CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation I

NDA 20757 **SUBMISSION DATES**: July 30, 2004
Supplement (b) (4) 034 September 2, October 1, 2004
Supplement Amendment (b) (4) 034 BB

Avapro ® (irbesartan) Tablets
Bristol-Myers Squibb Company
Princeton, NJ

Reviewer: Peter H. Hinderling, MD

TYPE OF SUBMISSION: Pediatric Exclusivity Supplement (b) (4) 034 and Supplement Amendment (b) (4) 034 BB to NDA 20757

Reference is made to the approved NDA 20757 for Avapro® (irbesartan) tablets of 75 mg, 150 mg and 300 mg strengths. Irbesartan is indicated in adults for the treatment of hypertension and treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension.

Supplement (b) (4) 034 to NDA 20757 dated July 30, 2004 includes the reports of:

1. Study CV131171: Bioequivalence Study of 18.75 mg (b) (4) Irbesartan Tablets Relative to 18.75 mg Pediatric Small Irbesartan Tablets in Healthy Subjects

2. Study CV 13172: Bioequivalence Study of 37.5 mg (b) (4) Irbesartan Tablets Relative to 37.5 mg Pediatric Small Tablets in Healthy Subjects

3. Validation Report LCMSB 232: Quantitation of Irbesartan in Human Plasma via HPLC with MS/MS Detection

4. Formulation Qualification Proposal for Irbesartan Tablets containing the results on the dissolution testing (b) (4)

5. Study CV 131154: Study of Blood Pressure Reduction with Irbesartan in Children and Adolescents

6. Study CV 131141: The Pharmacokinetics of a Single Dose of Irbesartan in Children 1 Month to 6 Years of Age

7. Study CV 131175: Use of Irbesartan in Children

Earlier submissions in 2000 and 2003 contained the report of Study CV 131076, the single and multiple dose pharmacokinetics of irbesartan in hypertensive children and adolescents (SE5-014) and the Formulation Qualification Proposal for the irbesartan tablets (Original Amendment N (000)PG), respectively. The pharmacokinetic data obtained in the 2 older pediatric populations were acceptable to OCPB/DPE1. Also the Formulation Qualification Proposal was acceptable to OCPB/DPE1. However, the dissolution data contained in that document were to be evaluated together with the final reports on the bioequivalence studies.

Supplement Amendment (b) (4)034 BB submitted on October 4, 2004, contained data on the values of the apparent terminal half-life and volume of distribution of irbesartan for the single and multiple dose study in school age children and adolescents. These data were requested by this Reviewer. They were not contained in the report of study CV 131076 submitted in 2000, but were stipulated in the Written Request.

In addition the Supplement Amendment contained information on the composition and dissolution performance of tablets used to qualify the clinical tablets used in study 131154. These data were requested by this Reviewer for the qualification and linkage of the different tablet formulations used in the pediatric program.

TABLE OF CONTENT

1. EXECUTIVE SUMMARY

The results of the two bioequivalence studies indicate that the 18.75 mg and the 37.5 mg (b) (4) tablets are bioequivalent to the PS tablets of the corresponding strengths.

The evidence provided by the results of the bioequivalence studies and in vitro dissolution testing links the (b) (4) the clinical tablets used in the dose ranging study in the pediatric target population, and the marketed Avapro® tablets.

The accuracy of the LC/MS/MS method used in the two bioequivalence studies when assessed at the highest concentration of the QC samples exceeded the 15 % limit. However, it is very unlikely that the observed small bias impacted the study results. The validation report of the LC/MS/MS method used in the two bioequivalence studies is acceptable.

The earlier submitted single and multiple dose pharmacokinetic study with extensive sampling enrolled 9 school-children and 12 adolescents, predominantly males of African-American origin. The dose of irbesartan administered to the children was approximately 2 mg/kg. The resulting exposure values were similar to those in adults. The data of the study were reviewed by OCPB/DPE1 in 2000 and found to be appropriate (b) (4) It should be noted that in the pharmacokinetic study one dose level (2.0 mg/kg) was tested whereas in the efficacy and safety study a dose range of 0.5 mg/kg - 4.5 mg/kg was evaluated.

The results of the dose ranging study in hypertensive school children and adolescents indicated that irbesartan elicits a statistically significant antihypertensive effect in a hypertensive pediatric population. Irbesartan lowered the through sitting systolic blood pressure (primary endpoint) and the through sitting diastolic blood pressure statistically significantly during the up-titration phase compared to baseline and during the withdrawal phase compared to placebo. During the up-titration phase respective decreases in the systolic blood pressure from baseline of -11.7, -9.3 and -13.2 mm Hg after doses of 0.5 mg/kg, 1.5 mg/kg and 4.5 mg/kg, were observed. The corresponding decreases in the diastolic blood pressure were -3.8, -3.2, and -5.6 mmHg, respectively. During the withdrawal phase the difference in systolic and diastolic blood pressure between subjects receiving the active treatment and subjects on placebo was identically small, namely -2.3 mm Hg. There was no dose-response relationship observed for the effect on systolic blood pressure. The antihypertensive effect of -2.3 mmHg measured is considered therapeutically insignificant by the Cardiorenal Division. (b) (4)

1.1 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE1) has reviewed the study reports of the bioequivalence studies CV 131171 and CV 131172 and the results of the dissolution tests with the proportionally similar (b) (4), PS and PL tablets submitted under Supplement (b) (4) 034 and the Supplement Amendment (b) (4) 034 BB to NDA 20757.

(b) (4)

Based on the results of the dissolution testing in 3 media the biowaivers requested by the sponsor for the 37.5 mg PL and (b) (4) tablets and the 75 mg PL tablets should be granted. The pH 2 medium used by the sponsor instead of the customary pH 4.5 medium is acceptable for irbesartan. The submitted data also support the qualification of the formulations used in the efficacy and safety trial. (b) (4)

The pharmacokinetic and biopharmaceutic data provided by the sponsor meet the requirements of the Written Request.

(b) (4)

The PK data indicate that the small antihypertensive effect of the drug is not due to diminished exposure (AUC, Cmax).

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Peter H. Hinderling, M.D. Date
Clinical Pharmacology & Biopharmaceutics Reviewer

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Patrick Marroum, Ph.D.
Team-Leader Cardio-Renal

The CPB briefing was held on December 3, 2004. Attendees: Drs. S-M. Huang, C. Sahajwallah, J. Hunt, A. Rahman, P. Marroum, G. De Los Reyes, A. Bhattaram, J. Pravin

1.2. SUMMARY OF CPB FINDINGS

Of the 7 reports submitted, reports 1-4 and 6 are in the Clinical Pharmacology and Biopharmaceutics realm.

The validation report of the LC/MS/MS method used in the two bioequivalence studies is acceptable.

The accuracy of the LC/MS/MS method used in the two bioequivalence studies when assessed at the highest concentration of the QC samples exceeded the 15 % limit. However, it is very unlikely that the observed small bias impacted the study results

The results of the two bioequivalence studies indicate that the 18.75 mg and the 37.5 mg (b) (4) tablets are bioequivalent to the PS tablets of the corresponding strengths.

The evidence provided by the results of the bioequivalence studies and in vitro dissolution testing links the (b) (4) the clinical tablets used in the dose ranging study in the pediatric target population, and the marketed Avapro® tablets.

The single dose pharmacokinetic study of irbesartan in children 1 month to 6 years of age was terminated after enrollment of 2 subjects in the study. Only one of the 2 subjects was dosed, but a data analysis was not performed.

The results of the dose ranging study in hypertensive school children and adolescents indicated that irbesartan elicits a statistically significant antihypertensive effect in a hypertensive pediatric population. Irbesartan lowered the through sitting systolic blood pressure (primary endpoint) and the through sitting diastolic blood pressure statistically significantly during the up-titration phase compared to baseline and during the withdrawal phase compared to placebo. During the up-titration phase respective decreases in the systolic blood pressure from baseline of -11.7, -9.3 and -13.2 mm Hg after doses of 0.5 mg/kg, 1.5 mg/kg and 4.5 mg/kg, were observed. The corresponding decreases in the diastolic blood pressure were -3.8, -3.2, and -5.6 mmHg, respectively. During the withdrawal phase the difference in systolic and diastolic blood pressure between subjects receiving the active treatment and subjects on placebo was identically small, namely -2.3 mm Hg. There was no dose-response relationship observed for the

effect on systolic blood pressure. The antihypertensive effect of -2.3 mmHg measured is considered therapeutically insignificant by the Cardiorenal Division. (b) (4)

The earlier submitted single and multiple dose pharmacokinetic study with extensive sampling enrolled 9 school-children and 12 adolescents, predominantly males of African-American origin. The dose of irbesartan administered to the children was approximately 2 mg/kg. The resulting exposure values were similar to those in adults. The data of the study were reviewed by OCPB/DPE1 in 2000 and found to be appropriate (b) (4) It should be noted that in the pharmacokinetic study one dose level (2.0 mg/kg) was tested whereas in the efficacy and safety study a dose range of 0.5 mg/kg - 4.5 mg/kg was evaluated.

On September 10, 2004 the sponsor submitted the requested values for the apparent terminal half life, T-half, and volume of distribution, Vdbeta/F for the single and multiple dose pharmacokinetic study CV 1131076. This information had not been provided in the report of the study that was submitted in 2000, but was requested by the Written Request. The mean and median data are provided in Table 2 for the school-age children and the adolescents:

Table 2:
SUMMARY STATISTICS FOR BMS-186295 PHARMACOKINETIC PARAMETERS BY AGE-GROUP

		LAST DOSE	
AGE-GROUP	Statistics	T-HALF (H)	VdBeta/F (L)
6-12 yrs	N	9	9
	MEAN	23.9	668.560
	SD	21.3	556.973
	GEOMEAN	18.2	444.929
	CV	89	83
	MEDIAN	14.6	510.897
	MIN	6.6	59.124
	MAX	74.8	1589.099

Table 2:
SUMMARY STATISTICS FOR BMS-186295 PHARMACOKINETIC PARAMETERS BY AGE-GROUP

		LAST DOSE	
AGE-GROUP	Statistics	T-HALF (H)	VdBeta/F (L)
13-17 yrs	N	12	12
	MEAN	15.6	381.036
	SD	8.7	297.519
	GEOMEAN	13.8	292.552
	CV	56	78
	MEDIAN	12.5	265.786
	MIN	7.4	97.737
	MAX	34.2	1037.567

The median data indicate that the T-half of irbesartan in hypertensive school children and adolescents is 14.6 hours and 12.5 hours, respectively. The corresponding values for Vdbeta/F are 510.9 L and 265.8 L, respectively, suggesting a trend for a smaller value in school age children than in adolescents. In contrast, the T-half values appear to be similar in the two pediatric populations. However, it should be noted that samples were only collected for a period of 24 hours in most children. Thus, the t1/2 and VD beta values may be biased. Overall, based on the more reliable CL/F values, the pharmacokinetics among the pediatric populations and compared to adults appear to be similar.

2. QUESTION BASED REVIEW

What Does the Written Request Stipulate?

- A dose-ranging trial of effectiveness in hypertensive pediatric patients and safety data data from the controlled trials, a 6 month open-label treatment phase following the effectiveness trial. At least 50% of the participants should be school age children of black and non-black origin.

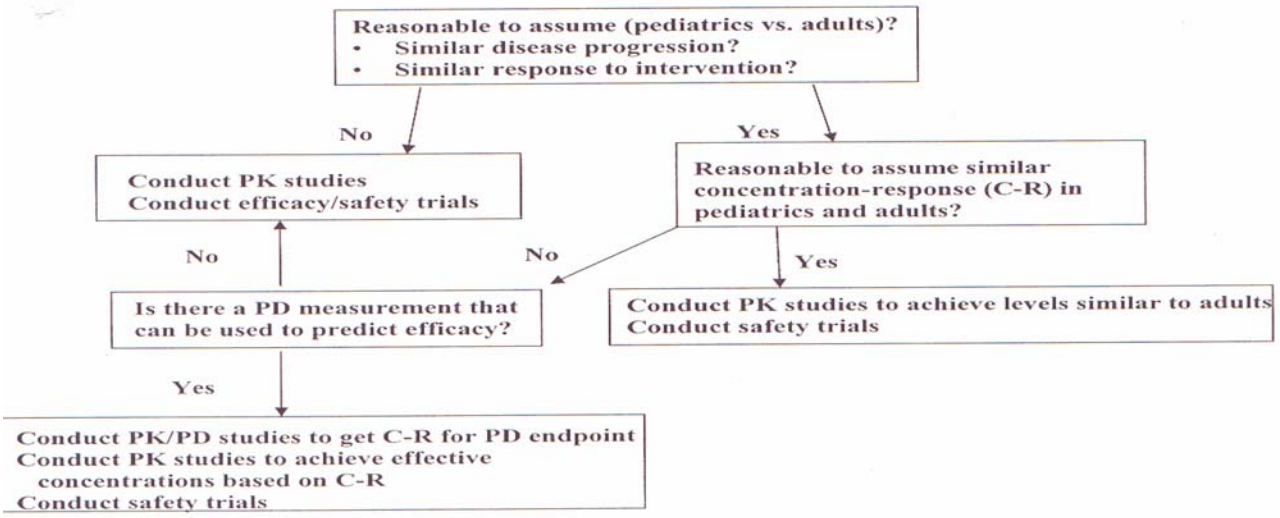
- Pharmacokinetic information on AUC, t1/2, Cl/f, Vd/F, Cmax, and Tmax in hypertensive patients spanning the same age range as those to be studied for effectiveness

- Formulations that are well characterized and appropriate to the age and clinical setting

What is the Rationale for the Requested Studies?

In accordance with the Decision Tree criteria shown in the following scheme:

Figure 1. Pediatric Decision Tree, Integration of PK/PD
(Refer to "Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications" [Word] or [PDF])



it is not a given that disease progression and the response to drug intervention in hypertensive patients is the same in the pediatric and adult population. Blood pressure is a surrogate endpoint whose congruence with endpoints has been demonstrated only in the adult population. In addition, efficacy in the pediatric population could not be demonstrated for all 4 ACE-inhibitors and for both calcium antagonists that have been submitted thus far. Also, there is evidence that the magnitude of the blood pressure lowering effect of some antihypertensives is smaller in the pediatric than in the adult population. Thus, the stipulation of the Written Request for the performance of an efficacy and safety study is justified. Also, the requirement for a PK study to generate a

base for adjusting the dose regimen in pediatrics in case identical mg/kg based doses result in different exposure (AUC, Cmax) in pediatric and adult populations is in order.

What are the Documents Submitted in Supplement (b) (4) 034 and Supplement Amendment (b) (4) 034 BB to NDA 20757?

The application provides additional information on the pediatric development program for irbesartan that was conducted in accordance with the amended Written Request of November 8, 2002. Supplement (b) (4) 034 contains:

- Reports of two bioequivalence studies in adults (CV 131171, CV 131172) of two (b) (4) tablets of 18.75 mg and 37.5 mg strengths

- Validation report on the LC/MS/MS method used to assay irbesartan in the two bioequivalence studies (LCMSB 232)

- Formulation qualification strategy and results of in vitro dissolution comparisons of the (b) (4) tablets and the clinical formulations used in the dose-ranging efficacy and safety study in children

- Report of the dose ranging efficacy and safety study of irbesartan with an extended open-label phase in school age children and adolescents (CV 131154).

- Abbreviated report on the single dose pharmacokinetics of irbesartan in infants and preschool children (CV 131141). Study CV 131141 was discontinued after enrollment of 2 subjects.

- Report on pediatric use of irbesartan (CV131175)

Supplement Amendment (b) (4) 034 BB contains information on volume of distribution and half-life of irbesartan in the single and multiple PK study in school age children and adolescents approved in 2000.

In addition the Supplement Amendment contains information on the composition and dissolution performance of tablets used to qualify the clinical tablets administered to the children in study 131154.

What is the Relevant Regulatory History?

The report on the single and multiple dose pharmacokinetic study of irbesartan in school-age children and adolescents was submitted in 2000 (CV 131076). The study results were considered acceptable by OCPB/DPE1 (b) (4) It should be noted that there is a 4 year gap between submission of the pharmacokinetic data and the results of the pivotal efficacy and safety study conducted in the same age groups.

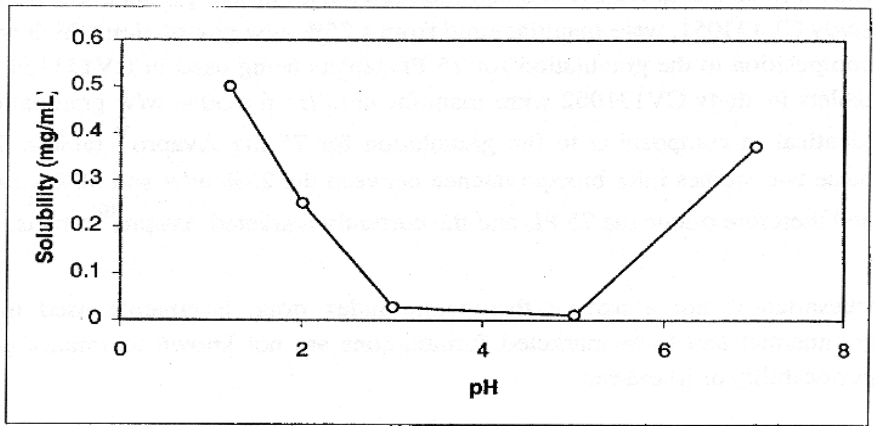
The formulation qualification program was submitted in 2003. It proposed linkage of (b) (4) clinical formulations used in the pivotal study and the already marketed formulations by performing bioequivalence studies and in vitro dissolution tests. The program was considered acceptable by OCPB/DPE1. The also submitted dissolution data were to be only analyzed after the final reports of the bioequivalence studies were available.

What are The Salient Characteristics of Irbesartan Drug Substance and Product?

Irbesartan was approved 1997 for the treatment of hypertension and the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. The currently marketed formulations include 75, 150 and 300 mg strength tablets.

Irbesartan is a zwitter ion with pKa's in the range of 3.3 - 3.9 and 4.2- 4.8 resulting in negligible water solubility in the pH range 3 to 5 as shown in Figure 3.2.1:

Figure 3.2.1 Aqueous Solubility of Irbesartan as a Function of pH at 25°C



The absolute bioavailability of irbesartan is 60-80%. Food does not impact the bioavailability of the drug. The pharmacokinetics of irbesartan are linear over a dose range of 10 mg to 900 mg. The therapeutic dose range is 150 mg to 300 mg qd.

What are the Different Formulations of Irbesartan?

Among the irbesartan tablet formulations clinical, current commercial formulations (75 mg, 150 mg and 300 mg Avapro® tablets), and (b) (4) formulations (18.75 mg and 37.5 mg (b) (4) tablets) can be differentiated.

The existing marketed formulations include the 75 mg, 150 mg and 300 mg strength Avapro® tablets. The composition of the 75 mg and 150 mg Avapro® tablets is shown in Table 3.3.2.1:

Table 3.3.2.1 Composition of Current Commercial (b) (4) Irbesartan Tablets

(b) (4)

It should be noted that table 3.3.2.1 contains a typographical error: 50 mg Avapro® tablet should read 150 mg Avapro® tablet.

The following clinical formulations were used in the dose-ranging study in the pediatric population (CV131154):

- 18.75 mg pediatric small tablet (18.75 PS)
- 37.5 mg pediatric small tablet (37.5 PS)
- 37.5 mg pediatric large tablet (37.5 PL)
- 75 mg pediatric small tablet (75 PS)
- 75 mg pediatric large tablet (75 PL)
- 150 mg pediatric large tablet (150 PL)

(b) (4)

Table 3.3.1.2: Composition of Irbesartan Clinical Tablets

It should be noted that in the PK study CV 131076 capsules of different strengths (2.5, 12.5, 37.5, 50 and 100 mg) were used.

Is the Bioequivalence Program Proposed by the Sponsor Acceptable?

Yes.

The Sponsor proposed scheme to link (b) (4) the clinical tablets and the presently commercialized Avapro® tablets is shown below:

Proposed Strategies for Qualification of Irbesartan Formulations

(b) (4)

(b) (4)

Two bioequivalence studies comparing:

(1) 18.75 mg (b) (4) tablet (test) vs. 18.75 mg PS tablet (reference)

(2) 37.5 mg (b) (4) tablet (test) vs. 37.5 mg PS tablet (reference)

Dissolution profiles comparing:

(1) 37.5 mg PL tablet (test) vs. 18.75 mg PS tablet (reference) (both clinical formulations, (b) (4))

(2) 37.5 mg (b) (4) tablet (test) vs. 18.75 mg (b) (4) tablet (reference) (b) (4)

(3) 75 mg PL tablet (test) vs. 37.5 mg PS (reference) (both clinical formulations, (b) (4)).

(b) (4)

The proposed bioequivalence program was found to be acceptable by OCPB/DPE I (letter of 12/5/03 to BMS).

Are the Results Obtained in the Bioequivalence and Dissolution Studies [redacted] Acceptable?

Yes. The sponsor conducted the above described 2 bioequivalence studies and performed the in vitro dissolution tests for the 3 tablet pairs.

Bioequivalence Studies

Study CV 131171: Bioequivalence Study of 18.75 mg [redacted] Irbesartan Tablets Relative to 18.75 mg Pediatric Small Irbesartan Tablets in Healthy Subjects

Study CV 13172: Bioequivalence Study of 37.5 mg [redacted] Irbesartan Tablets relative to 37.5 mg Pediatric Small Tablets

The subjects participating in both studies were healthy adults with acceptable demographics. There was a majority of male, Caucasian subjects in both studies. 18 blood samples were obtained from the subjects at scheduled times up to 72 hours after administration. The method used to measure irbesartan in plasma samples is a validated, specific and sensitive LC-MS/MS assay with internal standard. The inter-run and intra-run precisions measured using spiked QC samples were adequate in both studies. However, the respective deviations by – 20.6 % and -21.7% of the 2500 ng/mL QC sample pools found in the 2 studies exceeded the upper limit of 15% indicating a trend of the assay to underestimate the true value of the irbesartan concentrations in the 2500 ng/mL range. The PK analysis and the statistical evaluation of the bioequivalence measures (point estimates and confidence intervals) were state of the art.

As shown in the following table for study CV 131171:

Irbesartan CV131171
BMS-186295 Clinical Study Report

Statistical Analysis of AUC_{0-T}, AUC_{0-inf}, and C_{max} for Irbesartan

Pharmacokinetic Parameter	Adjusted Geometric Mean		Treatment B/Treatment A
	Irbesartan 18.75 mg [redacted] tablet (Treatment B) N=30	Irbesartan 18.75 mg PS tablet (Treatment A) N=30	Point Estimate (%) (90% CI)
AUC_{0-T} (ng.h/mL)	1773.2	1862.6	0.952 (0.877, 1.033)
AUC_{0-inf} (ng.h/mL)	1862.1	1962.5	0.949 (0.878, 1.025)
C_{max} (ng/mL)	525.4	522.6	1.005 (0.912, 1.108)

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and in the following table for study CV 131172:

Statistical Analysis of AUC_{0-T}, AUC_{0-inf}, and C_{max} for Irbesartan

Pharmacokinetic Parameter	Adjusted Geometric Mean		Treatment B/Treatment A
	Irbesartan 37.5 mg (b) (4) tablet (Treatment B) N=28	Irbesartan 37.5 mg PS tablet (Treatment A) N=28	Point Estimate (90% CI)
AUC_{0-T} (ng.h/mL)	4366.2	4299.0	1.016 (0.952, 1.083)
AUC_{0-inf} (ng.h/mL)	4540.8	4441.6	1.022 (0.958, 1.091)
C_{max} (ng/mL)	1052.6	1146.8	0.918 (0.839, 1.004)

Abbreviations: FC=film coated; PS=pediatric small; N=number; CI=confidence interval; T= time of last

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point estimates and 90% confidence intervals for Cmax and AUC in both studies were fully contained within the 80-125% boundaries.

In Vitro Dissolution Testing

The in vitro dissolution tests were conducted in 3 media (1) 0.1 N HCl, pH 1.2 corresponding to the approved medium) (2); Sodium citrate buffer, pH 2; and (3) Potassium phosphate buffer, pH 6.8 using apparatus II at 50 rpm in a volume of 1000 mL at 37 °C. The rationale of the sponsor to use a medium of pH 2 instead of pH 4.5 is the low solubility for irbesartan in the pH range of 3 to 5. This rationale is acceptable.

The results show that the dissolution profiles of the respective test and reference formulations are similar with f2 values exceeding 50%. The dissolution profiles for the 37.5 mg (test) and 18.75 mg (reference) (b) (4) tablets are shown in Figure 4.2.2:

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Is the validation of the LC-MS/MS assay used in the bioequivalence trials adequate?

Yes.

Were the pediatric populations enrolled and doses used in the pharmacokinetic trial adequate?

Yes.

The pharmacokinetic study was performed in hypertensive school-age children (6-12 years of age) and adolescents (13-17 years of age) who in the majority were males of African-American background. The dose ranging efficacy and safety trial also enrolled only school-age children (6-12 years of age) and adolescents (13-16 years of age). However, the enrollees were in the majority males of Caucasian background. The amended Written Request of November 8, 2002, requested that the same age groups be studied in the PK as in the dose-ranging efficacy and safety trial. The Written Request defined 4 age groups: infants, pre-school children, school-age children and adolescent as target subpopulations. However, in the Minutes from a teleconference with the sponsor on October 18, 2002, it can be derived that evaluation of efficacy, safety and pharmacokinetics in the 2 older pediatric groups was acceptable to the Agency.

It should be noted that the dose ranging study used irbesartan doses of between 0.5 mg/kg and 4.5 mg/kg. The PK trial used a dose of 2 mg/kg.

Were the PK parameters AUC, Cmax, Tmax, clearance, volume of distribution and t1/2 in the school children and adolescents determined?

Yes. Estimates for AUC, Cmax, Tmax and Cl/F were reported in the report of study CV131076 approved in 2000. The estimates for t1/2 and Vβ/F were provided in Supplement Amendment (b) (4) 034 submitted on October 4, 2004.

The pharmacokinetics of irbesartan in pediatric and adult populations are comparable.

What are the major findings of the dose-ranging efficacy and safety trial in school children and adolescents?

This was a multi-center, randomized, double-blind study in hypertensive school children and adolescents performed in 4 phases: Phase A was a lead-in phase with withdrawal of previous antihypertensive medicines, Phase B was a three week treatment titration phase

in which subjects were randomly assigned to 1 of 3 active treatments. Study medication was titrated up to the assigned target dose after the first week and the dose was continued for the next 2 weeks. Subjects not able to tolerate up-titration were eligible for the Phase D open-label therapy. The target titrated doses in the 3 treatment groups ranged from 0.5 mg/kg to 4.5 mg/kg. Period C was a double-blind placebo controlled withdrawal phase. Upon entry into Phase C subjects were randomized to either placebo or irbesartan at the assigned target dose. Period D was a 26 week open-label extension phase. The primary endpoint was sitting trough systolic blood pressure. Sitting trough diastolic blood pressure was a secondary endpoint.

A total of 146 school-age children and 172 adolescents were enrolled. The mean changes from baseline to week 3 of period B were -11.7, -9.3, and -13.2 mm Hg for the low, medium and high dose treatment groups, respectively. The corresponding values for the diastolic blood pressure were -3.8, -3.2, and -5.6 mm Hg, respectively. However, although statistically significantly different from zero, the estimated mean difference between treatment and placebo was for the systolic and diastolic blood pressure small and identical, i.e. -2.3 mm Hg. There was a lack of a significant dose-response relationship for the effect on systolic blood pressure. The antihypertensive effect of -2.3 mmHg was not considered therapeutically relevant by the Cardiorenal Division. (b) (4)

The antihypertensive effect of irbesartan is smaller in the pediatric population than in adults.

(b) (4)

3. (b) (4)

(b) (4)

4. REPORT SUMMARIES

Validation Report LCMSB 232: Quantitation of Irbesartan in Human Plasma via HPLC with MS/MS Detection

Laboratory: (b) (4)

Method

The method is capable of measuring irbesartan in human plasma containing tri-potassium EDTA. A 100 µL sample aliquot is spiked with 50 µL internal standard, irbesartan^{13}C, d4. After addition of 200 µL 0.2 N sodium hydroxide, all tubes are vortexed and centrifuged. Analytes are isolated through solid phase extraction using Oasis HLB SPE cartridges. The eluate is evaporated and the remaining residue is reconstituted with 250 µL of reconstitution solution. The final extract is analyzed via HPLC with MS/MS detection.

Linearity and Calibration

Linearity was evaluated by analyzing 10 calibration standards in duplicate over the nominal concentration range 2.50 to 2500 ng/mL using a linear weighted, 1/concentration, least squares regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. The data from three runs were used. Linearity was indicated by an average correlation coefficient from three standard curves which was > 0.990 for irbesartan as shown in Table 1:

Table 1. Regression Equations and Correlation Coefficients

The average back-calculated values and the reproducibility from each level of the calibration curve are given in Table 2:

Table 2. Average Back-calculated Calibration Standards

Limit of Quantitation

The lower limit of quantitation, LLOQ, was the lowest non-zero concentration level that could be quantitated accurately and reproducibly. For irbesartan the LLOQ is nominally 2.5 ng/mL.

Precision and Accuracy

Precision and accuracy were evaluated by analyzing the quality control pools prepared at the LLOQ, three times the LLOQ, the approximate mid point of the calibration range, approximately 30% of the upper limit of quantitation, ULOQ, and approximately 80% of ULQ. Precision was expressed as the percent coefficient of variation, %CV, of each pool. Accuracy was measured as the percent difference from the nominal value.

Intra-assay Precision and Accuracy

Intra-assay precision and accuracy were evaluated for each quality control pool by multiple analyses (n=6) of the pool during validation runs 1 SWK2, 2SWK2, and 4SWK2. The data met the performance criteria specified in applicable (b) (4) SOPs. The intra-assay QC data are shown in Tables 3A, B and D. The results excluding an outlier value for Run 2SWK2 are shown in Table 3 C. The data are from 3 runs.

Table 3A. Intra-assay Precision and Accuracy (Run 1SWK2)

(b) (4)

Table 3B. Intra-assay Precision and Accuracy (Run 2SWK2)

(b) (4)

Table 3C. Intra-assay Precision and Accuracy Excluding Statistical Outliers (Run 2SWK2)

(b) (4)

Table 3D. Intra-assay Precision and Accuracy (Run 4SWK2)

(b) (4)

Inter-Assay Precision and Accuracy

Inter-assay precision and accuracy were evaluated by analyzing six replicates of each QC level in three runs. The inter-assay results obtained met the performance criteria specified in applicable (b) (4) SOPs. The results are displayed in Table 4A. Table 4B

lists the results when an outlier values is excluded form the calculations. The data are from 3 runs.

Table 4A. Inter-assay Precision and Accuracy

(b) (4)

Table 4B. Inter-assay Precision and Accuracy Excluding Statistical Outliers

Intra-assay Precision and Accuracy of Diluted Samples (Parallelism and Accuracy)

The precision and accuracy of the measurements of samples with original concentrations above the ULQ that were diluted were validated by analyzing six replicate of diluted QCs in Run 2SWK2. The precision and accuracy of samples with original concentrations above the ULQ and with insufficient volumes for a full aliquot were also validated by duplicate, diluted, medium level QCs in Run 2SWK2. The data from 1 run are displayed in Table 5:

Table 5. Parallelism Precision and Accuracy

Recovery

In Run 4SWK2 the recovery of the analytes from human plasma was determined by comparing the respective responses of extracted samples and external standards representing 100 % recovery. The measured recovery of irbesartan from extracted samples ranged from 67% to 71%.

Stability

Freeze/thaw stability of irbesartan was evaluated by analyzing low-and high- level QCs that were subjected to three freeze/thaw cycles. The samples were thawed at room temperature and left at this temperature for 24 hours. The results are shown in Tables 7 and 8A. Table 8B shows data after exclusion of one outlier result.

Table 7. Freeze/thaw Stability

(b) (4)

Table 8A. Analyte Stability in Thawed Matrix

(b) (4)

Table 8B. Analyte Stability in Thawed Matrix Excluding Statistical Outliers

(b) (4)

[redacted]

Post-preparative stability was demonstrated by analyzing calibration standards and QC samples which were extracted and injected as part of Run ISWK2 and stored at room temperature for 108 hours prior to re-analysis as RUN 55WK2. The data demonstrating stability of irbesartan are shown in Table 9:

Table 9. Post-preparative Stability

(b) (4)

[redacted]

Short-term analyte stability in frozen matrix was evaluated for a period of 15 days which corresponded to the maximum age some of the calibrators and quality controls reached that were used during the validation (Run 7SWK2). The data indicating 15 day stability of irbesartan in frozen matrix are shown in Table 10:

Table 10. Short-term Stability in Frozen Matrix

(b) (4)

[redacted]

The stability of irbesartan (100 µg/mL) and the internal standard, irbesartan ^{13}C, d4 (1.0 mg/mL) was evaluated in methanol solution for 6 days and 9 days, respectively. The data are on file (b) (4) [redacted]

Specificity

Plasma samples containing irbesartan, internal standard and tri-potassium EDTA of six individuals were extracted and analyzed during validation of Run 1SWK2. No significant chromatographic peaks were detected at the mass transitions and expected retention times of the analytes. Potential matrix suppression effects of QC samples containing a nominal concentration of 2.50 ng/mL irbesartan were also evaluated in an experiment in which a pooled blank matrix was used as a control. There was no evidence for a matrix suppression effect in Table 11:

Table 11. Fortified Specificity Samples

(b) (4)

[redacted]

Cross-Analyte Interference

Aliquots of blank human plasma were spiked with only analyte or internal standard and analyzed in triplicate in Run 4SWK2. No significant chromatographic peaks at the expected retention times of the analytes in the unfortified samples were found.

Carry-Over

The potential for carry-over from high-concentration analyte levels was evaluated by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards in each validation run. There were no contributions from chromatographic peaks at the expected retention times of the analytes in the blank samples, that were greater than 20% of the mean analyte response for the LLOQ calibration standards and QC's in the validation runs. There was one exception for Run 4SWK2 which had one blank> 20%.

Figures 1- 4 depict chromatograms for a blank human plasma without internal standard, a human blank plasma with internal standard , a QC sample with a nominal irbesartan plasma concentration of 2.50 ng/mL and a QC sample with a nominal irbesartan plasma concentration of 2500 ng/mL, respectively:

Figure 1. Blank Human Plasma without Internal Standard

Figure 2. Blank Human Plasma with Internal Standard

Figure 3. Lower Limit of Quantitation Standard
nominally 2.50 ng/mL

Conclusion

The method is validated and applicable for the quantitation of irbesartan from a 100 μL human plasma aliquot, containing tri-potassium EDTA, within the nominal range of 2.50 to 2500 ng/mL.

Comments

- There are a number of outlier values. The statistics used obtained should be indicated in the report.
- All experimentally obtained data should be reported in the report

Clinical Study Report- CV 131171: Bioequivalence Study of 18.75 mg (b) (4) Irbesartan Tablets Relative to 18.75 mg Pediatric Small Irbesartan Tablets in Healthy Subjects

Study Investigator and Site: Dr. A. Laurent PPD Phase I Unit
706A Ben White Boulevard West
Austin, TX 78704

Objectives

Primary: To demonstrate bioequivalence of the irbesartan 18.75 mg (b) (4) tablet with the irbesartan 18.75 mg pediatric small (PS) tablet

Secondary: To assess the safety of irbesartan 18.75 mg administered as an (b) (4) tablet and as a PS tablet

Formulations

Test product: Irbesartan 18.75 mg (b) (4) tablets, product identification number: 186295-K18X-181, batch # 3L67933 (expiration date: 9-30-05) Lot size: Commercial sized lot of (b) (4)
Reference product: Irbesartan 18.75 mg PS tablets, product identification number: 186295-A18X-169, batch # 3L67909 (expiration date: 9-28-05)

Study Design

This is an open label, randomized, 2-period, 2-treatment, crossover study in healthy subjects. For each of the two periods subjects were admitted to the clinic in the evening prior to dosing. By randomization, 30 subjects were assigned to receive a single, 18.75 mg irbesartan (b) (4) tablet and a single 18.75 mg irbesartan PS tablet in 1 of 2 treatment sequences. Subjects must have fasted for at least 10 hours before dosing. There was a 7-day wash-out period between the 2 treatments. For each treatment period the subjects were confined to the clinic until 72 hours after dosing. Healthy male and female subjects in the age between 18 and 55 years of age were eligible to participate in the study. Women of child bearing age must have been using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks prior to study enrollment.

Assay

The plasma concentrations of ibersartan were analyzed by a validated LC/MS/MS method using a stable analog of irbesartan as internal standard (irbesartan-^{13}C, d4). A 100 µL sample aliquot was spiked with the internal standard. After addition of 0.2 N sodium hydroxide, all tubes were vortexed and centrifuged. Analytes were isolated through solid

phase extraction. The eluate was evaporated and the remaining residue was reconstituted. The final extract was analyzed via high performance liquid chromatography using MS/MS detection. The standard curve ranged from 2.5 -2500 ng/mL defining the lower (LLQ) and upper limit of quantitation (ULQ), respectively. If the predicted concentration of a study sample was greater than ULQ, the sample was re-analyzed with appropriate dilution in another analytical run. Analytical quality control (QC) samples of irbesartan were assayed in triplicate in each analytical run to assess accuracy and precision of the method. The following acceptance criteria were applied to each analytical run: (1) The predicted concentrations of at least three-fourth of all calibration standards were to be within ±15% (except ±20% for the lowest concentration of the standard curve) of their individual concentrations (2) At least one replicate of the lowest concentration in the standard curve was to be within ± 20% of the nominal concentration at that level to qualify as the lower limit of quantitation (LLOQ). If this criterion was not met, the next level was subjected to the same test and the LLQ raised accordingly. (3) The predicted concentrations of at least two-thirds of all QC samples were to be within ± 15% of their individual nominal concentrations (4). At least one replicate of each QC was to be within ± 15% of the nominal concentrations to qualify the analytical run for the analysis of samples.

A total of 9 analytical runs were performed. The between - and within run coefficient of variation of the analytical QC samples for irbesartan were less than 3.5% and 5.3% CV, respectively. Mean observed concentrations of the analytical QC samples deviated from the nominal values by -4.5%,-2.1% and -20.6% for the 7.5 ng/mL, 750 ng/mL and 2500 ng/mL QC samples, respectively.

Blood Sample Collection

Blood samples (5 mL) for the measurement of irbesartan were obtained pre-dose, 0.17, 0.33, 0.67, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours after administration.

PK and Statistical Analysis

The plasma concentration time curves of irbesartan were analyzed applying a non-compartment model method using SAS version 8.02. The actual sampling times were used for the calculation of the PK parameters. The maximum observed plasma concentration, Cmax, and the corresponding time, Tmax, were recorded directly from the experimental observations. The first order rate constant of decline in the terminal phase of the plasma concentrations, λz, was estimated by log-linear regression, using no weight factor, of at least 3 data points. T1/2 was obtained from $\ln 2/\lambda z$. AUC0-T was obtained by linear trapezoidal summation and AUCT-inf from extrapolation to infinity, $Ct/\lambda z$. AUC0-inf was the sum of AUC0-T and AUCT-inf.

Sample size and power were calculated on the following assumptions: Cmax and AUC0-inf are log-normally distributed with intra-subject standard deviations of 0.19 for log Cmax and 0.2 for log AUC0-inf, as determined form the results of a previous study

(protocol 131159). If there was ≤ 5% difference in AUC0-inf between test and reference formulation a study with 26 subjects had at least 91% power (AUC0-inf) to conclude bioequivalence.

For the assessment of bioequivalence an analysis of variance was performed on log-transformed Cmax, AUC0-inf, and AUCo-T. Factors in the analysis were sequence group, period, formulation, and subject within sequence as a random effect. Modeling used a mixed effect linear model. Fixed effects were tested by Wald tests (F-tests). Point estimates and 90% CI for formulation differences on the log scale were exponentiated back to obtain estimates for ratios of population geometric means on the original scale. No adjustments were made for multiplicity. Bioequivalence was concluded if the 90% CI for the ratio of the population geometric means of the test and reference tablets were contained within 80% and 125% range for Cmax and AUC0-inf.

Results

Thirty (30) subjects entered and completed the study according to the protocol. The mean age of the 30 subjects was 34 years (range 20 to 53 years of age) and the mean (SD) body weight was 75.9 (13.0) kg. The majority were male and Caucasian. No subject had taken any medication concomitantly with irbesartan in this study. Six subjects had taken a previous medication prior to study initiation, but none of these were considered to be clinically relevant.

PK

Table 11.2.1A shows the geometric means of Cmax, AUC0-T and AUC0-inf of the test 18.75 (b)(4) tablet and the 18.75 mg PS reference irbesartan formulations

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Table 11.2.1A: Summary Statistics for Irbesartan Pharmacokinetic Parameters

Pharmacokinetic Parameter	Irbesartan formulation	
	Treatment B Irbesartan 18.75 mg (b) (4) N=30	Treatment A Irbesartan 18.75 mg PS N=30
C_{max} (ng/mL)		
Geometric mean	525.41	522.57
CV%	42	39
AUC_{0-inf} (ng.h/mL)		
Geometric mean	1862.11	1962.46
CV%	41	41
AUC_{0-T} (ng.h/mL)		
Geometric mean	1773.18	1862.64
CV%	43	42
T_{max} (hours)		
Median	1.00	0.69
Range	0.33, 3.00	0.33, 2.00
T_{half}		
Mean	15.52	16.91
SD	5.75	8.23

CV131171
Source: Supplemental Table S.11.2.1C
Abbreviations: (b) (4) PS=pediatric small; N=number; SD=standard deviation; h=hour; mL=milliliter; ng=nanogram; T=time of last quantifiable concentration; AUC_{0-T}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (T); AUC_{0-inf}=area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}=maximum observed plasma concentration; T_{max}=time of maximum observed concentration; T_{half}= elimination half-life; CV%=coefficient of variation.

Table 11.2.1B displays the point estimates and the 90% CI of the bioequivalence measures for the irbesartan 18.75 mg (b) (4) test tablet

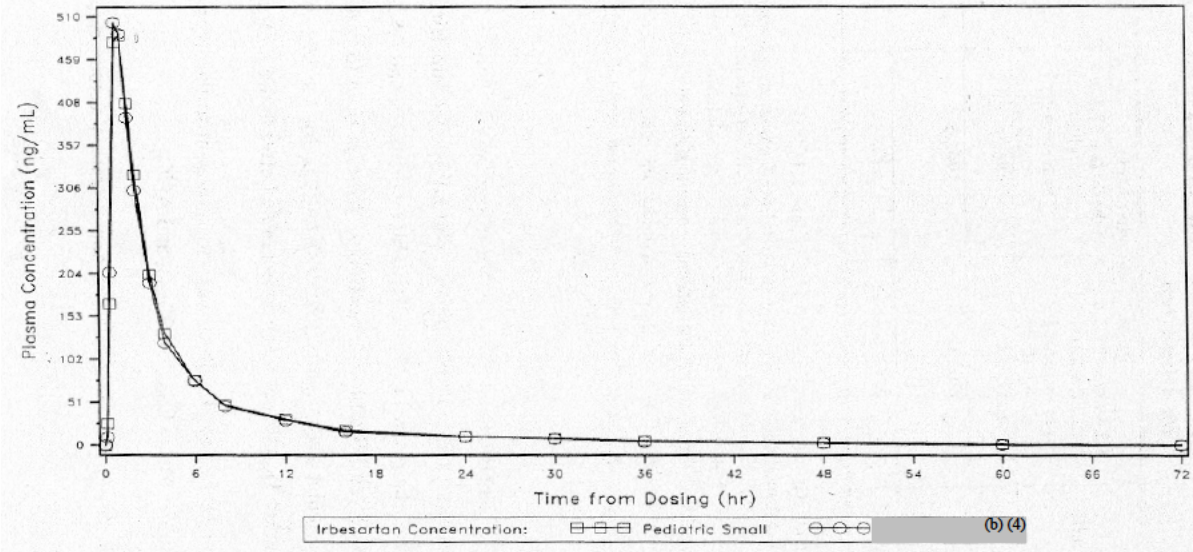
Statistical Analysis of AUC_{0-T}, AUC_{0-inf}, and C_{max} for Irbesartan

Pharmacokinetic Parameter	Adjusted Geometric Mean		Treatment B/Treatment A
	Irbesartan 18.75 mg (b) (4) tablet (Treatment B) N=30	Irbesartan 18.75 mg PS tablet (Treatment A) N=30	Point Estimate (%) (90% CI)
AUC_{0-T} (ng.h/mL)	1773.2	1862.6	0.952 (0.877, 1.033)
AUC_{0-inf} (ng.h/mL)	1862.1	1962.5	0.949 (0.878, 1.025)
C_{max} (ng/mL)	525.4	522.6	1.005 (0.912, 1.108)

Abbreviations: (b) (4) PS=pediatric small; N=number; CI=confidence interval; T= time of last quantifiable concentration; C_{max}=maximum observed plasma concentration; ng=nanogram; mL=milliliter; AUC_{0-T}=area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (T); AUC_{0-inf}=area under the plasma concentration-time curve from time 0 extrapolated to infinity area under the plasma concentration-time curve from time 0 extrapolated to infinity; ng=nanogram; inf=infinity; h=hour.
Note: The ANOVA model to assess bioequivalence: Ln(PK parameter)=sequence, period, and formulation as fixed effects and subject within sequence as a random effect; Ln=logarithm base e.

Figure 11.2.1 displays the arithmetic mean plasma concentrations after administration of the irbesartan 18.75 mg (b) (4) test and 18.75 mg PS reference irbesartan formulations

Figure 11.2.1: Plot of Mean Plasma Irbesartan Concentration Versus Time Profiles



Conclusions

Extent and rate of bioavailable irbesartan following release from the irbesartan test (b) (4) tablet and the 18.75 mg standard PS tablet appear to be equivalent. However, the accuracy of the LC-MS/MS assay measured in the QC samples exceeded the allowable upper limit of deviation from the nominal value at the highest concentration tested of 2500 ng/mL. It cannot be excluded that the insufficient accuracy of the assay may have impacted the values in the concentration range between 750 ng/mL and 2500 ng/mL, particularly Cmax. Peak concentrations up to 1140 ng/ml were measured in the study. The method may have underestimated Cmax. The upper limit of the 90% CI for Cmax was 1.108 and clearly smaller than 1.249. Thus, it is not very likely that an assay with the

required accuracy would have shown that the test and reference tablets are bioinequivalent.

Comments

- The accuracy of the assay as measured in the QC samples should have been for all 3 concentration levels within the allowable limits.
- The inclusion of semi-logarithmic plots of the plasma concentration against time would have been helpful.
- The report did not indicate which laboratory performed the LC-MS/MS assay.
- On p. 53 the label of Table 11.2.1B should read Irbesartan 18.75 mg (b) (4) Tablet and Irbesartan 18.75 mg PS Tablet

Clinical Study Report- CV 131172: Bioequivalence Study of 37.5 mg (b) (4) Irbesartan Tablets Relative to 37.5 mg Pediatric Small Irbesartan Tablets in Healthy Subjects

Study Investigator and Site: Dr. M. Hoelscher PPD Phase I Unit
706A Ben White Boulevard West
Austin, TX 78704

Report No.: CV 131172

Objectives

Primary: To demonstrate bioequivalence of the irbesartan 37.5 mg (b) (4) tablet with the irebsartan 37.5 mg pediatric small (PS) tablet

Secondary: To assess the safety of irbesartan 37.5 mg administered as (b) (4) tablet and as PS tablet

Formulations

Test product: Irbesartan 37.5 mg (b) (4) tablets, product identification number: 186295-K37X-182, batch # 3L67916. Lot size: Commercial sized lot (b) (4)

Reference product: Irbesartan 37.5 mg PS tablet, product identification number: 186295-A37X-170, batch # 3L67978

Study Design

This is an open label, randomized, 2-period, 2-treatment, crossover study in healthy subjects. For each of the two periods subjects were admitted to the clinic in the evening prior to dosing. By randomization, 30 subjects were assigned to receive a single, 37.5 mg irbesartan (b) (4) tablet and a single 37.5 mg irbesartan PS tablet in 1 of 2 treatment sequences. Subjects must have fasted for at least 10 hours before dosing. There was a 7-day wash-out period between the 2 treatments. For each treatment period the subjects were confined to the clinic until 72 hours after dosing. Healthy male and female subjects in the age between 18 and 55 years of age were eligible to participate in the study. Women of child bearing age must have been using an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks prior to study enrollment.

Assay

The plasma concentrations of ibersartan were analyzed by a validated LC/MS/MS method using a stable analog of irbesartan as internal standard (irbesartan-^{13}C, d4). A 100 µL sample aliquot was spiked with the internal standard. After addition of 0.2 N sodium

hydroxide, all tubes were vortexed and centrifuged. Analytes were isolated through solid phase extraction. The eluate was evaporated and the remaining residue was reconstituted. The final extract was analyzed via high performance liquid chromatography using MS/MS detection. The standard curve ranged from 2.5 -2500 ng/mL defining the lower (LLQ) and upper upper limit of quantitation (ULQ), respectively. If the predicted concentration of a study sample was greater than ULQ, the sample was re-analyzed with appropriate dilution in another analytical run. Analytical quality control (QC) samples of irbesartan were assayed in triplicate in each analytical run to assess accuracy and precision of the method. The following acceptance criteria were applied to each analytical run: (1) The predicted concentrations of at least three-fourth of all calibration standards were to be within ±15% (except ±20% for the lowest concentration of the standard curve) of their individual concentrations (2) At least one replicate of the lowest concentration in the standard curve was to be within ±20% of the nominal concentration at that level to qualify as the lower limit of quantitation (LLOQ). If this criterion was not met, the next level was subjected to the same test and the LLQ raised accordingly. (3) The predicted concentrations of at least two-thirds of all QC samples were to be within ± 15% of their individual nominal concentrations (4). At least one replicate of each QC was to be within ± 15% of the nominal concentrations to qualify the analytical run for the analysis of samples.

A total of 8 analytical runs was performed. The between - and within run coefficient of variation of the analytical QC samples for irbesartan were less than 2.5% and 3.8% CV, respectively. Mean observed concentrations of the analytical QC samples deviated from the nominal values by -4.3%,-2.8% and -21.7% for the 7.5 ng/mL, 750 ng/mL and 2500 ng/mL QC samples, respectively.

Blood Sample Collection

Blood samples (5 mL) for the measurement of irbesartan were obtained pre-dose, 0.17, 0.33, 0.67, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours after administration.

PK and Statistical Analysis

The plasma concentration time curves of irbesartan were analyzed applying a non-compartment model method using SAS version 8.02. The actual sampling times were used for the calculation of the PK parameters. The maximum observed plasma concentration, Cmax, and the corresponding time, Tmax, were recorded directly from the experimental observations. The first order rate constant of decline in the terminal phase of the plasma concentrations, λz, was estimated by log-linear regression, using no weight factor, of at least 3 data points. T1/2 was obtained from ln2/0.693. AUC0-T was obtained by linear trapezoidal summation and AUCT-inf from extrapolation to infinity, $Ct/\lambda z$. AUC0-inf was the sum of AUC0-T and AUCT-inf.

Sample size and power were calculated under the following assumptions: Cmax and

AUC0-inf are log-normally distributed with intra-subject standard deviations of 0.19 for log Cmax and 0.2 for log AUC0-inf as determined from the results of a previous study (protocol 131159). If there was ≤ 5% difference in AUC0-inf between test and reference formulation inclusion of a study with 26 subjects had at least 93% power (AUC0-inf) to conclude bioequivalence.

For the assessment of bioequivalence an analysis of variance was performed on log-transformed Cmax, AUC0-inf, and AUC0-T. Factors in the analysis were sequence group, period, formulation, and subject within sequence as a random effect. Modeling used a mixed effect linear model. Fixed effects were tested by Wald tests (F-tests). Point estimates and 90% CI for formulation differences on the log scale were exponentiated back to obtain estimates for ratios of population geometric means on the original scale. No adjustments were made for multiplicity. Bioequivalence was concluded if the 90% CI for the ratio of the population geometric means of the test and reference tablets were contained within 80% and 125% range for Cmax and AUC0-inf.

Results

Thirty (30) subjects entered and 28 completed the study according to the protocol. Two (2) subjects discontinued from the study early after receiving 37.5 mg (b) (4) tablets. One subject, a 35 year old female, withdrew her consent, another subject, a 19 year old female, no longer met the study criteria. The mean age of the 30 subjects was 31 years (range 18 to 55 years of age) and the mean (SD) body weight was 72.4 (10.9) kg. There was a majority of male Caucasian subjects. No subject had taken any medication concomitantly with irbesartan in this study. Three subjects had taken a previous medication prior to study initiation, but none of these were considered to be clinically relevant.

PK

Table 11.2.1A shows the geometric means of Cmax, AUC0-T and AUC0-inf of the irbesartan 37.5 mg (b) (4) test and 37.5mg PS reference formulations.

Table 11.2.1A: Summary Statistics for Irbesartan Pharmacokinetic Parameters

Pharmacokinetic Parameter	Irbesartan formulation	
	Treatment B Irbesartan 37.5 mg (b) (4) N=28	Treatment A Irbesartan 37.5 mg PS N=28
C_{max} (ng/mL)		
Geometric mean	1058.34	1152.97
CV%	40	33
AUC_{0-inf} (ng.h/mL)		
Geometric mean	4561.77	4468.87
CV%	44	38
AUC_{0-T} (ng.h/mL)		
Geometric mean	4387.94	4324.69
CV%	42	35
T_{max} (hours)		
Median	0.68	1.00
Range	0.33, 4.00	0.67, 2.00
T_{half} (hours)		
Mean	17.09	15.38
SD	7.44	6.98

CV131172.
Source: Supplemental Table S.11.2.1C
Abbreviations: (b) (4) PS=pediatric small; N=number; SD=standard deviation; h=hour; mL=milliliter; ng=nanogram; T=time of last quantifiable concentration; AUC_{0-T}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (T); AUC_{0-inf}=area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}=maximum observed plasma concentration; T_{max}=time of maximum observed plasma concentration; T_{half}=terminal elimination half-life; CV%=coefficient of variation.

Table 11.2.1B lists the point estimate and the 90% CI for the irbesartan 37.5 mg (b) (4) test tablet:

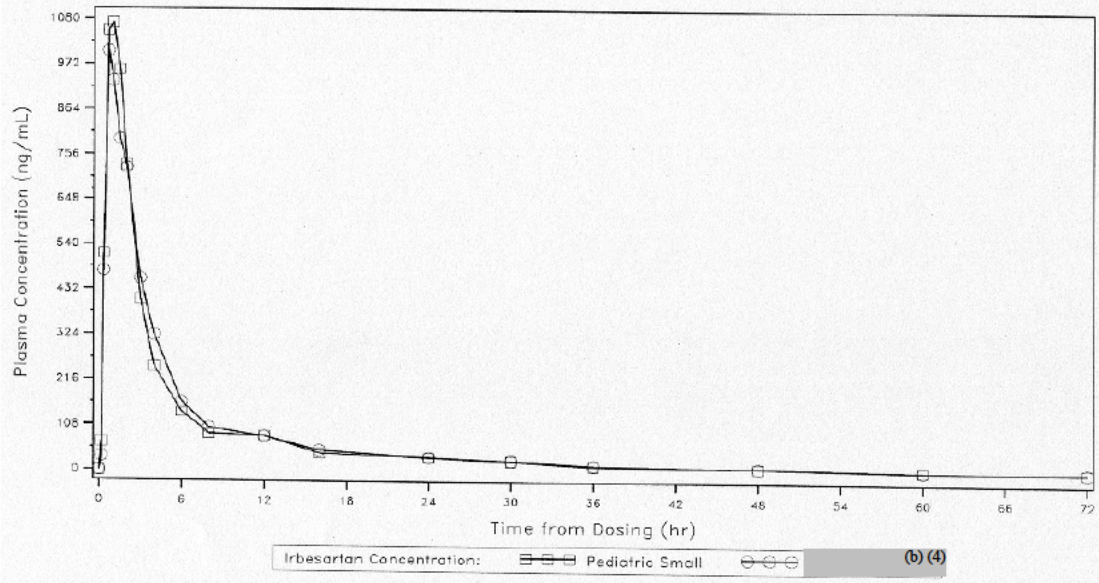
Table 11.2.1B: Results of Statistical Analyses of AUC_{0-T}, AUC_{0-inf}, and C_{max} for Irbesartan

Pharmacokinetic Parameter	Adjusted Geometric Mean		Treatment B/Treatment A
	Irbesartan 37.5 mg (b) (4) tablet (Treatment B) N=28	Irbesartan 37.5 mg PS tablet (Treatment A) N=28	Point Estimate (90% CI)
AUC_{0-T} (ng.h/mL)	4366.2	4299.0	1.016 (0.952, 1.083)
AUC_{0-inf} (ng.h/mL)	4540.8	4441.6	1.022 (0.958, 1.091)
C_{max} (ng/mL)	1052.6	1146.8	0.918 (0.839, 1.004)

CV131172
Source: Supplemental Tables S.11.2.1D, S.11.2.1E, S.11.2.1F
Note: The ANOVA model to assess bioequivalence: Ln(PK parameter)=sequence, period, and formulation as fixed effects and subject within sequence as a random effect; Ln=logarithm base e.
Abbreviations: (b) (4) PS=pediatric small; CI=confidence interval; T=time of last quantifiable concentration; AUC_{0-T}=area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration (T); AUC_{0-inf}=area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}=maximum observed plasma concentration; ng=nanogram; mL=milliliter; h=hour.

Figure 11.2.1 displays the arithmetic mean plasma concentrations after administration of the irbesartan 37.5 mg (b) (4) test and 37.5 mg PS reference formulations

Figure 11.2.1: **Plot of Mean Plasma Irbesartan Concentration Versus Time Profile**



Conclusions

Extent and rate of bioavailable irbesartan following release from the test (b) (4) tablet and the standard PS tablet appear to be equivalent. However, the accuracy of the LC-MS/MS assay measured in the QC samples exceeded the allowable upper limit of deviation from the nominal value at the highest concentration tested of 2500 ng/mL. It cannot be excluded that the insufficient accuracy of the assay may have impacted the values in the concentration range between 750 ng/mL and 2500 ng/mL, particularly Cmax. Peak concentrations up to 2400 ng/ml were measured in the study. The method may have underestimated Cmax. The upper limit of the 90% CI for Cmax was 1.004 and clearly smaller than 1.249. Thus, it is not very likely that an assay with the required accuracy would have shown that the test and reference tablets are bioinequivalent.

Comments

- The accuracy of the assay as measured in the QC samples should have been within the allowable limits at all 3 concentration levels.
- The inclusion of semi-logarithmic plots of the plasma concentration against time would have been helpful.
- The report does not indicate which laboratory performed the LC-MS/MS assay.

Formulation Qualification Proposal for Irbesartan Tablets

Laboratory: Bristol-Myers Squibb Pharmaceutical Research Institute

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Background

(b) (4) The qualification strategy of the company proposes the performance of 2 bioequivalence studies and in vitro dissolution tests for proportionately similar formulations to establish bioequivalence of 2 (b) (4) pediatric formulations and to connect formulations used in the dose ranging study in children.
The results of the comparative in vitro dissolution tests performed with 4 tablets used in the dose-ranging study in children and with 2 (b) (4) tablets are also presented in this report.

The proposed strategy was considered acceptable to OCPB/DPE1 in 2003. However, the results of the dissolution tests should be evaluated together with the results of the dissolution tests.

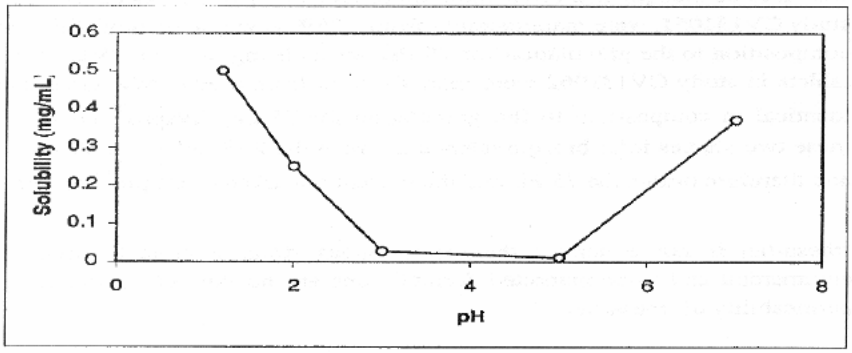
Irbesartan (Avapro®) is a potent angiotensin II receptor (subtype AT1) antagonist indicated for the treatment of hypertension. Irbesartan, a zwitter ion, contains two pKa's: pKa1 is between 3.3 and 3.9 and pKa2 is between 4.2 and 4.8. The solubility profile of irbesartan is shown in Table 3.2.1 and depicted in Figure 3.2.1:

Table 3.2.1 Aqueous Solubility of Irbesartan as a Function of pH at 25°C

pH	Solubility (mg/mL)	Highest dose strength/ Solubility of irbesartan[a] (mL)
1.2	0.50	75
2.0	0.25	150
3.0	0.03	1250
5.0	0.01	3750
7.0	0.37	101

[a] The highest (b) (4) pediatric dose of irbesartan is 37.5 mg

Figure 3.2.1 Aqueous Solubility of Irbesartan as a Function of pH at 25°C



Due to the zwitter ion characteristics the solubility of irbesartan is negligible in the pH range between pH 3 and 5. The average absolute bioavailability of irbesartan is 60-80%. Tmax is 1.5 to 2 hours. The PK of irbesartan are linear /dose proportionate in the dose range between 10 mg and 600 mg. Safety of irbesartan is established up to 300 mg. The drug is not a narrow therapeutic range drug.

Currently marketed formulations include tablets of 75 mg, 150 mg and 300 mg strengths, and are referred to as "commercial" formulations.

In the dose ranging study in the pediatric population (CV131154: Study of Blood Pressure Reduction with irbesartan in Children and Adolescents") the following "clinical" formulations were used:

- 18.75 mg pediatric small tablet (18.75 PS)
- 37.5 mg pediatric small tablet (37.5 PS)
- 37.5 mg pediatric large tablet (37.5 PL)
- 75 mg pediatric small tablet (75 PS)
- 75 mg pediatric large tablet (75 PL)
- 150 mg pediatric large tablet (150 PL)

These 6 "look alike" irbesartan tablets were developed (b) (4)

Table 3.3.1.1: Composition of Clinical Irbesartan (b) (4)

(b) (4)

The two tablet series were designated as pediatric small, PS tablets, and pediatric large, PL tablets (b) (4) The composition of the 6 clinical tablets is shown in Table 3.3.1.2:

Table 3.3.1.2: Composition of Irbesartan Clinical Tablets

(b) (4)

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The similarity factor, f2, characterizing the dissolution kinetics of the 3 pairs of test and reference tablets at all pH conditions exceeded 50 % indicating nearly super-imposable profiles. (b) (4)

Conclusions

Formulation Qualification Strategy

(b) (4)

Dissolution Testing

The submitted in vitro dissolution data show that the test and reference formulations for the selected (b) (4) tablets perform similarly in all 3 media tested. The choice of a pH 2 medium in lieu of the usual pH 4.5 medium makes sense considering the negligible water solubility of irbesartan at pH 4.5. Given the linear kinetics and therapeutic range of irbesartan the requested biowaivers for the higher strength tablets 37.5 mg PL, 37.5 mg (b) (4) and 75 mg PL should be granted.

Comments

- From the two earlier conducted bioequivalence studies (CV 1131051 and CV 131062) that were conducted with higher strength tablets a link between the 75 mg PL and the 75 mg Avapro ® could be established if dissolution data would indicate that the PL tablets of different strengths and the Avapro tablets of different strength perform comparably at pH 1.2. (b) (4)

- (b) (4)

- The units of the x-axis of the dissolution profiles depicted in Figures 4.2.1, 4.2.2 and 4.2.3 should be minutes not hours.

- There is a typo in Table 3.3.2.1: The Avapro tablet contains 150 mg irbesartan and not 50 mg.

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20757 SES-034**	**Brand Name**	**Avapro**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Irbesartan**
Medical Division	**Cardio-Renal Drug Products**	**Drug Class**	**Antihypertensive**
OCPB Reviewer	**Peter Hinderling**	**Indication(s)**	**Treatment of hypertension**
OCPB Team Leader	**Patrick Marroum**	**Dosage Form**	**Tablets**
		Dosing Regimen	**18.75 mg qd for bw≤20 kg, 37.5 mg qd ≥ 50 kg**
Date of Submission	**July 30, 2004**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**October 15, 2004**	**Sponsor**	**Bristol-Myers-Squibb**
PDUFA Due Date	**February 2, 2005**	**Priority Classification**	**S**
Division Due Date	**December 1, 2005**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	**X**			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	3			

Filability and QBR comments

	"X" if yes	Comments
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered	**Bioequivalence of new pediatric film coated tablet**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Peter H. Hinderling , 09/07/04**	
Secondary reviewer Signature and Date		

CC: NDA 20757, HFD-860 (Electronic Entry), HFD-110(CSO), HFD-860(Marroum,Mehta, Rahman), CDR (B. Murphy)

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/s/

Peter Hinderling
12/6/04 04:06:43 PM
BIOPHARMACEUTICS

Patrick Marroum
12/6/04 04:13:23 PM
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