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Committee for Medicinal Products for Human Use (CHMP)

Aprovel

INN: Irbesartan

Procedure No. EMEA/H/C/141/P45/019

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

I. INTRODUCTION

On 11 December 2008, the MAH submitted 2 additional paediatric studies for Irbesartan (Aprovel, Irbesartan Winthrop (now Irbesartan Zentiva) and Karvea; additional studies not previously provided to the EMEA/CHMP), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the 2 additional paediatric studies submitted do not influence the benefit risk for Irbesartan and that there is no a consequential regulatory action.

1. Neither data/information available nor line-listing on the paediatric studies listed in the MAH previous submissions has been included in the current submission. Reference is made to the Final Assessment Report on Paediatric data for Aprovel/Karvea 75, 150 and 300 mg Tablets (Ibersartan) (EMEA/H/C/141-2). The final conclusion of the mentioned procedure was that "The data provided are insufficient to support an extension of the use of Irbesartan to children". Nevertheless, it was agreed with the proposal of including relevant paediatric data in sections 4.8., 5.1. and 5.2., and to include a statement in sections 4.2. and 4.4. of the SPC explaining that existing data are insufficient to recommend its use in children. As a conclusion, paediatric data included in the Irbesartan SmPCs were modified as follows (variations: Aprovel/H/141/II/75; Irbesartan Winthrop/H/C/785/II/18; Karvea/H/142/II/80; Irbesartan BMS: H/C/786/II/18):

- ***Section 4.2:*** *Paediatric patients: irbesartan is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.8, 5.1 and 5.2).*

- ***Section 4.4:*** *Paediatric patients: irbesartan has been studied in paediatric populations aged 6 to 16 years old but the current data are insufficient to support an extension of the use in children until further data become available (see sections 4.8, 5.1 and 5.2).*

- ***Section 4.8:*** *Paediatric patients: in a randomised trial of 318 hypertensive children and adolescents aged 6 to 16 years, the following related adverse events occurred in the 3-week double-blind phase: headache (7.9%), hypotension (2.2%), dizziness (1.9%), cough (0.9%). In the 26-week open-label period of this trial the most frequent laboratory abnormalities observed were creatinine increases (6.5%) and elevated CK values in 2% of child recipients.*

- ***Section 5.1:*** *Reduction of blood pressure with 0.5 mg/kg (low), 1.5 mg/kg (medium) and 4.5 mg/kg (high) target titrated doses of irbesartan was evaluated in 318 hypertensive or at risk (diabetic, family history of hypertension) children and adolescents aged 6 to 16 years over a three week period. At the end of the three weeks the mean reduction from baseline in the primary efficacy variable, trough seated systolic blood pressure (SeSBP) was 11.7 mmHg (low dose), 9.3 mmHg (medium dose), 13.2 mmHg (high dose). No significant difference was apparent between these doses. Adjusted mean change of trough seated diastolic blood pressure (SeDBP) was as follows: 3.8 mmHg (low dose), 3.2 mmHg (medium dose), 5.6 mmHg (high dose). Over a subsequent two week period where patients were re-randomized to either active medicinal product or placebo, patients on placebo had increases of 2.4 and 2.0 mmHg in SeSBP and SeDBP compared to +0.1 and -0.3 mmHg changes respectively in those on all doses of irbesartan (see section 4.2).*

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

In the descriptive study **CV131-175** (see section 4 of this Assessment Report), pharmaceutical formulations used were Avapro 75 mg tablets (INN: irbesartan; 4 patients), Avapro 150 mg tablets (INN: irbesartan; 7 patients), Avapro 300 mg tablets (INN: irbesartan; 6 patients), Avalide 150/12.5 mg tablets (INN: irbesartan / hydrochlorothiazide; 3 patients) and Avalide 300/12.5 mg tablets (INN: irbesartan / hydrochlorothiazide; 2 patients).

In the study **EFC 7372** (Publication by Franscini et al. AJH. 2002; see section 4 of this Assessment Report), irbesartan was delivered once a day by commercially available tablets (75, 150, and 300 mg), starting with a dose of 37.5 (body weight ranging 10 to 20 kg), 75 (body weight 21 to 40 kg), or 150 mg (body weight >40 kg) on awakening.

II.2 Non-clinical aspects

1. Introduction

The MAH has not submitted additional non-clinical documentation.

2. Non clinical studies

The MAH has not submitted additional non-clinical documentation.

3. Discussion on non-clinical aspects

Not applicable.

II.3 Clinical aspects

1. Introduction

The MAH has submitted the following two additional clinical reports (a descriptive study and one publication):

- **Ref. 1: CV131-175:** Clinical Study Report for CV131175: Experience with Irbesartan Use in Children 16 Years of Age and Younger: A Descriptive Study in Two Medical Claims Databases. Bristol Myers Squibb, 2004. Document Control No. 930007612.

- **Ref. 2 : EFC7372:** Franscini LM, Von Vigier RO, Pfister R, et al. Effectiveness and safety of the angiotensin II antagonist irbesartan in children with chronic kidney diseases. Am J Hypertens. 2002; 15: 1057-63.

The studies are discussed hereafter.

2. Clinical studies

2.1 Study CV131-175: Clinical Study Report for CV131175: Experience with Irbesartan Use in Children 16 Years of Age and Younger: A Descriptive Study in Two Medical Claims Databases. Bristol Myers Squibb, 2004. Document Control No. 930007612.

2.1.1 Description

Bristol-Myers Squibb (BMS) performed a descriptive study CV131175 to comply with the FDA's revised Pediatric Written Request of November 12, 2002, which states that "unpublished data on the use of irbesartan in hypertensive children should be sought from organizations participating in healthcare delivery to the pediatric population." BMS conducted a descriptive study among paediatric patients in 2 large geographically heterogeneous source populations to examine the use of irbesartan, Medical and pharmacy claims were derived from the Ingenix Research Database (RDB) and the Premier Healthcare Informatics database.

2.1.2 Methods

- ***Objective(s)***

To describe the experience with Irbesartan use in children 16 years of age and younger with data from two medical claims databases.

- ***Study design***

Medical and pharmacy claims were derived from the Ingenix Research Database (RDB) and the Premier Healthcare Informatics database. These data sources were chosen because of their large size and coverage of the US population; their ability to capture the most robust number of irbesartan users; and their complementary nature - on comprised of mainly outpatient encounters and the other predominantly inpatient encounters.

After all paediatric patients with dispensing of irbesartan were identified, detailed chronological profiles of claims from each patient's entire history in the health plan were constructed using the initial irbesartan dispensing date as the starting point. From these profiles the health care providers who prescribed irbesartan was identified, if possible, and the medical record from the prescribing provider was sought.

A waiver of patient authorization was obtained from The Privacy Board of the New England Institutional Review Board (NEIRB) before medical records were requested.

- ***Study population /Sample size***

The two databases covered over 4.2 million paediatric lives in the US during the study time period. The Ingenix population included commercial UnitedHealthcare members/subjects enrolled from January 1, 1997 through June 30, 2003 (n=2,607,658). The Premier population included patients with inpatient hospital and pharmacy claims from January 1, 2001 through December 31, 2003 (n=1,668,490).

- ***Treatments***

Based on results from the medical record review, patients were classified into three categories of irbesartan use: confirmed user, confirmed non-user, and unknown user status. Prescribing rates (number of users divided by number of children in the database ages 16 and under) were calculated for all irbesartan users identified on the basis of claims information alone and by chart abstraction, and compared to prescribing rates of another antihypertensive medication, enalapril.

- ***Outcomes/endpoints***

The standard study abstraction form included the following variables (see also Abstraction Form in Appendix V of the final study report): indication for irbesartan therapy; patient's race, age, gender; height and weight at each encounter; medical record history, including disabilities; diagnoses present at irbesartan initiation; major surgery and prescription medications prior to irbesartan initiation; additional prescription medications during irbesartan therapy; dates of irbesartan therapy; all blood pressure measurements from one year before irbesartan initiation until patient's 19th birthday; irbesartan treatment status and reason if discontinuation; results of serum creatinine, creatinine clearance, and serum potassium laboratory tests; a list of potential adverse events that occurred during irbesartan therapy grouped by body system type; list of comorbid conditions and diagnoses.

- ***Statistical Methods***

From the completed abstraction forms of confirmed irbesartan users, summary statistics were derived to characterize the study population, including age, race, gender, average height and weight at time of irbesartan initiation, number of prescriptions of irbesartan, duration of use and average daily dose, average systolic and diastolic blood pressure at time of initiation, and other variables of interest.

2.1.3 Results

- ***Recruitment/ Number analysed***

The combined total identified 82 patients as having at least one claim for irbesartan within the study period. After careful evaluation of the claim or chart, 21 patients were confirmed irbesartan users, 19 were confirmed non-users, and 10 were classified as unknown user status.

Ingenix: A total of 26 children 16 years of age or younger were identified by at least one pharmacy claim for an irbesartan dispensing within the date range of the study, seven (27%) females and 19 (73%) males (Table 1). For two children, the claims contained insufficient information to identify an irbesartan-prescribing physician. Neither of these children had claims for office visits to any type of provider, nor did they have diagnosis codes for hypertension. Each had only a single claim for irbesartan. These two patients were classified as "unknown" irbesartan status. Therefore, the final number of children identified for chart review was 24.

Premier: A total of 56 discharges among children 16 years of age or younger were identified by at least one pharmacy claim for an irbesartan dispensing within the date range of the study - 20 (36%) females and 36 (64%) males (Table 1). Thirty of the claims identified were found to be duplicate ID numbers, thus the final number of children identified for chart review was 26.

The study documented that the use of irbesartan among insured pediatric patient in the US was extremely low. Overall, from the medical-record confirmed data, irbesartan was prescribed to 0.23 children per 100,000 patients (2.3 per million patients) in the Ingenix database. In the Premier database, irbesartan was prescribed to 0.90 children per 100,000 patients (9.0 per million patients). After the medical charts abstraction effort, for various reasons, there were only 6 patients identified as irbesartan confirmed users with the medical record available in the Ingenix database and 15 irbesartan confirmed users with the medical record in the Premier database (Table 1).

Table 1. Disposition of Patients in Medical Record Abstraction Effort and Irbesartan User Status Ingenix (n=26); Premier (n=56)

Healthcare Company	No. of Patients Identified from Claims	Minus Patients Dropped	Total No. of Patients Identified for Chart Abstraction	Medical Records Obtained	Unable to Obtain Medical Records		Confirmed Irbesartan Status		
					Obtained Info Verbally from Provider	No Further Info Available	Users	Non-Users	Unknown
Ingenix	26	2 Unable to locate provider	24	9	9*	6	6	12	6*
Premier	56	30 Duplicate**	26	22	---	4	15	7	4
Combined Totals	82	32	50	31	9	10	21	19	10

* Totals include two patients that the provider verbally identified as age ineligible.
** Thirty patients had duplicate ID numbers.

- ***Baseline data***

After the medical record review, 21 patients were classified as confirmed irbesartan users. Table 2 lists the demographics and baseline characteristics for these patients.

Table 2. Demographic and Baseline Characteristics of Confirmed Irbesartan Users

	Premier N=15	Ingenix N=6	Overall N=21
Characteristic			
Age (years) at date of irbesartan initiation, N			
<6	2	0	2
6 – 10	2	0	2
11-12	1	1	2
13 – 15	6	2	8
16	4	3	7
Male N (%)	10 (67)	5 (83)	15 (71)
Female N (%)	5 (33)	1 (17)	6 (29)
Race N (%)			
Caucasian	8 (53)	4 (67)	12 (57)
African American	7 (47)	1 (17)	8 (38)
Missing	0	1 (16)	1 (5)
Mean height, inches (SD)	58.9 (13.2)	67.5 (3.7)	61.1 (12.0)
Mean weight, pounds (SD)	134.8 (82.2)	241.3 (91.6)	162.8 (95.3)
Mean body mass index (SD)	26.9 (10.6)	35.9 (14.7)	29.5 (12.6)
Mean blood pressure, mmHg (SD)			
Systolic	123.7 (19.9)	140.4 (29.0)	129.0 (22.9)
Diastolic	67.1 (11.4)	89.2 (19.7)	73.0 (16.4)
Evidence of Hypertension N (%)	11 (73)	4 (67)	15 (71)
Region N (%)			
South	14 (93)	4 (67)	18 (86)
Midwest	0	2 (33)	2 (9)
West	1 (7)	0	1 (5)

- ***Efficacy results***

Not applicable. Only adverse events are assessable in this study (see safety results).

- ***Safety results***

An indication for irbesartan was recorded in 13/15 charts, and in 10 (77%) of these the indication was for hypertension. Disabilities noted in the 15 Premier confirmed users included end stage renal disease, idiopathic cardiomyopathy, asthma, obesity, and retardation. The most commonly recorded diagnosis at irbesartan initiation was hypertension (11/15 patients, 73%), followed by focal segmental glomerulosclerosis (7/15 patients, 47%). None of the records indicated surgical procedures in the year before irbesartan initiation. Other antihypertensive medications recorded were captopril and furosemide. Diagnoses that were documented in the chart during irbesartan therapy are listed in Table 3.

Table 3. Diagnoses Reported During Irbesartan Treatment

Type of Event	Premier N=15	Ingenix N=6	Overall N=21
	N (%)	N (%)	N (%)
GASTROINTESTINAL			
Abdominal pain	5 (33)	2 (33)	7 (33)
Diarrhea	2 (13)	0	2 (9.5)
Dyspepsia/heartburn	1 (7)	0	1 (4.8)
Jaundice	0	0	0
Nausea/vomiting	4 (27)	0	4 (19)
Other GI event	2 (13)	1 (17)	3 (14)
CARDIOVASCULAR			
Chest pain	3 (20)	0	3 (14)
Hypertension	8 (53)	4 (67)	12 (57)
Hypotension	1 (7)	0	1 (4.8)
Tachycardia	4 (27)	0	4 (19)
Other Cardiovascular event	5 (33)	0	5 (24)
EDEMA/ALLERGIC REACTION			
Angioedema	0	0	0
Edema	3 (20)	0	3 (14)
Rash	1 (7)	0	1 (4.8)
Urticaria	0	0	0
Other Edema/allergic reaction	0	0	0
RESPIRATORY			
Influenza	0	1 (17)	1 (4.8)
Pharyngitis	1 (8)	1 (17)	2 (9.5)
Rhinitis	2 (17)	1 (17)	3 (14)
Sinus abnormality	2 (17)	0	2 (9.5)
Other Respiratory event	8 (53)	1 (17)	9 (43)
LABORATORY FINDINGS			
Elevated liver function tests (all)	0	0	0
Decreased hemoglobin	8 (53)	0	8 (38)
Hyperkalemia	3 (20)	0	3 (14)
Other laboratory finding (abnormal)	13 (87)	1 (17)	14 (67)
MISCELLANEOUS			
Anxiety/nervousness	1 (7)	0	1 (4.8)
Dizziness	0	1 (17)	1 (4.8)
Fatigue	3 (20)	0	3 (14)
Musculoskeletal pain	3 (20)	1 (17)	4 (19)
Urinary tract infection	0	0	0
Other event	4 (27)	2 (33)	6 (29)

Hypertension, respiratory illness and abdominal pain were the most frequent diagnoses during irbesartan treatment. No deaths were reported in this study.

In the review of 6 outpatients from the Ingenix database 1 case of elevated creatinine was found. In the Premier Healthcare database, serum potassium and creatinine records for hospitalized 15 patients were available in 14 cases. Six patients had elevated creatinine, all of whom had a documented history of renal disease. Six subjects had elevated serum potassium, all of whom also had a documented history of renal disease.

2.2 EFC7372: Franscini LM, Von Vigier RO, Pfister R, et al. Effectiveness and safety of the angiotensin II antagonist irbesartan in children with chronic kidney diseases. Am J Hypertens. 2002; 15(12): 1057-63.

2.2.1 Description

The efficacy of irbesartan in reducing blood pressure or proteinuria or both was evaluated in paediatric population in a study by Franscini et al. [Ref. 2]. This study was performed at 2 centers in Switzerland and Italy. This was an open label longitudinal study with no control group. In this study 36 paediatric outpatients, aged 3.7 to 18 years (median 10 years), with arterial hypertension and various underlying renal conditions were prospectively evaluated. Twenty-one outpatients, aged 4.8 to 14 (median 10 years), with overt proteinuria (defined as urinary protein excretion > 6 mg/[m^2 x h]) were also evaluated. In those 2 studied populations, the treatment schedules were slightly different and the results were evaluated separately.

2.2.2 Methods

- ***Objective(s)***

To assesss the efficacy of irbesartan in reducing blood pressure or proteinuria or both in the paediatric population.

- ***Study design***

Open label longitudinal study with no control group.

- ***Study population /Sample size***

A total of 44 pediatric outpatients with chronic kidney disease (27 male and 17, aged 3.7 to 18 years, median 10 years) were given irbesartan once a day during 18 weeks for arterial hypertension (N = 23), proteinuria (N = 8), or both (N = 13). No sample size calculation is included in the publication.

- ***Treatments***

Hypertension: Commercially available irbesartan tablets (75, 150 and 300 mg) were taken once daily after awakening, starting with a dose of 37.5 mg (body weight 10 to 20 kg), 75 mg (body weight 21 to 40 kg) or 150mg (body weight >40 kg). The dose of irbesartan was doubled if systolic blood pressure was not lowered at least by 10 mmHg 3 to 5 weeks after study initiation, or if systolic blood pressure was above the 95% CI for body length and sex after 8 to 12 weeks of treatment. The total duration of the study was 18 weeks.
Proteinuria: Commercially available irbesartan tablets (75, 150 and 300 mg) were taken once daily after awakening, at a dose of 37.5 mg (for body weights 10-20 kg), 75 mg (for body weights 21-40 kg) or 150 mg (for body weights >40 kg) for 18 weeks.

- ***Outcomes/endpoints***

Patients with Hipertension:
a) Arterial pressure: Sitting (>10 min) arterial pressure (first and fifth Korotkoff sounds) was measured after overnight by means of a mercury sphygmomanometer with a cuff covering approximately three quarters of the upper arm length from the acromion to the olecranon; each recorded value was the mean of at least three consecutive measurements. The effect of irbesartan on arterial pressure was evaluated 24 h postdose.

b) Other outcomes: heart rate, and body weight were measured, and blood was taken for the determination of packed cell volume (microhematocrit centrifuge), sodium and potassium (ion selective electrodes), creatinine (kinetic alkaline picrate assay), uric acid (allantoin-uricase assay), albumin (bromcresol purple assay), and aminotranferases and creatine kinase (kinetic assays) from each patient before entering the trial and after 18 weeks of irbesartan. The whole blood cyclosporine trough level was measured using a specific monoclonal fluorescent polarization immunoassay in the patients treated with this agent. Patients were monitored by a written questionnaire before and during irbesartan treatment for the presence of abdominal pain, constipation, cough, diarrhea, dizziness, edema, fatigue, headache, insomnia, myalgia, nausea, orthostasis, and rash.

Patients with Proteinuria: Every patient carried out a timed overnight urine collection during 3 consecutive days both before and with irbesartan for determination of total protein (Coomassie blue assay) and creatinine (kinetic alkaline picrate assay). The urinary protein excretion (in mg/[m^2 x h]) and the urinary protein/creatinine ratio (in mg/mmol) were calculated. The mean of the three determinations was used for analysis. Arterial pressure, heart rate, body weight, laboratory values, and the written questionnaire were also evaluated as in patients with arterial hypertension.

- ***Statistical Methods***

Results were given as median and interquartile range (which extends from the value at centile 25 to that at centile 75 and includes half of the data points), as relative frequency, or depicted as a “box and whiskers plot” (boxes are median and interquartile ranges, vertical lines are ranges). Nonparametric analysis of variance for repeated measurements, the McNemar change test (with the Yates correction for continuity), and simple regressions with the coefficient of correlation r_s were used for analysis. A P value < 0.05 was regarded as statistically significant.

2.2.3 Results

- ***Recruitment/ Number analysed***

Hypertension: Thirty-six pediatric outpatients (22 male and 14 female, aged 3.7 to 18 years, median 10 years) with arterial hypertension were prospectively evaluated in Berne and Milan between 1999 and 2001. The underlying renal conditions were glomerular diseases (N = 13), urinary tract malformations (N = 12), polycystic kidney disease (N = 3), nephronophthisis (N = 1), renal artery stenosis (N = 1), and renal transplant (N = 6).
Proteinuria: Twenty-one outpatients (12 male and 9 female subjects, aged between 4.8 and 14, median 10 years) with overt proteinuria, defined as urinary protein excretion >6 mg/[m^2 x h], were prospectively evaluated. They were 13 of the aforementioned patients with arterial hypertension (glomerular diseases, N = 12; nephronophthisis, N = 1; see Arterial Hypertension) and eight normotensive patients (five male and three female subjects, aged 4.1 to 14 years, median 12 years) with chronic glomerular diseases. Renal function was either normal (N = 16) or mildly reduced (N = 5).

- ***Baseline data***

Hypertension: Renal function ranged from normal to mild and moderate renal failure and 5 patients were on regular dialysis. A total of 12 of the 36 hypertensive patients were already taking various antihypertensive medications at study entry. The mean systolic blood pressure at baseline was 152 mmHg (range: 142-166 mmHg) and mean diastolic blood pressure was 92 mmHg (range: 85-96 mmHg).

Proteinuria: In the group of patients with proteinuria and chronic kidney disease, 13 had hypertension and 8 had normal blood pressure. Renal function was either normal (in 16 patients) or mildly reduced (in 5 patients). In the 20 patients who completed the study baseline proteinuria ranged from 51 to 204 mg/(m2x h) (median 126 mg/(m2 x h)).

Age distribution and disease conditions of 44 pediatric patients included are shown in Figure 1.

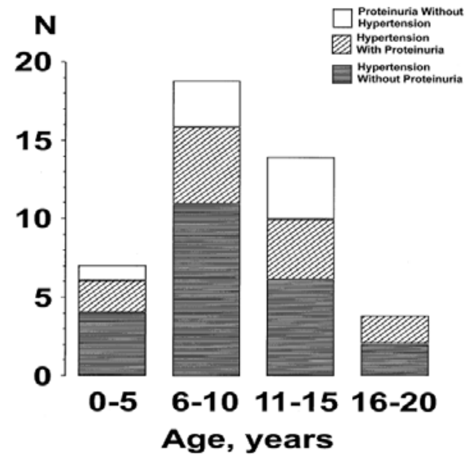

FIG. 1. Age distribution and disease conditions in 44 pediatric patients with chronic kidney diseases (27 male and 17 female subjects) included in the study.

- ***Efficacy results***

Hypertension: The use of irbesartan 4.1 (3.1–5.3) mg/kg body weight daily (median and interquartile range) was associated with a decrease (P < 0.005) in arterial pressure by 17 (13–22)/10 (7–12) mm Hg. The mean initial dose of irbesartan was 2.6mg/kg body weight (range: 2.2-2.9 mg/kg) once daily (71 mg/m2 body surface area (range 59-102 mg/m2)) and this dose was doubled in 26 of the 36 patients. After 18 weeks of treatment with irbesartan, the mean systolic blood pressure decreased by 17 mmHg (13-22) and mean diastolic blood pressure decreased by 10 mmHg (7-12). In 20 of 36 patients both systolic and diastolic blood pressures were below the 95% CI at the end of the study. There was no difference in the results between the subgroups of patients with and without renal failure. The blood pressure reduction was similar in those patients previously treated for hypertension and those who had not received the drug.

Proteinuria: The urinary protein excretion decreased (P < 0.01) during treatment with irbesartan (2.9 [2.0–4.8] mg/kg body weight) by 52 (0 –75) mg/[m2 x h]), whereas plasma albumin increased (P < 0.05) by 4 (1–5) g/L.

- ***Safety results***

Adverse events reported in this study included abdominal pain, constipation, cough, diarrhea, dizziness, edema, fatigue, headache, insomnia, myalgia, orthostasis and rush. Overall, the frequency of those adverse events was similar before and after administration of irbesartan (Table 4).

Table 4. Adverse events before and with irbesartan in 44 pediatric patients with chronic kidney diseases

	Hypertension Without Proteinuria		Hypertension and Proteinuria		Proteinuria Without Hypertension		All Patients	
	Before Irbesartan	With Irbesartan	Before Irbesartan	With Irbesartan	Before Irbesartan	With Irbesartan	Before Irbesartan	With Irbesartan
Patients, *N*	23	23	13	13	8	8	44	44
Abdominal pain, *N*	1	1	1	1	0	0	2	2
Constipation, *N*	1	3	0	0	1	1	2	4
Cough, *N*	1	0	2	2	0	0	3	2
Diarrhea, *N*	0	0	2	2	1	1	3	3
Dizziness, *N*	0	0	2	2	1	1	3	3
Edema, *N*	0	0	0	0	0	1*	0	1*
Fatigue, *N*	3	3	0	0	0	0	3	3
Headache, *N*	0	0	0	0	0	0	0	0
Insomnia, *N*	1	2	0	0	0	0	1	2
Myalgia, *N*	0	0	0	0	0	0	0	0
Nausea, *N*	0	0	0	0	0	0	0	0
Orthostasis, *N*	2	0	0	0	0	0	2	0
Rash, *N*	0	0	0	0	0	0	0	0
Patients with adverse events, *N*	5	6	3	2	3	3	11	11

* Elevated, erythematous pruritic wheals surrounded by an area of erythema involving the head and trunk 2 h after a first dose of irbesartan (see text). Patient withdrew from study.

A 12-year-old normotensive boy with pathologic proteinuria reported the appearance of elevated, erythematous pruritic wheals surrounded by an area of erythema involving the head and the trunk 2 h after a first dose of irbesartan. Swelling of the mouth, tongue, and eyelids was not reported. As a consequence, he withdrew from irbesartan. No further patient withdrew from irbesartan. Plasma sodium slightly but significantly decreased, whereas plasma potassium significantly increased. Packed cell volume, plasma aminotransferases, creatine kinase, creatinine, and uric acid were not influenced by the use of irbesartan. In none of the patients did plasma potassium and sodium levels change by >0.5 mmol/L and 5 mmol/L. In none of the patients did circulating uric acid and creatinine levels change by >20%.

3. Discussion on clinical aspects

The descriptive study CV131175 (Ref. 1; see section II.3) of medical records of off label use of irbesartan in US paediatric populations covered by the selected databases showed that use of irbesartan was very rare (0.23 children per 100,000 patients in the Ingenix database and 0.90 children per 100,000 patients (9.0 per million patients).). The number of records available and assessable (N = 21) was very limited and numerous comorbid conditions and concomitant medications were reported in addition to irbesartan which makes it difficult to establish any casual association between irbesartan use and the occurrence of adverse events. In the limitations associated with the overall infrequent use of irbesartan in the US paediatric populations covered by the selected databases, the limited amount of available records and the content of the records, as well as a notably sicker population in the Premier database (hospitalized patients) hinder evaluation of the safety of irbesartan use in children.

In the publication by Franscini et al (Ref.2; see section II.3), irbesartan dosed at 37.5 mg (body weight 10 to 20 kg), 75 mg (body weight 21 to 40 kg) or 150mg (body weight > 40 kg) daily was found to be effective in reducing arterial pressure and proteinuria in paediatric patients [Ref. 2]. The major limitation of this study is uncontrolled design and lack of comparison group, as well as open label design, which prevents from definitive conclusions, specially taking into account that a previous double-blind clinical trial (description included in section 5.1 of current Irbesartan SPC) showed no statistically/clinically significant decrease in arterial pressure with irbesartan compared with placebo. Also in the available summary of the data it is not possible to identify individual subjects with newly reported AEs vs subjects in which the same AEs were present before and after administration of irbesartan. Thus, the frequency of new AEs cannot be compared with previously reported paediatric studies and presented in away consistent with the frequencies currently presented in the label.

Comment:

Although hypertension is an infrequent problem among children and adolescents, hypertension has a greater likelihood of developing and requiring drug therapy in certain patients, including those with renal or cardiac disease, diabetes mellitus, parents with hypertension, or obesity. For irbesartan, a small pharmacokinetic study was published several years ago that appeared to indicate that starting doses of 75 to 150 mg/day were effective in children with hypertension [3]. This preliminary study was included in a further review by the MAH, which concluded that "irbesartan may be a treatment option for pediatric hypertensive patients" and that "irbesartan is an excellent choice for management of hypertension across all patient groups" [4]. However, more recently a larger efficacy study was completed that apparently failed to show a significant anti-hypertensive effect of irbesartan in children 6 to 16 years old. These results have not been published in the medical literature, but the FDA review is available [5] and the description of the pivotal study in children with hypertension was also included in the EU SPC of Irbesartan [6] after reviewing the data [Final Assessment Report on Paediatric data for Aprovel/Karvea 75, 150 and 300 mg Tablets (Ibersartan) (EMEA/H/C/1412)]. Therefore, use of this agent in children with hypertension cannot be endorsed at this time, as stated in current EU SmPC.

OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

The additional data provided in this submission do not change the current benefit/risk ratio of Irbesartan use in children, which is considered negative, as stated in currently approved SPC. According to the MAH's conclusion, due to the limited scope and methodological limitations, the additional data provided in this submission do no warrant an update of the product information.

➢ **Recommendation**

X Fulfilled

No further action required

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