020757—5028

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-757/S-028

Sanofi-Synthelabo
C/o Bristol-Myers Squibb Company
Attention: David Ziering, Ph.D.
P. O. Box 5400
Princeton, NJ 08543-5400

Dear Dr. Ziering:

Please refer to your supplemental new drug application dated May 8, 2003, received May 9, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) Tablets, 75 mg, 150 mg and 300 mg.

This supplemental new drug application provides for the commercialization of new reduced mass, film coated formulations for all strengths of irbesartan tablets.

We have completed our review of this supplemental application. This supplement is approved. Please note that an expiration date of 24 months is approved for Avapro Tablets of all strengths packaged in all containers.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any question, please call Edward Fromm, Regulatory Health Project Manager, at (301) 594-5332.

Sincerely,

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I for the
Division of Cardio-Renal Drug Products (HFD-110)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Hasmukh Patel
9/9/03 03:59:22 PM
Signed for Kasturi Srinivasachar, Ph.D.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

CHEMIST'S REVIEW	1. **ORGANIZATION** HFD - 110	2. **NDA Number** 20-757
3. **Name and Address of Applicant (City & State)** Bristol-Myers Squibb Company P. O. Box 5400 Princeton, NJ 08543-5400		4. **Supplement(s) Number(s) Date(s)** SCF-028 05/08/03
5. **Drug Name** Avapro	6. **Nonproprietary Name** Irbesartan	7. **Amendments &** SCF-028(BC) 09/02/03 SCF-028(BC) 09/08/03

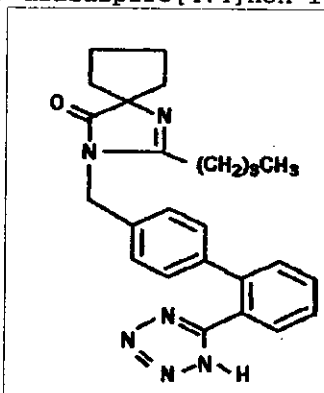
7. **Supplement Provides for: Prior Approval Supplement**

the commercialization of new reduced mass, film coated formulations for all strengths of irbesartan tablets.

9. **Pharmacological Category**	10. **How Dispensed**	11. **Related IND(s)/ NDA(s)/DMF(s)**
Angiotensin II Receptor Antagonist/Hypertension	/x / RX / / OTC	NDA 20-758
12. **Dosage Form(s)** Tablets	13. **Potency(ies)** 75, 150, and 300 mg.	

14. **Chemical Name and Structure**

2-Butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl) methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.



15. **Records/Reports**

Current

/x / Yes / / No

Reviewed

/x / Yes / / No

16. **Comments:**

Division of Clinical Pharmacology & Bio-pharmaceutics has recommended approval. EER status is acceptable.

17. **Conclusions and Recommendations:**

The supplement provides complete CMC information for the manufacture of Film-coated/reduced mass Avapro Tablets. The new Avapro tablets have been shown equivalent to the currently approved Avapro tablets. The applicant requested same expiration date of for the product packaged in HDPE bottles and 24 months for the product in blisters. Based on stability data and various changes in formulation, the supplement may be approved with an expiration date of 24 months for the film-coated/reduced mass Avapro Tablets of all strengths packaged in all containers.

18. **REVIEWER**

Ramsharan D. Mittal

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Ramsharan Mittal
9/9/03 03:20:10 PM
CHEMIST

Hasmukh Patel
9/9/03 03:53:39 PM
CHEMIST

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 20-757
Supplement SCF/028

SUBMISSION DATE: May 8, 2003

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

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplemental New Drug Application

SYNOPSIS:

Reference is made to the approved NDA 20-757 for Avapro® (irbesartan) 75, 150, and 300 mg Tablets. Irbesartan is a selective angiotensin II receptor antagonist. Avapro® was approved by the Agency on September 30, 1997 for the treatment of hypertension and for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension.

This application contains information related to the development of a new formulation for irbesartan tablets. Currently, the Avapro tablet formulation consists of — drug load and is uncoated. The new irbesartan tablets have a — % drug load, thereby reducing the total weight of the tablet, and are film-coated to mask the bitter taste of Avapro tablets. The new formulation has been referred to as "reduced mass" or "film-coated" tablets within this application.

Detailed quality (chemistry, manufacturing and controls) information for the new formulation was provided in this application. In order to get approval of the new formulation of the 75, 150, and 300 mg irbesartan tablets, a bioequivalence study was conducted for the new reduced mass, film-coated 300 mg tablet vs. the currently commercialized 300 mg Avapro tablet. A biowaiver was requested for the approval of the 75 and 150 mg lower strengths of the new formulation.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information included in the Supplement SCF/0 28 dated May 8, 2003 to NDA 20-757 for Avapro (irbesartan) Tablets and has the following Comments:

- ***Bioequivalence Study:*** The results of the bioequivalence study showed that the 300 mg reduced mass film-coated tablets and the 300 mg commercial tablets pass the Agency's 90% CI

criteria with respect to Cmax and AUC, thus the BE data support the approval of the new formulation.

- ***Waiver Request:*** Based on the review of the submitted information, OCPB is of the opinion that the sponsor has provided appropriate data to support their request of a bio-waiver for the requirement of the submission of in vivo bioequivalence data for the 75 mg and 150 mg film-coated tablets. Therefore, a bio-waiver for these lower strengths of the new formulation of irbesartan tablets is granted.

- ***Labeling:*** The clinical pharmacology and biopharmaceutic information for irbesartan included in the revised labeling is appropriate and acceptable.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D. /S/

cc: NDA 20-757, HFD-110 (Mittal), HFD-860 (Dorantes, Mehta, Sahajwalla), and CDR (Biopharm).

QUESTION BASED REVIEW

1. How do the currently approved and proposed formulations compare?

The modifications to the commercial approved formulation were made to improve the palatability of the product by masking its bitter taste and making the tablet smaller. The changes include the binder [ ] removing [ ], reducing the total tablet mass by about ~ and applying a film- coat to the tablet. The revised formulation tablets are known as 'reduced mass' and/ or 'film- coated' irbesartan tablets. The next table presents a comparison of the quantitative compositions of the currently approved formulations and the proposed reduced mass, film-coated formulations for Avapro 75, 150, and 300 mg Tablets.

Quantitative Composition of the Approved and Proposed Formulations

Component	Approved formula			Proposed formula		
	Quantity per unit dose (mg)			Quantity per unit dose (mg)		
	75mg	150mg	300mg	75mg	150mg	300mg
Engraved number	2771	2772	2773	2871	2872	2873
Irbesartan	75.00	150.00	300.00	75.00	150.00	300.00
Lactose monohydrate						
Pregelatinized starch						
Microcrystalline cellulose						
Croscarmellose sodium						
Poloxamer 188						
Hypromellose						
Purified water [a]						
Silicon dioxide						
Magnesium stearate						
white						
Purified water [a]						
Carnauba wax						
Tablet weight	150.00	300.00	600.00	130.00	260.00	520.00

[a] Removed during processing. Does not appear in the final product.

A common granulation is used to manufacture all three strengths. All three strengths are coated to the same level (equal to % of the core tablet weight) with the same coating formula to mask the bitter taste. In order to reduce the total mass of the product, hypromellose was

substituted for pregelatinized starch as the binder. [

]

The commercial manufacturing process for the marketed irbesartan tablets and the manufacturing process for the new proposed core tablets are similar, with the following modifications: [

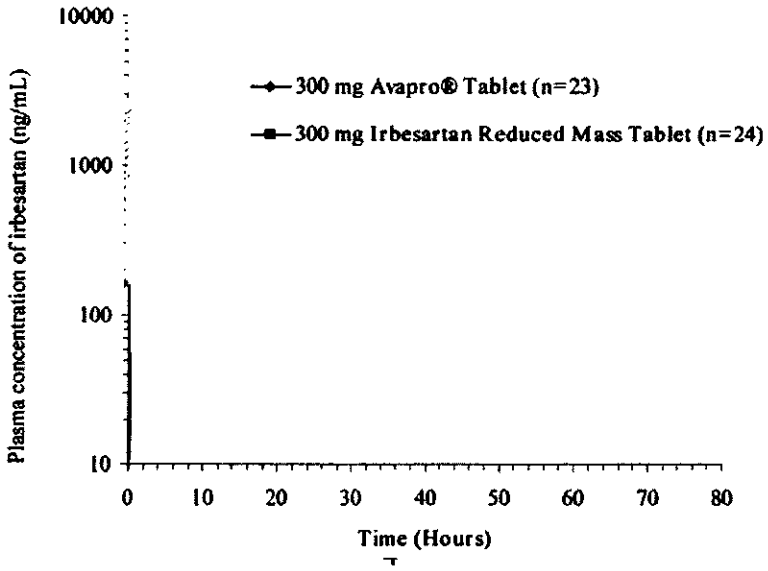
]

In addition to removing poloxamer and pregelatinized starch from the formula, the only other modification in the manufacturing process for the core tablets is that all excipients are added in [ ] except for silicon dioxide and magnesium stearate, which are [ ] Also, a coating step is added for the new proposed core tablets. The release specifications of the commercial tablets and the proposed film-coated tablets are the same.

3. Are the data from the bioequivalence study acceptable?

A bioequivalence study was conducted to demonstrate the equivalence of the proposed formula with the approved one. In this study, the 300 mg approved tablets (commercial batch 1MBE23) were administered in comparison with the proposed formula (test) batch 8MCE120 - 300 mg tablets. Note that the process used to manufacture the test batch used in the bioequivalence study is equivalent to that used for the proposed commercial batches.

The plasma concentrations of irbesartan vs. time for the reference and test products are illustrated in the next Figure.



The results of the statistical analysis are summarized in the next table.

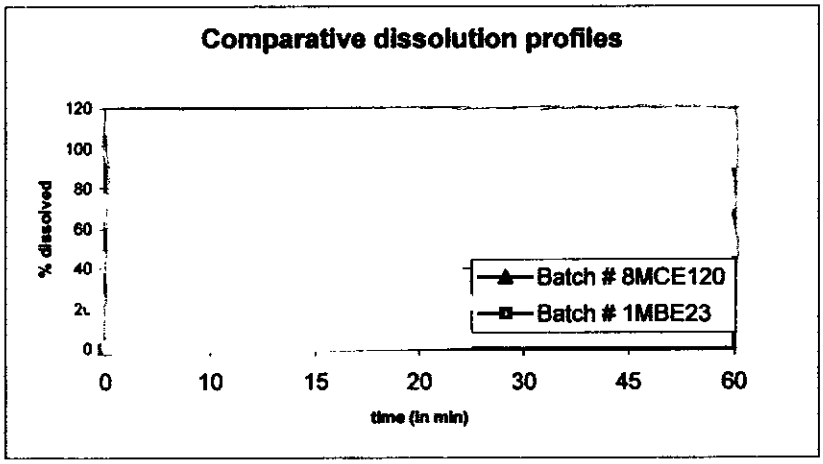
STUDY CV% [redacted] ANALYSIS OF CMAX, AUC0-t AND AUC0-Inf					
Pharmacokinetic Parameter	Treatment	[redacted] Mean	Contrast	[redacted] Ratio of Adj. Geo. Means Pt. Estimate	90% CI
Cmax (ng/ml)	A	3405.5	B vs. A	1.067	97-116%
	B	3633.6			
AUC Inf (ng.h/ml)	A	22846.3	B vs. A	0.986	92-106%
	B	22536.6			
AUC 0-t (ng.h/ml)	A	21785.9	B vs. A	0.985	92-105%
	B	21458.2			

Treatment A: 1x 300/12.5 mg Avapro Tablet (reference) Treatment B: 1x 300 mg irbesartan reduced mass Tablet (test)

Reviewer Comments:

- *The results of this BE study showed that the 90% CI for Cmax and AUC parameters are within the Agency's 80-125% acceptance criteria. Therefore, the proposed irbesartan 300 mg film-coated tablet is bioequivalent to the currently marketed irbesartan 300 mg tablet.*

- *Please note that the sponsor also included the dissolution profiles for the reference and test products used in the BE study. The data were generated according to the approved method: USP Apparatus 2 (paddles), [redacted] rpm. The dissolution for both products was greater than [redacted] at 15 minutes. The next figure presents these profiles.*



3. Is the requested bio-waiver acceptable?

Since the two lower strengths of 75- mg and 150- mg film- coated tablets are manufactured from the same granulation as the 300- mg film- coated tablet, Bristol-Myers Squibb is requesting a waiver for bioequivalence studies for these two lower tablet strengths based on the "proportional similarity" criterion. Data submitted in this biowaiver justification indicate similar in vitro dissolution profiles in multiple media between the 300 mg strength film-coated tablet (Reference Product) and the 75 mg and 150 mg strength film-coated tablets (Test Product).

Dissolution assessments of the Test products (75 and 150- mg film- coated tablets) and Reference product (300- mg film- coated tablets) were performed using USP Apparatus 2 (paddles) at rpm in a volume of the following media: 1) (the approved method/ medium); 2) 3) 4) Dissolution tests in each medium were performed using 12 units/batch. Since irbesartan has minimal solubility at medium was selected over the medium. Since dissolution data in were provided in the original application, was an added test media. Since sink conditions are not maintained at four 75 mg and two 150 mg film-coated tablets were compared with one 300- mg film- coated tablet. This was done to normalize for the amount of irbesartan per dissolution vessel. An additional dissolution comparison was made between one tablet each of the 75, 150, and 300- mg strengths in the approved release medium

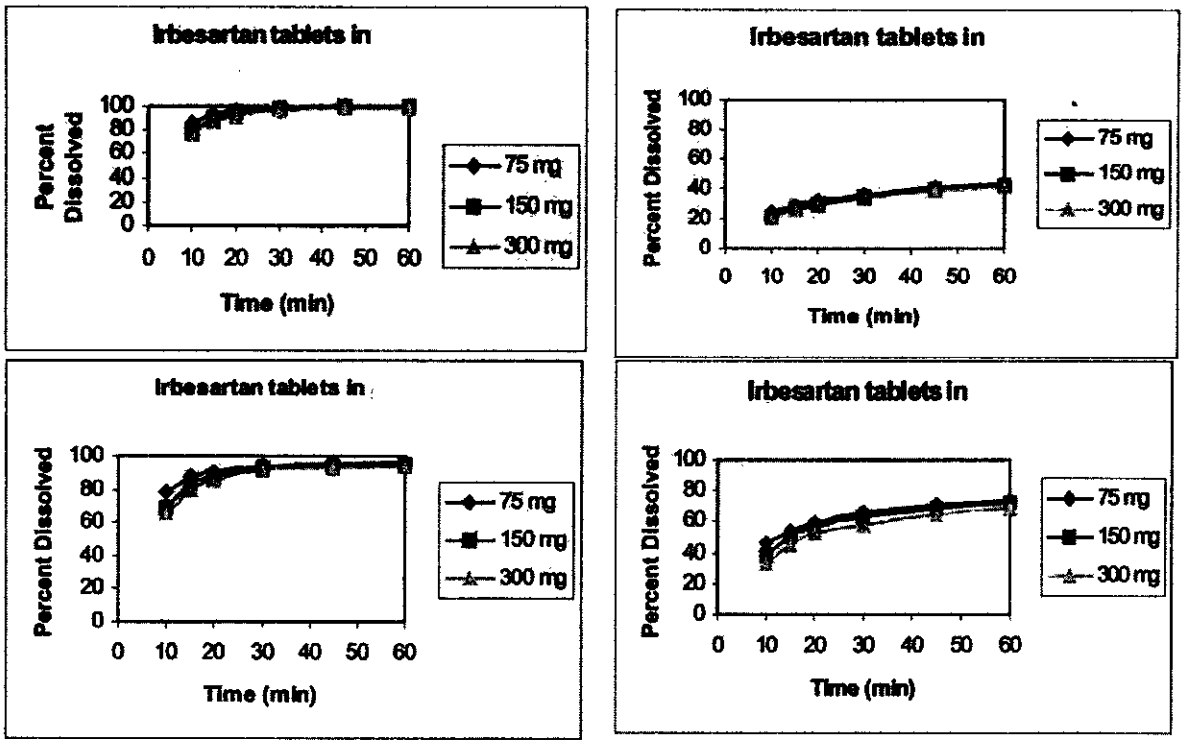
The next table presents the strengths and lot numbers of the test and reference products used for determination of in vitro dissolution.

Product Name	Label Strength	Lot Number
Irbesartan film-coated tablet, 75-mg (Test)	75-mg	8MCE118
Irbesartan film-coated tablet, 150-mg (Test)	150-mg	8MCE119
Irbesartan film-coated tablet, 75-mg (Reference)	300-mg	8MCE120

The next table presents the similarity factor (f2) results for the dissolution testing of the test and reference film coated tablets.

Dissolution [illegible] pH	f2 Test [illegible] 4 x 75 mg (Test) vs. 1 x 300 mg (reference)	f2 Test [illegible] 2 x 150 mg (Test) vs. 1 x 300 mg (reference)
pH	64	81
pH	74	91
pH	53	65
pH	57	78

The Mean dissolution profiles of test and reference film coated tablets at pHs
are illustrated in the next figures.



For each product (75 mg, 150 mg and 300 mg film- coated tablet), over of the label claim was dissolved in 15 minutes in Therefore, the irbesartan film-coated tablets exhibit fast dissolution. Thus, dissolution similarity is "self- evident" in where sink conditions exist. However, in sink conditions do not exist and, hence, the dissolution is slow and incomplete.

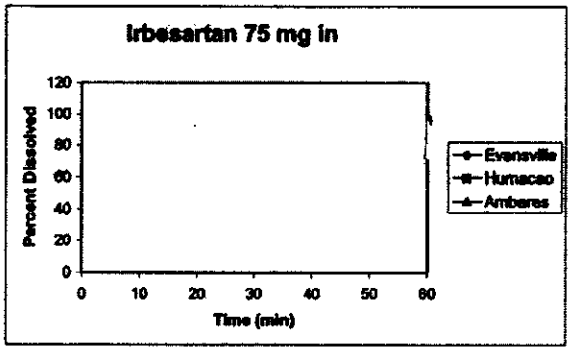
To ensure that the absence of sink conditions at did not influence the dissolution comparison, the amount of irbesartan being dissolved in each dissolution vessel was normalized. This was done by comparing the dissolution of one 300- mg tablet vs. four 75- mg tablets vs. two 150- mg tablets. The dissolution profiles of the Test and Reference products at all pH conditions were almost superimposable. Accordingly, the similarity factor (f2) comparisons between the Test and Reference products at all pH conditions exceeded 50, which is indicative of similar dissolution.

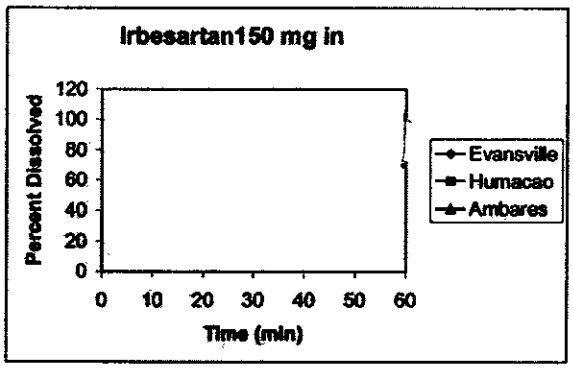
Reviewer Comments:

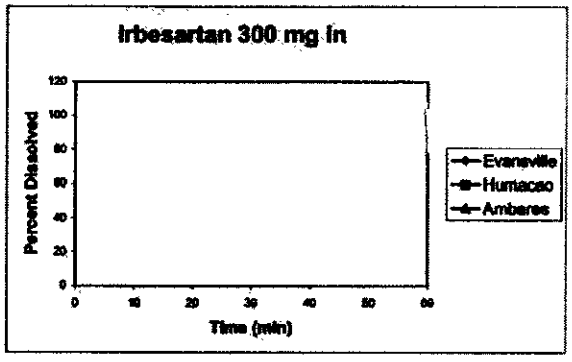
1. *Since; **1)** the pharmacokinetics of irbesartan is linear over the dose range of 75 to 300 mg, **2)** the 300 mg film-coated/ reduced mass tablet is bioequivalent to the 300 mg current marketed tablet, and 3) the in vitro dissolution results showed that in the approved medium, the dissolution profiles of the 75 mg and 150 mg film-coated tablets were similar to the corresponding dissolution profiles*

of the 300 mg film-coated tablets. OCPB is of the opinion that the sponsor has provided appropriate data to support their biowaiver request for the 75 and 150 mg film-coated reduced mass tablets and is granted.

2. *Additionally, dissolution profiles for drug product manufactured at the proposed commercial manufacturing facilities (1) the Bristol-Myers Squibb facility in Evansville, Indiana USA, (2) the Bristol-Myers Squibb facility in Humacao Puerto Rico, USA, and (3) the Sanofi Winthrop Industrie facility in Ambares, France, were generated according to the approved method ,[ ] USP Apparatus 2, [ ] and the sampling points were 10, 15, 20, 30, 45. and 60 minutes). For the Evansville, Humacao, and Ambares facilities typical batch sizes are [ ] respectively. The site comparison dissolution profiles for the 75, 150, and 300 mg film-coated tablets are illustrated in the next figures.*







As shown in these plots, more than ~ of irbesartan is dissolved in 15%, thus, so that calculation of the similarity factor f2 was unnecessary. In conclusion, the dissolution profiles support the similarity of the products regardless of the manufacturing site.

3. *It should be noted that the batch size of the test product used in the BE study and test and reference products used in the comparative dissolution testing was — and these products were manufactured at the Evansville facility in Indiana, USA.*

The next tables show the batch size information for the 3 facilities that are proposed for the manufacturing of new reduced mass film-coated formulations of 75, 150, and 300 mg Avapro Tablets.

Batch Size Information for the products manufactured at the facility located at Evansville, Indiana, USA

Product Name	Stability Batch Size	Maximum Commercial Batch Size	Minimum Commercial Batch Size
Irbesartan 75 mg			
Irbesartan 150 mg			
Irbesartan 300 mg			

Batch Size Information for the products manufactured at the facility located at Humacao, Puerto Rico

Product Name	Stability Batch Size	Maximum Commercial Batch Size	Minimum Commercial Batch Size
Irbesartan 75 mg			
Irbesartan 150 mg			
Irbesartan 300 mg			

Batch Size Information for the products manufactured at the facility located at Ambares, France

Product Name	Stability Batch Size	Maximum Commercial Batch Size	Minimum Commercial Batch Size
Irbesartan 75 mg			
Irbesartan 150 mg			
Irbesartan 300 mg			

Attachment I

Includes

NDA 20-757

Summary of Bioequivalence Study No. CV131159

Study Report Summary

Study No.: CV131159

Study Name: Bioequivalence Study of 300 mg Irbesartan Reduced Mass Tablets Relative to Avapro Tablets in Healthy Subjects

Investigator/Study Center: Howard D. Uderman, M.D./Bristol-Myers Squibb Clinical Research Center

Objectives:

- ***Primary:*** To demonstrate bioequivalence of the 300 mg irbesartan reduced mass tablet relative to the marketed 300 mg Avapro tablet.
- ***Secondary:*** To assess the safety of 300 mg irbesartan administered as a reduced mass tablet and as the marketed Avapro tablet.

Study Design: This was an open-label, randomized, two-period, two-treatment, crossover study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days prior to study enrollment. For each of the 2 periods, subjects were admitted to the clinical facility the evening prior to dosing (Day -1) and fasted for at least 10 hours before dosing. Twenty-four (24) subjects were randomized to receive 1 x 300 mg Avapro tablet and 1 x 300 mg irbesartan reduced mass tablet in one of two treatment sequences. There was at least a 7-day washout period between each dose. For each treatment period, subjects were confined to the clinical facility until 72 hours post-dose. Blood samples were collected for pharmacokinetic (PK) analysis for 72 hours post-dose. Physical examinations, vital sign measurements, 12-lead electrocardiograms, and clinical laboratory evaluations were performed at selected times. Subjects were closely monitored for adverse events throughout the study. Approximately 250 mL of blood was drawn from each subject during the study.

Study Population: A total of 24 healthy male and female subjects (18-57 years of age) meeting the inclusion/exclusion criteria were enrolled in the study. Twenty-four subjects received irbesartan reduced mass tablets and 23 subjects received Avapro tablets. One subject discontinued after receiving 300 mg of reduced mass irbesartan.

Study Products:

- ***Test:*** Irbesartan reduced mass 300 mg tablets, single oral dose of 1 x 300 mg, product identification number 186295-K300-178, batch number 8MCE120.
- ***Reference:*** Currently-marketed Avapro 300 mg tablets, single oral dose of 1 x 300 mg, lot number MBE23.

Please note that the 300 mg irbesartan reduced mass tablets were manufactured at the Evansville facility, Indiana, USA. The batch size was [redacted] that is the minimum size of a commercial batch.

Assessments:

- ***Safety, Tolerability:*** Safety assessments were based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms, physical examinations, and clinical laboratory tests. The incidence of adverse events was tabulated and reviewed for potential significance and clinical importance.

- ***Collection of Samples:*** Blood samples (5 mL each) for the measurement of irbesartan were obtained pre-dose, 0.17, 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 8 12, 16, 24, 30, 36, 48, 60 and 72 hrs post-dose.

- ***Analytical Methods:*** Plasma samples were analyzed for irbesartan by a validated [ ] method using a stable isotope analog of irbesartan as the internal standard. The standard curve ranged from [ ] ng/mL in human plasma, 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.

- ***Pharmacokinetics:*** Single-dose pharmacokinetic parameters (Cmax, Tmax, AUC(inf), and AUC(0-T)) were derived from plasma concentration versus time data for irbesartan. Calculation of Pharmacokinetic Parameters: The plasma concentration vs. time data for irbesartan were analyzed by non-compartmental methods using PKMENU.

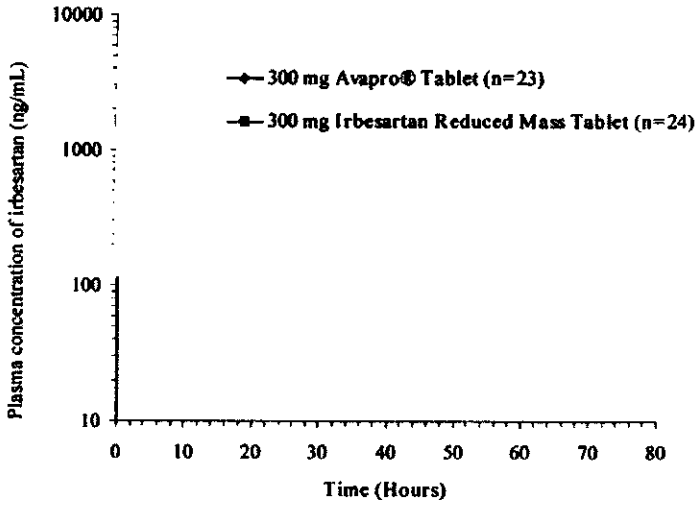
- ***Bioequivalence:*** To determine the bioequivalence of 1 x 300 mg Avapro tablet to irbesartan 1 x 300 mg reduced mass tablet, analyses of variance were performed on log(Cmax), log(AUC(INF)) and log(AUC(0-T)). The factors in the analysis were sequence group, subject within sequence, period, and formulation. Bioequivalence was concluded if the 90% confidence intervals for the ratios of population geometric means of the irbesartan reduced mass tablets to the Avapro tablets were contained within 80% to 125% for Cmax and AUC(inf). The confidence intervals were constructed from the results of analyses of variance on log(Cmax) and log(AUC(inf).

- ***Statistics:*** Arithmetic means, standard deviations and coefficients of variation were calculated on the individual pharmacokinetic parameters. All recorded adverse events were listed and tabulated by primary term, body system, and formulation. Vital signs and clinical laboratory test results were listed and summarized by formulation. Any significant physical examination findings and clinical laboratory results were listed. ECG recordings were evaluated by the investigator and abnormalities, if present, were listed.

RESULTS:

- ***Safety And Tolerability:*** The types of AEs reported during the course of this study were varied and generally few in number. A total of 6 adverse events were reported in 5 subjects. All were mild to moderate in intensity. There were no deaths or serious adverse events. One subject discontinued prior to the initiation of Period 2 due to muscle aches. The subject had received a 300 mg reduced mass tablet 9 days earlier. One subject had an AE at discharge, a symptom-less increase in ALT. The cause of the elevation is unknown. The elevation was followed post-discharge until it approached baseline levels.

- ***Pharmacokinetics:*** The next figure illustrates the irbesartan plasma concentration vs. time for the 2 tested formulations.



The pharmacokinetic results were determined using a validated noncompartmental analysis. The pharmacokinetic parameters and statistical analysis of irbesartan following administration of 300 mg irbesartan reduced mass tablets relative to the 300 mg Avapro tablets are summarized in the following tables:

Summary Statistics for Irbesartan Pharmacokinetic Parameters (n = 23)

Pharmacokinetic Parameter	Treatment A	Treatment B
Cmax (ng/mL)		
Geometric Mean	3387.1	3618.2
(C.V.%)	(38)	(28)
AUC(INF) (ng•h/mL)		
Geometric Mean	22732.1	22445.1
(C.V.%)	(31)	(25)
AUC(0-T) (ng•h/mL)		
Geometric Mean	21682.7	21394.5
(C.V.%)	(29)	(24)
Tmax (h)		
Median	1.00	1.00
(min, max)	[	]

Statistical Analysis of CMAX, AUC(INF), and AUC (0-T) for Irbesartan

Pharmacokinetic Parameter	Adjusted Geometric Treatment	Mean	Contrast	Ratios of Adj. Geo. Means Pt. Estimate (90% C.I.)
Cmax (ng/mL)	A	3405.5		
	B	3633.6	B vs. A	1.067 (0.968, 1.176)
AUC(INF)	A	22846.3		
(ng•h/mL)	B	22536.6	B vs. A	0.986 (0.919, 1.059)
AUC(0-T)	A	21785.9		
(ng•h/mL)	B	21458.2	B vs. A	0.985 (0.921, 1.054)

Treatment A: 1x300 mg Avapro® tablet (Reference)

Treatment B: 1x300 mg irbesartan reduced mass tablet (Test)

The overall results showed that the 1 x 300 mg reduced mass tablet is bioequivalent to irbesartan 1 x 300 mg Avapro tablet with respect to irbesartan Cmax and AUC(inf). In addition, 1 x 300 mg Avapro tablet is also bioequivalent to irbesartan 1 x 300 mg reduced mass tablet with respect to irbesartan AUC(0-T). There were no statistically significant period and sequence effect detected in the analysis of either Cmax or AUC(inf) or AUC(0-T).

The 300 mg irbesartan reduced mass tablets and the 300 mg Avapro tablets were safe and well-tolerated in healthy subjects.

Reviewer Comments:

1. *The results from this study demonstrated that 1 x 300 mg irbesartan reduced mass tablet was bioequivalent to 1 x 300 mg Avapro tablet with respect to both irbesartan Cmax and AUC(inf). The 90% confidence intervals for the geometric mean ratios of these parameters were contained between the Agency's 80-125% BE criteria. Thus, bioequivalence study No. CV131159 is appropriate and acceptable.*

2. *Overall, the provided analytical validation report and quality control data showed adequate validation and assay precision/accuracy for irbesartan.*

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/s/

Angelica Dorantes
9/5/03 01:01:57 PM
BIOPHARMACEUTICS

Patrick Marroum
9/5/03 01:29:09 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-757/S-028

Sanofi-Synthelabo c/o Bristol-Myers Squibb
Attention: Elora Gupta, Ph.D.
Post Office Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gupta:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Avapro (irbesartan) 75, 150, and 300 mg Tablets

NDA Number: 20-757

Supplement number: 028

Date of supplement: May 8, 2003

Date of receipt: May 9, 2003

This supplemental application proposes to support the commercialization of new reduced mass, film-coated formulations for all strengths of irbesartan tablets.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 8, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 9, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Edward Fromm
Regulatory Health Project Manager
(301)-594-5332

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
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