratio is observed with dose escalation in the 6-<12 years old age group (727 ml/min vs 338 ml/min), whereas no limited and clinically insignificant decreases in CL/F are observed in the 12 to <18 years old age group, confirming that non-linearity PK profile is particularly evident in the younger age group.

The safety profile of telmisartan in the paediatric population cannot be completely elucidated by the CHMP on the basis of the submitted data, due to the small number of patients (n=57) and to the short period of follow-up (4 weeks). From the data submitted it appears that the frequency of most of the AEs in the both telmisartan treatment groups is higher than placebo. Of particular concern is the observation of the high frequency of AEs of Nervous system disorders.

Thus, the proposed changes of the SmPC (sections 4.2, 5.1, and 5.2) based on the initial submission were not acceptable and requests for supplementary information were agreed by the CHMP. The MAH was requested to address the choice of dosage in study 502.403, transferability of the data from study population to general European paediatric patients with normal weight, lack of information on important characteristics of the patients included in the study. Appropriate proposal for amended wording of the Product Information was also needed.

In their response, the MAH provided responses to all CHMP objections especially with respect to the description of the results from the clinical study 502.403. The CHMP noted that no scientific

justification for the use of high doses in diabetic nephropathy has been submitted and discussed by the MAH. The high doses were intended for a different indication from that currently approved for telmisartan and the reported effect on BP values is limited to the high doses used and has limited relevance for the treatment of hypertension in the general paediatric population. There is also a limitation on the choice of patients with certain body weight. The question of long-term effects of telmisartan on children is unresolved. On the basis of these considerations the relevance of the findings of Study 502.403 for the treatment of paediatric patients with hypertension is questionable, and the CHMP requested that this should be evident in the wording included in the SmPC section 5.1 where the indication of the use of supra-therapeutic doses (1 mg and 2mg/kg BW) not recommended in the treatment of hypertension in the adult population should be included. In addition, the wording should include the information that the safety of supra-therapeutic doses of telmisartan (1 mg and 2 mg/kg BW) during long-term treatment has not been evaluated. The mean weight of the patients who are overweight should be included and the placebo-uncorrected BP reductions should be mentioned in section 5.1 of the SmPC. The MAH complied with this request and proposed an updated wording that is considered acceptable by the CHMP (see section 2.5).

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

In accordance with Article 46 of regulation EC No 1901/2006, update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include the results of study 0502-0403, a study conducted to evaluate the safety, efficacy and pharmacokinetics of telmisartan in the paediatric population.

Furthermore, the Product Information is being brought in line with the latest QRD template version and minor editorial corrections were implemented in section 4 of the Package Leaflet of Micardis, Pritor and Kinzalmono, in section 6.4 of the SmPC of Pritor and Kinzalmono, and in section 9 of the outer labelling of Kinzalmono and Pritor.

The requested worksharing procedure proposed amendments to the SmPC, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

In accordance with Article 46 of regulation EC No 1901/2006, update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include the results of study 0502-0403, a study conducted to evaluate the safety, efficacy and pharmacokinetics of telmisartan in the paediatric population.

Furthermore, the Product Information is being brought in line with the latest QRD template version and minor editorial corrections were implemented in section 4 of the Package Leaflet of Micardis, Pritor and Kinzalmono, in section 6.4 of the SmPC of Pritor and Kinzalmono, and in section 9 of the outer labelling of Kinzalmono and Pritor.

The requested worksharing procedure proposed amendments to the SmPC, Labelling and Package Leaflet.

Summary

Please refer to the published CHMP assessment report.

6. Attachments

1. SPC, Labelling and Package Leaflet (changes highlighted) as adopted by the CHMP on 15 November 2012.
2. Rapporteur's preliminary variation assessment report circulated on 25 May 2012.
3. Rapporteur's updated assessment report circulated on 15 June 2012.
4. Request for supplementary information and extension of timetable adopted by the CHMP on 21 June 2012.
5. Rapporteur's preliminary assessment report on the MAH's responses circulated on 05 September 2012.
6. Rapporteur's updated assessment report on the MAH's responses circulated on 20 September 2012.
7. 2nd Request for supplementary information adopted by the CHMP on 20 September 2012.
8. Rapporteur's preliminary assessment report on the MAH's responses circulated on 29 October 2012.
9. Rapporteur's updated assessment report on the MAH's responses circulated on 9 November 2012.